MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Hyaluronic Acid (HA) Safety Profile

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Introduction

This Medical Device Materials Performance Report divides hyaluronic acid into three major categories:

1. Muscle/skeletal applications
2. Dermal, facial and eye applications
3. Adhesion barrier and bulking agent applications

Accordingly, the report has dedicated sections and discussions for each application. These include separate executive summaries, safety briefs, surveillance data, gap analyses, and appendices. The goal of this report structure is to allow the reader to focus on the current state of knowledge with regard to medical device material biocompatibility for each application in an organized and discrete manner.

Executive Summary – Muscle/Skeletal Applications

Key Points

1. Searches identified 1795 citations; 39 articles were selected for inclusion.
2. Thirty-six (92%) studies in the evidence base focused on viscosupplementation, the intra-articular (IA) injection of hyaluronic acid (HA). Of these 36 studies, 26 studies addressed knees, 4 studies addressed hips, while 2 studies each addressed hands or ankles, shoulders, and temporomandibular joint (TMJ) disorders. Three remaining studies examined HA as cartilage scaffolds.
3. The most commonly reported local responses included swelling, pain at injection site, arthralgia/joint pain, and effusion which were associated with moderate to low quality of evidence. Additionally, joint stiffness, musculoskeletal pain, post-injection pain, pain flare ups and edema were frequently reported, and they were associated with low quality of evidence. Outcomes infrequently reported (e.g., hematoma) or device categories with no evidence (HA as a material, and bone putty/filler) were rated very low quality of evidence.
4. Evidence for systemic responses was reported for viscosupplementation in knees, shoulders, and TMJ disorders. One systematic review (SR) investigating fatal adverse events (AEs) from intraarticular injections of HA listed in the Manufacturer and User Facility Device Experience (MAUDE) and Alternative Summary Reporting databases between 2014 and 2019 identified 63 unique fatalities from knee viscosupplementation. Eight (12%) fatalities were categorized as possibly related to the intraarticular injection of HA (IAHA), but available information was "insufficient to make a firm determination of causality." Two studies reporting skin reactions (1 rash, 1 peeling of skin on hands and toes) directly attributed the response to knee viscosupplementation.
5. Healthcare Technology Alerts identified 5 manufacturer issued alerts describing problems with adverse events, contamination, packaging issues, and impartially filled products.
6. Patient Safety Organization identified 7 complications associated with HA including wrong side procedure - 2 (28.5%), 2) wrong product - 2 (28.5%), 3) product expired - 2 (28.5%), and 4) wrong time – 1 (14.2%).
7. Evidence gaps:
    a. Additional research is needed in viscosupplementation in non-knee indications. Small evidence bases were identified for hip, hand, ankle, shoulder and TMJ disorders. While studies for other indications (e.g., plantar fasciitis, trigger finger, and rotator cuff) were identified, these studies were excluded at final prioritization level due to being low quality (e.g., single arm design) or having small enrollment (<100 patients).
    b. Evidence for viscosupplementation was mostly focused on 2 HA products (Hyalgan and Synvisc). Additional evidence is needed for Monovisc, HYADD, Sinovial, Gel-One, Supartz, Go-On, Hanox M-XL, Ostenil, and Hyalubrix which were investigated in ≤3 studies. Additionally, evidence is lacking for numerous HA products that were not evaluated for viscosupplementation (e.g., Synojoynt, Triluron, Trivisc), bone putty/filler (e.g., DBX Putty, Kinex Gel), cartilage scaffold or (e.g., Agili-C).
    c. While many studies were high-quality (SRs or randomized controlled trials (RCTs)), several studies did not report important study characteristics (e.g., HA products investigated, HA dose), or details on clinical results

(e.g., type of treatment-related AE (TRAE), number of events, number of patients experiencing events, timing of events).

d. Long-term human RCTs for local responses to HA as a material and for all device categories to better ascertain associations with these responses to HA.

e. Additional research on systemic responses, including those on patient or material factors, for all HA device categories. Systemic responses were only investigated in 13 (33%) studies with no studies investigating HA for viscosupplementation (in hips, hands, and ankles), bone putty/fillers, or cartilage scaffolds.

Overview - Muscle/Skeletal Applications

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions provided by FDA and summarized below, regarding a host's local and systemic response to Hyaluronic Acid in muscle/skeletal applications. If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to these materials?

Local responses/device events varied somewhat across different device categories and between human studies (see specific responses/events under 1a. below). The majority of ECRI surveillance data were related to wrong side application, packaging issues, and contamination, which were not related to material response due to insufficient biocompatibility or mechanical integrity and use of the device.

a. Can that response vary by location or type of tissue the device is implanted in or near?

i. Swelling occurred with viscosupplementation in knees and ankles, and scaffold placement in knees. This local response was the most commonly reported after viscosupplementation in knees. One study reported mild-to-moderate swelling of the knee joint occurred similarly with HA vs. platelet-rich plasma (PRP) with HA rates ranging from 87% (6 months) to 100% (6 weeks). Other studies reported higher but low incidence of knee swelling with IAHA vs. saline (3.7% Synvisc, 0.9% saline; 1.1% Monovisc, 0.5% saline). One RCT reported that swelling after injection of Synvisc was device-related**,** while 1 SR of 12 RCTs reported significantly more TRAEs (including joint swelling) occurred with HA vs corticosteroid (CS; 746 events vs. 606 events). Mild swelling was reported after scaffold placement in knees (n=3), and also after viscosupplementation in ankles.

ii. Pain at injection site occurred after viscosupplementation in knees, shoulders, ankles, and TMJ disorders. One study reported knee pain and local swelling at injection site in 21% of patients administered HA injections of different molecular weights and concentrations (DMW), high molecular weights (HMWs), and low molecular weights (LMWs). Studies also reported knee pain at injection site in 8 (13.4%) patients with IAHA, and a 0.5% incidence rate with Synvisc. This outcome was commonly reported in 1 SR of 15 studies addressing viscosupplementation in shoulders, and in 1 SR of 18 studies addressing viscosupplementation in ankles. Lastly, 2 SRs examining TMJ disorders reported a lower incidence of pain at injection site with HA vs. CS (37% vs. 70%) and HA vs. PRP or platelet-rich growth factor (PRGF; 60% vs. 76%).

iii. Arthralgia/joint pain was reported in 7 studies focused on viscosupplementation in knees. Studies reported a significantly higher occurrence of arthralgia with HA vs. nonsteroidal anti-inflammatory drugs (NSAIDs; 8.1% vs. 2.9%), but similar rates vs. saline (<4% in 2 studies). 1 SR reported severe joint pain in 28 (100%) patients with pseudoseptic arthritis, a rare complication after IAHA injection. 2 RCTs reported that arthralgia with Synvisc or Monovisc was device-related.

iv. Effusion was reported in 5 studies focused on viscosupplementation in knees. One SR (n=5,354) reported no significant difference in effusion after injection based on molecular weights (1.9% HMW,

1.7% medium molecular weight (MMW), 1.8% LMW), but a significantly higher incidence of effusion with products processed through extraction of avian-derived molecules (AD-HA) vs. bacterial processes of biological fermentation (Bio-HA; 3.4% vs. 0.5%). Another SR reported that 28 (100%) patients with pseudoseptic arthritis presented with effusion.

v. Joint stiffness only occurred with knee viscosupplementation. Studies reported no significant differences in stiffness with HA vs. PRGF, lower rates with Monovisc vs. saline (0.5% vs. 1.1%), and incidence rates of 7% with varying weights of IAHA.
vi. Musculoskeletal pain was reported after viscosupplementation in knees and shoulders. For knee viscosupplementation, 1 study reported more frequent musculoskeletal pain with HA vs. PRP (5% vs. 1.8%). For shoulder viscosupplementation, musculoskeletal pain was commonly reported in 13 (87%) studies in 1 SR; severe musculoskeletal, a serious adverse event (SAE), was reported in some cases.
vii. Post-injection pain was reported after viscosupplementation in knees and hips. For knee viscosupplementation, studies reported post-injection pain in 3 patients with IAHA, significantly more post-injection pain with HA vs. PRP, and lower incidence with Synvisc-One vs. cooled radiofrequency ablation (CRFA; 3% vs. 8%). For hip viscosupplementation, 1 study reported significantly higher post-injective pain with PRP vs. HA.
viii. Pain flare ups were reported with viscosupplementation in knees and hips. One SR (n=5,354) reported significantly more knee flare ups with HA products with HMWs vs. lower molecular weights (13.7% HMW, 3.3% MMW, 10.7% LMW), and a significantly lower incidence of acute flare ups with AD-HA vs. Bio-HA (3.0% vs. 13.2%). One RCT reported knee flare up rates of 6% to 36% with Synvisc. Lastly, a higher occurrence of hip pain flare ups were reported with HA vs. placebo (7% vs. 2.4%).
ix. Edema was reported after knee viscosupplementation and scaffold placement. Injection-site edema and peripheral edema were only reported with HA vs. placebo (0.5 % vs. 0%) in 1 RCT. Edema or cyst formation occurred similarly with a Hyalofast-based scaffold vs. a chitosan-glycerol phosphate/blood implant (BST-CarGel®) (8 (38%) Hyalofast, 10 (40%) BST-CarGel) in 1 nonrandomized comparative study.
x. Less commonly reported local responses included 1) device-related cutaneous vasculitis, Baker's cyst (n=2) with Synvisc-One, and elevated inflammatory cell count (n=16) after knee viscosupplementation; 2) hematoma after hip viscosupplementation and HA scaffold placement in the knee; 3) pseudogout after ankle viscosupplementation; 4) abscess after shoulder viscosupplementation; 5) postoperative discomfort and ear pressure after viscosupplementation for TMJ disorders; and 6) persistent pain after an HA scaffold placement in knees.
xi. The overall quality of evidence related to local host responses was moderate to very low, with variation across different device categories.
xii. Evidence was limited for HA as a scaffold, however no evidence was included for HA as a material, and bone putty/filler.

b. Over what time course does this local host response appear?

Swelling was reported after knee and ankle viscosupplementation, from 2 weeks to 6 weeks with an HA scaffold; and at 6 weeks, 3 months and 6 months with knee viscosupplementation. Pain at injection site was reported up to 3 days with viscosupplementation of knees, ankles, shoulders, and TMJ disorders. After knee viscosupplementation: 1) arthralgia was reported in 7 studies as immediately after up to 9 days; 2) effusion was reported immediately after up to 3 days; and 3) joint stiffness only occurred immediately after. Pain flare ups were described at weeks 6, 13, 26, 39, and 52 with Synvisc in knee viscosupplementation, and during or immediately after with hip viscosupplementation. Timing for musculoskeletal pain (viscosupplementation in knees, shoulders), post-injection pain (viscosupplementation in knees, hips), and edema was not reported.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

Overall, 13 studies investigated systemic responses; studies addressed viscosupplementation in knees (11), shoulders (1), and TMJ disorders (1). Of studies investigating, 11 (85%) studies identified persistent or exaggerated immune responses, while 26 (67%) did not investigate systemic responses.

b. What are the likely systemic manifestations?

For knee viscosupplementation, evidence for systemic responses was provided in studies examining IAHA alone, and studies grouped in the following categories (vs. PRP, anti-inflammatories, saline/placebo, miscellaneous treatments).

> *IAHA*: 1 SR indicated that 8 (12%) of 63 fatalities were possibly IAHA-related but available information was "insufficient to make a firm determination of causality." Authors noted the following responses occurred prior to death: septic shock followed by paralysis, necrotizing fasciitis, and septicemia. Another SR investigating acute pseudoseptic arthritis reported elevated C reactive protein (CRP), elevated erythrocyte sedimentation rates (ESR), elevated polymorphonuclear leukocytes (PMNs) in 10 (37%) patients, fever in 6 (22%) patients, and leukocytosis above 10,000 in 4 (15%) patients. Systemic responses in a related case report included a cell count of 123,260 and white blood cell count (WBC) of 15.5 in 1 patient.
>
> *IAHA vs. PRP*: 1 of 2 studies investigating identified nasopharyngitis and backache in 2 patients each, and headache in 1 patient.
>
> *IAHA vs. anti-inflammatories*: Of 3 SRs investigating, 1 SR reported significantly more headache vs. oral NSAIDs (8.4% vs. 4.4%), and cardiac-related complications (n=1). Data for other responses (nausea and vomiting) was not provided in another SR. Lastly, 1 SR (n=1794) did not identify any treatment-related systemic responses.
>
> *IAHA vs. saline/placebo*: 1 SR of 9 RCTs (n=1967), focused on TRAEs, reported no significant difference in system-organ class(SOC)-related AEs with IAHA vs. placebo. Cardiac disorders, vascular disorders, and renal/urinary disorders occurred in <10 patients each with IAHA. Skin/subcutaneous tissue disorders and hypersensitivity reactions occurred in 22 and 23 patients, respectively. Gastrointestinal (GI) disorders, respiratory/thoracic/mediastinal disorders, and nervous system disorders occurred in 66 to 71 patients each. Musculoskeletal and connective tissue disorders occurred in 145 patients with HA, and 149 patients with placebo. 1 RCT reported a Monovisc-related rash in 1 patient. Lastly, 1 SR of 10 RCTs attributed 1 serious AE (skin reaction characterized by peeling of skin on hands and toes) to IAHA.
>
> *IAHA vs. miscellaneous treatments*: GI complaints were reported in 3% to 7% of patients.

For shoulder viscosupplementation: 1 SR with followup up to 3 years, commonly reported systemic responses including diarrhea, flu symptoms, and headache. Serious AEs such as chest pain and cancer were also reported (N not reported). Responses were not deemed as device-related.

For viscosupplementation in TMJ disorders: 1 individual RCT in a SR reported slight chills in 5.7% of patients with HA, vs. 0% with CS.

c. What is the observed timeline(s) for the systemic manifestations?

Evidence for timing was limited to the following:

For knee viscosupplementation:

IAHA: death in 1 of 8 patients was reported 4 months post-IAHA injection. 1 SR addressing pseudoseptic arthritis indicated that most cases presented within 24 hours of injection, however time from injection to presentation ranged from 1 hour to 9 days. In the related case report, arthrocentesis was undertaken at 20 hours post-injection.

IAHA vs. saline/placebo: Skin reaction in 1 patient occurred 8 days post-IAHA injection.

IAHA vs. miscellaneous treatments: GI complaints were tracked at weeks 6, 13, 26, 39, and 52.

For viscosupplementation in TMJ disorders: Slight chills were reported at 1 week.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

No studies investigated cellular/molecular mechanisms for systemic responses.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

No studies investigated patient-related factors that may predict, increase, or decrease the likelihood of an exaggerated, sustained immunological/systemic response.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

1 SR indicated that the pathophysiological response for pseudoseptic arthritis (identified in 28 patients) may be due to the accumulation of viscous material (e.g., phagocytised HA). This same review noted that significantly more reactions occurred in patients receiving more than a single administration. Results indicated that 7 cases (25%) occurred after 2 injections, 5 cases (17.9%) after 3 injections, and 13 cases (46.4%) after ≥4 injections.

5. What critical information gaps exist and what research is needed to better understand this issue?

All gaps listed here could benefit from future research.

a. Additional research is needed in viscosupplementation in non-knee indications. Small evidence bases were identified for hip, hand, ankle, shoulder and TMJ disorders. While we did identify studies for other indications (e.g., plantar fasciitis, trigger finger, and rotator cuff), these studies were excluded at final prioritization level due to being low quality (e.g., single arm design) or having small enrollment (<100 patients).

b. Evidence for viscosupplementation was mostly focused on 2 HA products (Hyalgan and Synvisc). Additional evidence is needed for Monovisc, HYADD, Sinovial, Gel-One, Supartz, Go-On, Hanox M-XL, Ostenil, and Hyalubrix which were investigated in ≤3 studies. Additionally, evidence is lacking for numerous HA products that were not evaluated for viscosupplementation (e.g., Synojoynt, Triluron, Trivisc), bone putty/filler (e.g., DBX Putty, Kinex Gel), and cartilage scaffold (e.g., Agili-C).

c. While many studies were high-quality (SRs or RCTs), several studies did not report important study characteristics (e.g., HA products investigated, HA dose), or details on clinical results (e.g., type of TRAE, number of events, number of patients experiencing events, timing of events).

d. Long-term human and animal RCTs for local responses to HA as a material and for all device categories to better ascertain associations with these responses to HA.

e. Additional research on systemic responses, including those on patient or material factors, for all HA device categories. Systemic responses were only investigated in 13 (33%) studies with no studies investigating HA for viscosupplementation (in hips, hands, and ankles), bone putty/fillers, or cartilage scaffolds.

Executive Summary – Dermal, Facial and Eye Applications

Key Points

1. Searches identified 1401 citations; 58 articles were selected for inclusion
2. For HA dermal fillers, the most common complications of facial injections included lumpiness, tenderness, swelling, and bruising. Delayed inflammatory reactions/events occurred in about 1% of patients; in rare instances granulomas formed that required surgical removal. Most complication rates were similar between different HA fillers, but delayed-onset nodules had a higher occurrence rate for Juvederm Volbella. Rare but serious events included partial or complete vision loss following upper face injections, as well as brain infarcts or hemorrhage. The overall quality of evidence is moderate.
3. For intraocular/ophthalmic viscoelastic HA solutions, intraoperative pressure (IOP) elevation was a common complication following eye surgery and injection of HA solutions. IOP usually decreased over time, but Healon GV and Healon5 were associated with lesser elevations and faster decreases in IOP over 1 week compared to other HA solutions. Corneal and/or macular edema were relatively rare events occurring at similar rates for different HA solutions. The overall strength of evidence is moderate for IOP elevation and corneal/macular edema, low for other adverse events.
4. For eye drops, reported adverse events included itching/stinging/irritation/erythema/keratitis, eye pain, eye disorders/dry eye, hyperemia/hemorrhage, and infection/viral conjunctivitis. Overall, most studies reported no difference in adverse event rates between HA eye drops and other treatments or controls. The overall quality of evidence is moderate.
5. Systemic responses. A small number of patients developed late-onset, inflammatory, non-infectious adverse reactions related to dermal fillers/implants (including HA fillers) that could be totally or partially considered as autoimmune/ inflammatory syndrome induced by adjuvants (ASIA)-related disorders. Reported symptoms of HA cases included myalgia, arthralgia/arthritis, fatigue, neurologic complaints, cognitive features, fever, Sicca syndrome, skin manifestations (including facial nodules), and autoimmune disease. The overall strength of evidence is low for systemic responses.
6. ECRI PSO identified one incident of hemorrhage/hematoma associated with a dermal implant composed of HA. There were no relevant reports found in ECRI's accident investigation, or PRN databases related to devices composed of HA.
7. Evidence gaps:
    a. Across all device categories, the overall quality of evidence was low to very low for potential systemic responses.

b. For intraocular/ophthalmic/viscoelastic solution/fluids, other than IOP elevation and corneal/macular edema (moderate quality of evidence), all identified local host responses (e.g., ocular tension, inflammation) were of low quality of evidence.
c. There were no studies that addressed any particular cellular or molecular mechanisms for systemic manifestations.
d. Additionally, no studies addressed patient-related or material-related factors that could predict the likelihood and/or severity of immunological/systemic responses.

Overview - Dermal, Facial and Eye Applications

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions provided by FDA and summarized below, regarding a host's local and systemic response to Hyaluronic Acid in muscle/skeletal applications. If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to these materials?

Local responses/device events varied somewhat across different device categories (see specific responses/events under 1a. below).

a. Can that response vary by location or type of tissue the device is implanted in or near?

i. For HA dermal fillers, the most common complications of facial injections included lumpiness, tenderness, swelling, and bruising. Most complication rates were similar between different HA fillers, but delayed-onset nodules had a higher occurrence rate for Juvederm Volbella. Delayed inflammatory reactions/events occurred in about 1% of patients; in rare instances granulomas formed that required surgical removal. Rare but serious events included partial or complete vision loss following upper face injections, as well as brain infarcts or hemorrhage. HA (Macrolane) injection of breasts was associated with cysts, capsular contraction, early absorption and sometimes removal of product was required.

ii. For intraocular/ophthalmic viscoelastic HA solutions, intraoperative pressure (IOP) elevation was a common complication following eye surgery and injection of HA solutions. IOP usually decreased over time, but Healon GV and Healon5 were associated with lesser elevations and faster decreases in IOP over 1 week compared to other HA solutions. Corneal and/or macular edema were relatively rare events occurring at similar rates for different HA solutions. One study reported Descemet membrane detachment (DMD) in 7% of patients following canaloplasty and Healon GV injection (most cases resolved without further surgery). One study reported 34 cases of toxic anterior segment syndrome (TASS) after cataract surgery; the source was identified as HA solution derived from rooster comb.

iii. For eye drops, reported adverse events included itching/stinging/irritation/erythema/keratitis, eye pain, eye disorders/dry eye, hyperemia/hemorrhage, and infection/viral conjunctivitis. Overall, most studies reported no difference in adverse event rates between HA eye drops and other treatments or controls.

b. Over what time course does this local host response appear?

i. For dermal fillers, most events occurred within the first 2 weeks; a smaller percentage of patients experienced delayed-onset inflammatory reactions/events that occurred months or even years after injection (3 to 10 years for granulomas).

ii. For intraocular HA solutions, IOP tended to peak at 1 day post-surgery and decrease afterward. Other complications occurred within 6 hours to 3 months post-surgery, most within the first week.

iii. For eye drops, adverse responses occurred within the first 3 months, most within the first month.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

Two retrospective single-arm case series reported on cases of patients suffering from late-onset, inflammatory, non-infectious adverse reactions related to dermal fillers/implants that could be totally or partially considered as autoimmune/ inflammatory syndrome induced by adjuvants (ASIA)-related disorders.

b. What are the likely systemic manifestations?

Reported symptoms of HA cases in the larger study included 4 myalgia, 6 arthralgia/arthritis, 6 fatigue, 2 neurologic complaints, 2 cognitive features, 1 fever, 1 Sicca syndrome, 7 skin manifestations (3 facial nodules), 3 evolvements into autoimmune disease.

c. What is the observed timeline(s) for the systemic manifestations?

The symptoms occurred between 6- and 317-months following exposure to dermal filler.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

The search did not identify any studies that addressed this question.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

The number of cases related to HA was low and analyzed with cases who had received other dermal fillers, so the evidence was unclear concerning patient-related factors that predict sustained systemic response.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

The number of cases related to HA was low and analyzed with cases who had received other dermal fillers, so the evidence was unclear concerning material-related factors that predict sustained systemic response.

5. What critical information gaps exist and what research is needed to better understand this issue?

All gaps listed here could benefit from future research.

a. Across all device categories, the overall quality of evidence was low to very low for potential systemic responses.

b. For intraocular/ophthalmic/viscoelastic solution/fluids, other than IOP elevation and corneal/macular edema (moderate quality of evidence), all identified local host responses (e.g., ocular tension, inflammation) were of low quality of evidence.

c. There were no studies that addressed any particular cellular or molecular mechanisms for systemic manifestations.

d. Additionally, no studies adequately addressed patient-related or material-related factors that could predict the likelihood and/or severity of immunological/systemic responses.

Executive Summary – Adhesion Barrier and Bulking Agent Applications

Key Points

1. Searches identified 1217 citations; 52 articles were selected for inclusion
2. Adhesion barriers was the most studied application of hyaluronic acid (34 human studies). There are few adverse events or complications caused by HA-containing products, and the quality of evidence is High (for both local and systemic responses). One trial found statistically significantly higher adverse event rates with HA adhesion barriers in the context of colorectal or small bowel surgery while another trial involving gastrointestinal surgery also found higher adverse event rates with HA adhesion barriers. It is possible that the powder formulation of HA adhesion barriers was a contributing factor to increased frequency of adverse events due to the potential for greater diffusion and migration away from the application site to anastomoses
3. For nasal packaging as well as barrier gel for oral lesions, there are few adverse events or complications caused by HA-containing products. For both of these categories, the evidence was Moderate for local responses and Very Low for systemic responses. .
4. In two trials of bulking agents, statistically significantly higher adverse event rates with HA were found in the context of treatment for fecal incontinence or urinary incontinence which occurred within 12 months of surgery.
5. There were no relevant reports found in ECRI's PSO, accident investigation, or PRN databases related to adhesion barriers composed of HA. Healthcare Technology Alerts search returned 4 manufacturer issued alerts describing problems with compromised sterility and off label use.
6. Evidence gaps:
    a. For 7 of 9 device categories, no local adverse events were statistically significantly more likely in patients receiving HA devices compared to patients receiving non-HA devices. This is predominantly because of a lack of studies with strong design that investigated these events. The exceptions were adhesion barrier and bulking agents.

b. For 7 of 9 device categories, no systemic adverse events were statistically significantly more likely in patients receiving HA device compared to patients received non-HA devices. This is predominantly because of a lack of studies with strong design that investigated these events. The exceptions were adhesion barrier and bulking agents.
c. Only one study related to HA as a material was identified. However, because treated patients received HA as well as chondroitin sulfate, one cannot determine whether the reported adverse events were due to HA or chondroitin sulfate or other factors
d. For 8 of 9 device categories, only study involving adhesion barriers investigated the cellular or molecular mechanisms for systemic manifestations.

Overview - Adhesion Barrier and Bulking Agent Applications

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions provided by FDA and summarized below, regarding a host's local and systemic response to Hyaluronic Acid in Adhesion Barrier and Bulking Agent applications. If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to these materials?

For 7 of 9 device categories, no local adverse events were statistically significantly more likely in patients receiving HA devices compared to patients receiving non-HA devices. The exceptions were adhesion barrier and bulking agents.

a. Can that response vary by location or type of tissue the device is implanted in or near?

i. In two trials of adhesion barriers, statistically significantly higher adverse event rates with HA were found in the context of colorectal or small bowel surgery (one trial), and "gastrointestinal surgery" (the other trial. In two trials of bulking agents, statistically significantly higher adverse event rates with HA were found in the context of treatment for fecal incontinence or urinary incontinence.

b. Over what time course does this local host response appear?

i. In the two aforementioned trials of adhesion barriers, adverse events occurred within 30 days of surgery. In the two aforementioned trials of bulking agents, adverse events occurred within 12 months of surgery.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

For 7 of 9 device categories, no systemic adverse events were statistically significantly more likely in patients receiving HA device compared to patients received non-HA devices. The exceptions were adhesion barrier and bulking agents.

b. What are the likely systemic manifestations?

For adhesion barriers, creatinine was significantly higher in HA patients than in non-HA patients. For bulking agents, fever was significantly higher in HA patients than in non-HA patients.

c. What is the observed timeline(s) for the systemic manifestations?

Creatinine was significantly higher in HA patients on day 5 but not day 7 after surgery. Fever occurred within the first 6 months after injection of the bulking agent.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

The study authors suggested the HA barrier may cause a temporary increase in serum creatinine in the early stage after surgery, but the effect is transitory. In the other study, authors did not speculate as to why fever was more likely in HA-treated patients.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

For adhesion barriers, one systematic review of laparoscopic gynecologic surgery[1] stated "Filmy mobile adhesions resulted in the highest verbal pain scores followed by dense mobile adhesions, filmy fixed adhesions, and dense fixed adhesions. Pain scores were highest when adhesions were between a segment of bowel and an ovary.

4. **Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**

For adhesion barriers, an RCT of laparoscopic colorectal and/or small bowel surgery stated, "The powder formulation of HA/CMC used in this study is likely to be an important contributing factor for the increased frequency of adverse events and serious adverse events." "Due to the potential for greater diffusion of the powder formulation, the authors speculate that migration away from the application site to anastomoses could have occurred in some cases. Furthermore, over-hydration of the HA/CMC powder might have resulted in pooling of the resulting gel away from the application site, raising the possibility of migration onto an anastomosis or provision of a nidus for abscess; such migration to anastomoses might increase the rate of SSIs."

5. What critical information gaps exist and what research is needed to better understand this issue?

All gaps listed here could benefit from future research.

a. For 7 of 9 device categories, no local adverse events were statistically significantly more likely in patients receiving HA devices compared to patients receiving non-HA devices. This is predominantly because of a lack of studies with strong design that investigated these events. The exceptions were adhesion barrier and bulking agents.

b. For 7 of 9 device categories, no systemic adverse events were statistically significantly more likely in patients receiving HA device compared to patients received non-HA devices. This is predominantly because of a lack of studies with strong design that investigated these events. The exceptions were adhesion barrier and bulking agents.

c. Only one study related to HA as a material was identified. However, because treated patients received HA as well as chondroitin sulfate, one cannot determine whether the reported adverse events were due to HA or chondroitin sulfate or other factors

d. For 8 of 9 device categories, only study involving adhesion barriers investigated the cellular or molecular mechanisms for systemic manifestations.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. For 2021, the following 18 topics have been chosen.

1. Magnesium (Mg)
2. Complications associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women
3. Polytetrafluoroethylene (PTFE)
4. Acrylics 1: PMMA
5. Acrylics 2: pHEMA
6. Acrylics 3: Cyanoacrylates (PET)
7. Correlations between complications with polypropylene mesh and surgical procedure/anatomical location and chemical/mechanical device properties
8. Dimethacrylates, Trimethacrylates (EDMA, EGDMA, TEGDMA, PEGDMA), and glycerol methacrylate (bis-GMA)
9. Polyethylene glycol (PEG)
10. Other Fluoropolymers (PFPE, PVDF, PVDF-HFP, PCTFE)
11. Silver
12. Small Molecule Per- and polyfluoroalkyl substances (SM-PFAS)
13. Hyaluronic Acid (HA) - Muscle/Skeletal Applications
14. Hyaluronic Acid (HA) - Dermal, Facial, and Eye Applications
15. Hyaluronic Acid (HA) – Adhesion Barriers
16. Polycaprolactone (PCL)
17. Zirconia
18. Nitinol

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions

1. What is the typical/expected local host response to Hyaluronic Acid?
    a. *Can that response vary by location or type of tissue the device is implanted in or near?*
    b. *Over what time course does this local host response appear?*
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
    a. *What evidence exists to suggest or support this?*
    b. *What are the likely systemic manifestations?*
    c. *What is the observed timeline(s) for the systemic manifestations?*
    d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps exist and what research is needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the six materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2011 and 2021 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
  - Strength
  - Embrittlement
  - Degradation
  - Migration
  - Delamination
  - Leaching

- **Host Response**
  - Local
    - Inflammation
    - Sensitization
    - Irritation
    - Scarring/fibrosis
      - *Keloid formation*
      - *Contracture*
    - Ingrowth
    - Erosion
  - Systemic
    - Cancer
    - Inflammation
    - Immune Response
    - Fatigue
    - Memory Loss
    - Rash
    - Joint Pain
    - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Resulting literature was screened by title review, then abstract review, and finally full article review. Data were extracted from the articles meeting our inclusion criteria to address the key questions for each material.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, problem reporting network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff; thus, reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through August 2021, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A (No Error)
Circumstances or events that have the capacity to cause error.

Category B (Error, no harm)
An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

Category C (Error, no harm)
An error occurred that reached the patient but did not cause patient harm.

Category D (Error, no harm)
An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, harm)
An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, harm)
An error occurred that required intervention necessary to sustain life.

Category I (Error, death)
An error occurred that may have contributed to or resulted in patient's death.

Definitions
Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.
Monitoring: To observe or record relevant physiological or psychological signs.
Intervention: may include change in therapy or active medical/ surgical treatment.
Intervention necessary to sustain life: includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation).

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile – Muscle/Skeletal Applications

Full Name: Hyaluronic Acid
CAS Registry Number: 9067-32-7

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of Hyaluronic Acid used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of Hyaluronic Acid. The devices in Table 1 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data.

Table 1: Medical Devices Containing HA for Muscle/Skeletal Applications provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Acid, hyaluronic, intraarticular (viscosupplement)	MOZ	III
Filler, Bone Void, Calcium Compound	MQV	II
Filler, Bone Void, Osteoinduction (W/O Human Growth Factor)	MBP	II
Prosthesis, Toe, Hemi-, Phalangeal	KWD	II

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of Hyaluronic Acid. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices below. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B1, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C1. Summary evidence tables with individual study data appear in Appendix D1, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on Hyaluronic Acid as a material as well as research on the various device categories.

In the discussion section, please note that a statement of "no difference" or "no significant difference" between devices/materials does not imply equivalence between devices/materials, as studies with low numbers of patients or events often lack sufficient statistical power to detect a difference between comparators. In addition, when we cite odds ratio(s), an odds ratio >1 means that the rate was higher in the HA group than in the non-HA group.

Table 2: Summary of Primary Findings from Systematic Review – Muscle/Skeletal Applications

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Hyaluronic Acid as a material	No studies	Very low (no evidence)	No studies	Very low (no evidence)

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Viscosupplementation – knee (26 human studies)	Arthralgia/joint pain, Baker's cyst, bleeding, cutaneous vasculitis, edema (injection-site, peripheral), effusion, erythema, heaviness of injection, joint stiffness, musculoskeletal pain, pain at injection site, pain flare ups, pain post-injection, purulent aspirate, skin reaction, swelling, tenderness of knee joint	Moderate for swelling, pain at injection site, arthralgia/joint pain, and effusion Low for all other local responses/device events	Backache, cardiac disorders, cellulitis, death possibly device-related, GI disorders, headache, hypersensitivity reaction, musculoskeletal and connective tissue disorders, nausea, nervous system disorders, paralysis, rash, renal and urinary disorders, respiratory/ thoracic/ mediastinal disorders, septic shock, septicemia, skin reaction, skin and subcutaneous tissue disorders, pseudoseptic arthritis (presenting with elevated CRP, ESR, PMN; leukocytosis and fever), nasopharyngitis,	Low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
			vascular disorders, vomiting	
Viscosupplementation – hip (4 human studies)	Hematoma, nausea, pain flare ups, pain post-injection, pruritus	Low	No studies investigated	Very low
Viscosupplementation – hand and ankle (2 human studies)	Enlarged lymph node in ipsilateral groin, pain at injection site, pseudogout, swelling	Low for swelling and pain at injection site Very low for all other local responses/device events	No studies investigated	Very low
Viscosupplementation – shoulder (2 human studies)	Abscess, musculoskeletal pain, pain at injection site	Low for musculoskeletal pain and pain at injection site Very low for all other local responses/device events	Cancer, chest pain, diarrhea, flu symptoms, headache	Very low .
Viscosupplementation – TMJ disorders (2 human studies)	Discomfort post-injection, ear pressure, pain at injection site	Low for pain at injection site Very low for all other local responses/device events	Chills	Very low
Cartilage scaffold (3 human studies)	Cyst formation, edema, hematoma, persistent pain, swelling	Low for swelling Very low for all other local responses/device events	No studies investigated	Very low
Bone putty/filler	No studies	Very low (no evidence)	No studies	Very low (no evidence)

GI: gastrointestinal; TMJ: temporomandibular joint

Hyaluronic Acid as a Material

Our literature searches did not identify any studies of these devices that met inclusion criteria.

Viscosupplementation

Due to the primary focus on viscosupplementation in this evidence base, we provide results separately for five indications for this device category (knee, hip, hand and ankle, shoulder, and TMJ disorders).

Viscosupplementation – knee

26 human studies (16 SRs[2-17] and 10 randomized controlled trials (RCTs)[18-27]). For further information see Table 1 Appendix D.

Local Responses/Device Events (human studies)

IAHA: 2 SRs addressed the use of IAHA injections. The first SR[2] investigated fatal adverse events (AEs) from IAHA injections listed in the MAUDE and Alternative Summary Reporting databases between 2014 and 2019. Brand names searched for in this review included Durolane, Euflexxa, Gel-One/Gel One/GelOne, Gelsyn, Genvisc/Gen Visc, Hyalgan/Hyalgan LL, Hymovis, Monovisc, Orthovisc, Sinovial, Supartz/Supartz FX, Suprahyal, Synojoynt, Synvisc/Synvisc-One, Triluron, Trivisc, and Visco-3. Of 63 unique fatalities identified, 8 (12%) fatalities were possibly IAHA-related. Local responses affiliated with these cases included pain after injection (3 patients), purulent aspirate (1 patient), and swelling of the knee (2 patients).

The second SR[3] investigated reporting of pseudoseptic arthritis, a rare complication after IAHA injection. 27 patients (28 knees) with acute pseudoseptic arthritis after HA injection (mostly Synvisc) were identified in 11 studies (5 single arm studies, 6 case reports). Results indicated that 22 cases (78.6%) of pseudoseptic arthritis presented within 24 hours of injection; 15 of the 22 cases (68.2%) presented within the first 12 hours. Time from injection to presentation ranged from 1 hour to 9 days. 7 cases (25%) occurred after 2 injections, 5 cases (17.9%) after 3 injections, and 13 cases (46.4%) after ≥4 injections. All patients presented with severe joint pain and effusion. 3 patients had synovial leucocyte elevation in the range typically concerning for septic arthritis (above 50,000), and 16 patients had elevations in an inflammatory cell count range of 5,000 to 50,000. Results from a separate case report included progressive and increasing pain with obvious suprapatellar effusion at 12 hours post-injection; inflammatory symptoms resolving by 4 weeks.

IAHA versus saline/placebo: 8 studies (4 SRs[12-15] and 4 RCTs[20-23] investigated the safety of IAHA vs. saline/placebo in mostly middle-aged women with mild-to-moderate OA. Overall, approximately 6,000 individuals enrolled in over 50 RCTs received IAHA. The SRs and 1 RCT[23] investigated the safety of several IAHAs, while the remaining RCTs focused on one IAHA (Synvisc,[20] Monovisc[21,22]). Dose was reported in 6 (75%) studies; and administrations ranged from 1 to 11 injections. Overall mean followup was 6 months, and ranged up to 1 year[13,14] and 2 years.[12,23]

Studies reported on overall rates for TRAEs,[13,14] AEs,[12,20] device-related AEs,[21] serious AEs (SAEs),[12,15,20,22,23] and non-serious AEs.[15]

- TRAEs: 2 SRs focused on TRAEs (not specified) up to 52 weeks.[13,14] The first SR[13] of 9 RCTs indicated significantly increased odds of TRAEs with IAHA vs. saline (Odds ratio (OR) 1.78, 95% CI: 1.21 to 2.63), but no significant differences in any severe AEs (OR 1.08, 95% CI: 0.50 to 2.31). The second SR[14] of 30 RCTs reported significantly more TRAEs with IAHA in studies using ≥5 injections vs. saline (RR 1.70, 95% CI: 1.12 to 2.59), but no significant difference for studies examining 1 injection or 2 to 4 injections vs. saline. This same SR reported no significant difference in number of patients experiencing a TRAE (RR 1.13, 95% CI: 0.95 to 1.35).
- AEs: 2 studies reported similar overall AEs with IAHA vs. saline.[12,20]
- Device-related AEs: 1 RCT reported device-related AEs occurred more frequently with Monovisc vs. saline (13 (7.1%) vs. 10 (5.4%)).[21]
- SAEs and non-serious AEs: 3 RCTs reported no SAEs[20,22,23] up to 104 weeks. 1 SR[11] reported no difference in risk of SAEs (1.8% vs. 1.2%, RR 1.44, 95% CI: 0.91 to 2.26, p=0.12)[12,15] or non-serious AEs (415 HA, 375 placebo; RR 1.03, 95% CI: 0.93 to 1.15) up to 2 years.

Arthralgia and joint swelling were the most common AEs reported in 6 studies.[12,15,20-23] Arthralgia was reported in 5 (83%) studies.[12,15,20-22] Rates were reported as similar versus saline and ranged from 1.3% to 3.8% up to 26 weeks.[20-22] 2 RCTs reported arthralgia with Synvisc and Monovisc was device-related.[20,22] Timing reported in 2 SRs (rates NR) was immediately post-injection[15] and up to 3 days post-injection.[12]

Joint swelling was reported in 4 (66%) studies;[12,15,20,21] one study indicated response was device-related.[20] Rates ranged from 1.1% to 3.7% with IAHA. 1 RCT reported a higher incidence of joint swelling with Synvisc (3.7% vs. 0.9%),[20] while another RCT reported no significant difference in incidence of joint swelling (1.1% Monovisc, 0.5% saline).[21] Timing reported in 2 SRs (rates NR) was immediately post-injection[15] and up to 3 days post-injection.[12]

Less frequently reported AEs were injection site pain,[12,20,23] injection site swelling,[20,23] and joint stiffness.[21,23] Incidence of *injection site pain* was 0.5% with Synvisc,[20] and 21% with IAHA.[23] Timing was immediately after[23] and up to 3 days post injection (rate NR).[12] Incidence of *injection site swelling* was 0.5% with Synvisc[20] and 21% with varying weights of IAHA.[23] Incidence of *joint stiffness* in the index knee ranged from 0.5% (with Monovisc)[21] to 7% (with varying weights of IAHA).[23] Rates were lower vs. saline (1.1%)[21] and timing was immediately post-injection.[23]

Additional AEs reported by 1 study each included the following:

- joint pain immediately post-injection[15]
- injection site joint pain (0.5% with Synvisc, 0% placebo)[20]
- device-related non-serious cutaneous vasculitis during 1st week post-injection[15]
- peripheral edema with Synvisc (0.5% HA, 0% placebo)[20]
- effusion immediately post-injection[15])
- joint effusion up to 3 days post-injection[12]
- injection site edema with Synvisc(0.5% HA, 0% placebo)[20]
- injection site erythema (12% overall rate for all IAHA weights)[23]
- joint tenderness immediately post-injection[15]
- transient increase in pain immediately post-injection[15]

IAHA versus platelet-rich plasma (PRP): 3 studies (1 SR[4] and 2 RCTs[18,19]) addressed this topic in 1,137 individuals with mild-to-moderate knee osteoarthritis (OA). A majority of patients were females with mean age of 60 years. The sample size was greater than 100 patients for the RCTs,[18,19] and ranged from 55 to 183 in the SR (mean 128 patients).[4] Dose was not reported. Administrations were reported in the 2 RCTs as single injections of HA,[18] and 3 weekly injections of Hyalgan (FidiaFarmaceutici S.p.A.).[19] Followup was 6 months[18] and 12 months.[4,19]

Local responses reported in the SR[4] included pain and swelling immediately after injection. Of the 7 included RCTs (n= 908), 3 RCTs reported no significant differences in AEs, 2 studies reported significantly more post-injection pain and/or swelling with PRP, while 2 studies reported no AEs.

The first individual RCT[18] reported no significant differences for mild-to-moderate AEs (musculoskeletal pain, swelling and tenderness of the knee joint) at 6 months in 110 individuals (55 each arm) receiving single injections of HA or PRP. Musculoskeletal pain occurred in 4 patients (3 (5%) HA, 1 (1.8%) PRP; timing NR). Mild-to-moderate swelling of the knee joint occurred similarly at 6 weeks (100%), and a lower incidence with HA at 3 months (85% vs. 96%), and 6 months (87% vs. 91%). Mild tenderness was reported in 3 patients (2 with HA at baseline and 6 weeks, 1 with PRP at baseline).

The second individual RCT[19] reported no significant differences in minor complications (stiffness and heaviness of injection site) immediately post-injection in 13 of 119 patients (3 (6%) HA, 10 (20%) PRP-derived growth factor (PRGF)).

IAHA versus intra-articular oxygen-ozone: One SR[5] of 4 RCTs addressed this topic in 298 individuals with end-staged knee OA. Sample size ranged from 42 to 141 patients. The population was 75% female aged 60 to 71 years. Dose was reported as 10 mg/ml x 2.0 ml (3 studies), and 10 mg/ml x 2.5 ml (1 study). Frequency of injection was not reported. Local responses included bleeding and skin reaction at 6 to 12 months. No significant differences were reported in incidence rate of AEs (risk difference 0.006, 95% CI: -0.047 to 0.058).

IAHA versus IAHA (different weights): 2 SRs[6,7] including 40 RCTs compared the safety of IAHA of varying molecular weights in individuals with knee OA. 1 SR reported the average molecular weight ranged from 500 to 3600 kDa with IAHA mostly being administered in 3 injections.[7] Mean followup was 6 months in 1 SR reporting.[7]

One SR[6] of 30 RCTs examined IAHA injections of high molecular weight (HMW), medium MW (MMW), and low MW (LMW), and whether the products were processed through extraction of avian-derived molecules (AD-HA) or through bacterial processes of biological fermentation (Bio-HA). 11 RCTs (n=2094) addressed HMW, 4 RCTs (n=621) addressed MMW, and 15 RCTs (n=2639) addressed LMW. Bio-HA and AD-HA treatments were administered to 1,776 and 3,070 patients, respectively. Local responses from products such as Euflexxa, Synvisc, Supartz, Orthovisc, and Durolane included effusion after injection and flare ups. Followup was NR.

> Results based on weight: HMW products had the highest rate of injection site flare-ups. Significantly more injection flare ups with HMW vs. MMW (13.73% vs. 3.31%) and HMW vs. LMW (13.73% vs. 10.73%). Significantly more flare ups with LMW vs. MMW (10.73% vs. 3.31%). No significant difference was reported in effusion after injection based on molecular weights (1.9% HMW, 1.7% MMW, 1.8% LMW).
>
> Results based on process: Use of AD-HA products resulted in a significantly lower incidence of acute flare ups (3.0% vs. 13.2%), but a significantly higher incidence of effusion (3.4% vs. 0.5%) versus Bio-HA.

Another SR[7] included 10 RCTs in a safety analysis comparing Synvisc of a relatively HMW versus IAHA with LMW (Artzal, Orthovisc, Bio-HA, Hyalgan, Sinovial, Variofil, Hydros) in 2,616 patients. Authors reported no significant difference in TRAEs at mean 26.8 weeks (14.7% Synvisc vs. 11.6% LMWHA; risk difference 0.02, 95% CI: -0.01 to 0.05; p=0.13) or number of TRAEs (23.2% Synvisc vs. 16.3% LMWHA; risk difference 0.03, 95% CI: -0.01 to 0.07; p=0.14).

IAHA versus anti-inflammatories: Of 4 SRs addressing this comparison,[8-11] 3 SRs examined local responses with IAHA,[8,10,11] while 1 SR only examined systemic responses (see below).[9]

2 SRs examined IAHA versus NSAIDs.[8,11] The first SR of 6 RCTs[8] included 831 middle-aged patients with mild-to-moderate knee OA. Sample size was 60 to 327 patients. Administrations were one injection (Durolane), 3 weekly injections (Synvisc, and Suplasyn), and 5 weekly injections (Hyalgan and Suvenyl). Responses from 5 weeks to 26 weeks included arthralgia, injection site pain, and lower leg effusion (1 (0.3%) HA, 2 (0.5%) NSAID). Results from a meta-analysis of 5 RCTs indicated:

- no significant difference in risk of serious AEs (1.2% vs. 0.9%, risk ratio 1.37, 95% CI: 0.26 to 7.14),
- a significantly lower risk of AEs with HA (19.8% vs. 29%; risk ratio 0.74, 95% CI: 0.59 to 0.94),
- a significantly higher risk of arthralgia with HA (8.1% vs. 2.9%).

The second SR of 5 RCTs (n=712) reported no IAHA-related AEs up to 12 weeks.[11]

TRAEs were reported in one SR of 12 RCTs (n=1794)[10] comparing IAHA with intraarticular corticosteroids (CS; triamcinolone hexacetonide, methylprednisolone acetate, 6-methylprednisolone acetate, triamcinolone acetonide). Sample size was 41 to 391 patients. IAHA doses ranged from 16 to 60 mg, while administrations ranged from 1 to 5 weekly injections. Knee pain, joint swelling, and joint stiffness were reported from 1 to 6 months. Results indicated significantly more TRAEs with HA (746 events vs. 606 events; risk ratio 1.66, 95% CI: 1.34 to 2.06) which may have been caused by the higher injection frequency

IAHA versus miscellaneous treatments: 6 studies (2 SRs,[16,17] and 4 RCTs[24-27] addressed this comparison. One study each compared IAHA with usual care,[26] debridement,[27] cooled radiofrequency ablation (CRFA),[24] acupotomy,[16] and polydeoxyribonucleotide (PDRN).[17] One study compared IAHA with physical therapy (PT), dextrose prolotherapy, and botulinum neurotoxin.[25] Over 100 patients were examined in each study; individuals with mild-to-moderate knee OA,[26,27] or at least moderate knee OA[24,25] in studies reporting. Dose was reported in all studies, and administrations ranged from 1 to 5 injections. Followup was mostly 6 months and 12 months.

One study noted no device-related responses with Hyalgan vs. PT, dextrose prolotherapy, and botulinum neurotoxin.[25] 2 RCTs reported fewer TRAEs with IAHA. One RCT[24] noted a TRAE rate of 14% with Synvisc-One versus 19% TRAE rate with CRFA up to 6 months. While procedural pain (3 (3%) in both arms), and post-procedural pain (3 (3%) with Synvisc-One, 7 (8%) with CRFA) occurred in both arms, Baker's cyst (a fluid-filled cyst that causes a bulging and feeling of stiffness behind the knee) only occurred in 2 (2%) patients with Synvisc-One. The other RCT (n=120)[27] reported pain at injection site in 8 (13.4%) patients after IAHA vs. pain and mild effusion in 13 (26%) patients after debridement up to 6 months.

The remaining 3 studies reported a similar incidence of TRAE/AEs. One SR of 5 RCTs[17] reported a similarly low incidence of TRAEs (unspecified) with HA and PDRN up to 12 months. One SR of 4 RCTs (n=309) reported AE incidence rates of 2.2% with HA, and 4.3% with acupotomy up to 6 months. AEs included redness and swelling post-injection in 3 patients with each treatment.[16] 1 RCT comparing 3 weekly injections of Synvisc (HMW-HA) vs. usual care[26] in 156 patients reported similar overall TRAEs (77 Synvisc, 79 UC). Events, described as flare-ups or "other", were reported at 6 weeks, 13 weeks, 26 weeks, 39 weeks, and 52 weeks. Flare-up rates with Synvisc were highest at 6 weeks (36%) and lowest at 52 weeks (6%).

Systemic Responses

IAHA: Both SRs addressing this topic reported systemic responses. The first SR[2] identified 63 unique fatalities, 8 fatalities were possibly IAHA-related. Of the 8 fatalities, 4 patient's experienced local responses such as pain and swelling (see above) prior to death. 1 death involved a suicide due to worsening pain. The remaining 4 patients experienced the following systemic responses prior to death:

- septic shock, followed by paralysis, and death 4 months post-injection.
- necrotizing fasciitis after starting chemotherapy and receiving an HA injection.
- septicemia, cause of death unknown.
- cellulitis.

Authors noted that the available information was "insufficient to make a firm determination of causality."

The second SR[3] reported results from 27 patients (11 studies) with acute pseudoseptic arthritis after mostly Synvisc injections. Systemic responses included elevated CRP above 50, elevated ESR, elevated PMNs above 75% in 10 (37%) patients, fever in 6 (22%) patients, and leukocytosis above 10,000 in 4 (15%) cases. Results from a separate case report included a cell count of 123,260 and white blood cell count of 15.5.

IAHA versus saline/placebo: Of the 8 studies addressing this comparison, 3 studies investigated systemic responses.[13,15,22] 1 SR, focused on TRAEs,[13] reported no significant differences in any system-organ class(SOC)-related AEs (GI, cardiac, vascular, respiratory, nervous system, skin and subcutaneous tissue disorders, musculoskeletal, renal and urinary disorders, and hypersensitivity reaction).

- GI disorders: 69 HA, 83 placebo; OR 0.81, 95% CI: 0.52 to 1.27
- cardiac disorders: 5 HA, 4 placebo; OR 1.25, 95% CI: 0.36 to 4.41
- vascular disorders: 5 HA, 3 placebo; OR 1.70, 95% CI: 0.39 to 7.29
- respiratory, thoracic and mediastinal disorders: 71 HA, 52 placebo; OR 1.21, 95% CI: 0.82 to 1.78
- nervous system disorders: 66 HA, 55 placebo; OR 1.15, 95% CI: 0.77 to 1.70
- skin and subcutaneous tissue disorders: 22 HA, 10 placebo; OR 1.71, 95% CI: 0.52 to 5.63
- musculoskeletal and connective tissue disorders: 145 HA, 149 placebo; OR 0.99, 95% CI: 0.71 to 1.39
- renal and urinary disorders: 6 HA, 12 placebo; OR 0.54, 95% CI: 0.21 to 1.41
- hypersensitivity reaction: 23 HA, 19 placebo; OR 0.64, 95% CI: 0.05 to 7.94

IAHA versus PRP: One RCT reported nasopharyngitis in both arms (2 HA, 1 PRP); and backache (2 HA) and headache (1) only with HA.[18] One SR investigated but did not identify any systemic responses.[4]

IAHA versus anti-inflammatories: 3 of 4 SRs addressing this comparison investigated systemic responses. One SR[9] comparing IAHA with intraarticular methylprednisolone only reported on systemic responses. Results from 4 of 5 included RCTs indicated headache, nausea, and vomiting with no significant difference in AE incidence up to 52 weeks (risk difference -0.042, 95% CI: -0.092 to 0.009). One SR[8] (n=831) reported a significantly higher risk of headache (8.4% vs. 4.4%) with HA and a rare occurrence of cardiac-related complications (1 (0.3%) HA, 0 NSAID). Lastly, one SR (n=1794) did not identify any treatment-related systemic responses.[10]

1 RCT reported rash in 1 patient with Monovisc, and indicated this response was device-related.[22] Lastly, 1 SR of 10 RCTs indicated 1 serious AE attributed to HA was skin reaction characterized by peeling of skin on hands and toes in 1 patient. This reaction occurred 8 days post-injection.[15]

IAHA versus miscellaneous treatments: 1 of 6 studies addressing this comparison reported systemic TRAEs included GI complaints from 6 weeks to 52 weeks. Rates ranged from 3% (at 26 weeks) to 7% (at 6 weeks).[26]

Overall Quality of Evidence

The evidence for swelling, pain at injection site, arthralgia/joint pain, and effusion was consistently reported across high quality studies, in agreement with reporting with other HA categories (e.g., viscosupplementation-hand and ankle, viscosupplementation-shoulder, viscosupplementation-TMJ; and cartilage scaffold), so the quality of evidence is moderate. For other local responses/events and systemic responses, the quality of evidence is low due to the large evidence base of high quality studies.

Viscosupplementation - hip

4 human studies (4 SRs[28-31]). For further information see Table 2 Appendix D.

Local Host Responses (human studies)

One SR[28] included 5 RCTs (n = 591) comparing HA (n=298) with placebo injection (n=293) for hip OA. The HA products used in the studies were Durolane 3 ml, hylan G-F 20 6 ml, Hyalubrix 8 ml, Hyalgan 6 ml, and Adant 2.5 ml, and follow-up ranged from 56 to 182 days. No meta-analysis of AEs was performed. The SR lists numbers of patients in each study who experienced slight or moderate pain flare during or after injection, permitting calculation of the following pooled AE rates: 21 of 298 patients in the HA groups (7%) and 7 of 293 patients in the placebo groups (2.4%). Pruritus and hematoma at the injection site was reported in 1 patient each in the HA group.

Another SR[29] included 9 RCTs (n=1,164) comparing HA (n=558), methylprednisolone (n=201), PRP (n=115), mepivacaine (n=20), and placebo (n=270) for hip OA. The HA products used in the studies were Durolane 3 ml, Hyalubrix 5 ml (2 studies), Synvisc 6ml, Hyalubrix 8 ml, Hyalgan 6 ml, Adant 2.5 ml, and hylan G-F 20 2 ml; follow-up ranged from 2 to 12 months. Meta-analysis of overall AEs was performed for comparisons of HA with placebo and methylprednisolone; otherwise, rates of overall AEs were reported by study, permitting calculation of pooled rates. A 29.0% overall AE rate was reported for patients in the HA groups across 9 studies (range: 0% to 49.7%). The rate was 23.7% for patients in the placebo groups across 4 studies

(range: 0% to 34.9%), 8.7% for patients in the PRP groups across 3 studies (range: 0% to 20%), 38.3% for patients in the methylprednisolone groups across 3 studies (range: 0% to 48.7%), and 5% for patients in the mepivacaine group in 1 study. In the meta-analyses, no statistically significant differences in rates of overall AEs were found for HA versus placebo or for HA versus methylprednisolone.

Another SR[30] included 4 RCTs (n=303) comparing HA (n=148) with PRP (n=155) for hip OA. The SR did not specify the products used in the studies. Follow-up time was 12 months. Meta-analysis revealed a relative risk of nausea of 1.15 (95% CI: 0.34 to 3.93) for PRP relative to HA. One included study reported significantly higher post-injective pain for PRP than for HA.

Another SR[31] included 6 RCTs (n=630) comparing HA (n=291) with placebo (n=114) or methylprednisolone (n=207) for hip OA. The HA products used in the studies were hylan G-F 20 2 ml, Hyalubrix 8 ml, Ostenil 2 ml, Durolane 3 ml, Adant 2.5 ml, and Hyalgan 6 ml. (One included study compared Ostenil with hylan G-F 20; the SR appears to have treated hylan G-F 20 as a control treatment in this study, although it treated the same product as HA in another included study.) Follow-up ranged from 56 to 180 days. Four of the six included studies reported AEs by treatment group; meta-analysis compared overall AEs in the HA groups versus the control groups (apparently both placebo and control treatments) and obtained a relative risk of 0.94 (95% CI 0.41 to 2.20).

Systemic Responses

We did not identify any studies reporting systemic responses to HA as viscosupplementation in hips.

Overall Quality of Evidence

The 4 systematic reviews included high quality studies with a high number of patients, and most outcomes were in agreement with other device categories. Since reporting of specific responses was limited to one systematic review each, the overall quality of evidence was rated low. Since systemic responses were not investigated in these studies, the evidence is very low.

Viscosupplementation – hand and ankle

2 human studies (2 SRs[32,33]). For further information see Table 3 Appendix D.

Local Responses/Device Events (human studies)

One SR[32] included 24 studies (n = 844) of intra-articular injective treatments for ankle lesions, 18 of which examined HA. Of the 24 studies, 8 were RCTs, 1 was a nonrandomized comparative study, and 15 were single-arm studies. The HA products used in the studies were Euflexxa 6 ml (2 studies), Durolane 1ml, Suplasyn 6 ml, Hanox M-XL 2.2 ml, Hyalgan 2 ml to 10 ml (4 studies), Synvisc 2 ml to 6 ml (3 studies), Supartz 2.5 ml to 12.5 ml (2 studies), Orthovisc 1 ml to 3 ml, Adant 7.5 mg, and unspecified HA products 6 ml to 12.5 ml (2 studies). 581 patients received HA; other treatments were PRP (n = 83), methylprednisolone (n = 48), botulinum toxin type A (n = 38), prolotherapy (n = 27), exercise therapy (n = 15), mesenchymal stem cells (n = 6), and placebo/saline (n = 46). Follow-up ranged from 1 to 45.5 months. AEs with HA in 1 patient each included enlarged lymph node in ipsilateral groin, osteochondritis dissecans (not considered treatment-related), and pseudogout. The SR also noted that "in some cases, pain and swelling were reported at the injection site soon after the injection."

The other SR[33] included 13 studies (n = 809) of intra-articular therapies for hand OA; 9 studies examined HA. Of the 13 studies, 12 were RCTs and one was a nonrandomized comparative study. The HA products used in the studies included hylan G-F 20 1 ml to 2 ml (3 studies) and unspecified sodium hyaluronate products 1.5 ml to 3 ml (6 studies). 360 patients received HA; other treatments were corticosteroids (n = 280), dextrose (n = 30), infliximab (n = 10), and placebo (n = 172). (These numbers total more than 809 because two studies were within-subject and each patient in those studies [33 HA/placebo, 10 infliximab/placebo] is counted as having received both treatments.) Follow-up time was 24 weeks. Of the nine studies including HA, one did not report numbers of patients experiencing AEs. In the 8 remaining studies, AE rates were as follows: HA, 11.5%; corticosteroid, 9.0%; placebo, 2.7%. Numbers of patients with specific types of AE were not reported, either overall or by group; AEs were described as minor, and included surgeries unrelated to study medication, pain and local swelling, skin and nail abnormalities, heat and/or redness, and unspecified "local AEs."

Systemic Responses

We did not identify any studies reporting systemic responses to HA as viscosupplementation in hands and ankles.

Overall Quality of Evidence

The evidence for swelling and pain at injection site was reported in 2 SRs that included numerous high-quality studies. These outcomes were also in agreement with other indications for viscosupplementation (e.g., knee, shoulder, TMJ), so we rated the quality of evidence as low. For other local responses and systemic responses, the quality of evidence is very low.

Viscosupplementation – shoulder

2 human studies (2 SRs[34,35]). For further information see Table 4 Appendix D.

Local Host Responses (human studies)

One SR evaluated the safety of HA in patients 18 years of age and older with glenohumeral OA. Follow-up time ranged from 12 weeks to 3 years and sample size for the HA arms of the studies varied from 15 to 265, with 50.5% to 76% male patients. Common AEs from 13 of the 15 included studies (5 RCTs, 10 single arm) were musculoskeletal pain, and pain at injection with HA.[34] Serious AEs such as severe musculoskeletal pain and abscess were also reported. Similar AEs were reported in individuals receiving intra-articular injections of corticosteroids or saline. The overall pooled AE rate (local and systemic) was 33.92% (406 of 1197 patients) and the serious AE rate was 5.35% (64 of 1197). Most events were deemed by study investigators to not be product-related.

Another SR of 4 RCTs investigated the safety of HA administration versus conventional adhesive capsulitis (AC) therapies (e.g., intra-articular corticosteroid injection and physical therapy) versus HA administration plus conventional therapy regimens in patients with AC.[35] Follow-up ranged from 2 weeks to 6 months. Doses ranged from 20 to 30 mg, while administrations ranged from 2 to 8 total injections. Mean patient age ranged from 54.5 to 64.2 years, and 69% were female. 2 studies reported no major AEs, and 1 study reported intra-procedural pain in 12 out of 45 participants undergoing capsular distension combined with intra-articular HA injection. It was unclear if the pain was a result of the capsular distension procedure, the intra-articular HA injection, or both.

Systemic Responses

Diarrhea, flu symptoms, and headache were commonly reported (data not provided) in 1 SR with up to 3 years followup.[34] Serious AEs such as chest pain and cancer were also reported (N not reported). Most responses were deemed by study investigators to not be product related.

Overall Quality of Evidence

Musculoskeletal pain and pain at injection site were both commonly reported in 2 high-quality studies and in agreement with other indications for viscosupplementation (e.g., knee, hand and ankle, TMJ), so we rated the quality of evidence as low. For other local responses and systemic responses, the quality of evidence is very low.

Viscosupplementation – TMJ disorders

2 human studies (2 SRs[36,37]). For further information see Table 5 Appendix D.

Local Responses/Device Events (human studies)

Studies analyzed HA injections as viscosupplementation versus other types of intra-articular injections (corticosteroid [CS], PRP, or platelet-rich growth factor [PRGF]) in the treatment of TMJ disorders. Dose ranged from 0.5 to 5 ml with single administration in both studies. Follow-up was 1 week to 8 years[36] and 12 months.[37] Sample size was 13 to 102 patients with a mean age of 25 to 50 years.

Pain at injection site: Three RCTs included in a SR[36] reported TMJ pain post-injection with HA compared to CS. Zero percent to 37% of patients receiving HA reported pain post-injection versus 0 to 70% patients reporting pain after CS injection (OR 2.98, 95% CI: 0.08 to 111.17). Overall, the review found no relevant difference between the HA and CS treatment groups in terms of adverse events. The SR comparing HA to PRP or PRGF[37] included one RCT reporting AEs, assessing that 60% percent of patients receiving HA reported pain during injection versus 88% of patients receiving PRP or PRGF.

Ear pressure: One RCT included in a SR[36] reported 5% of HA patients with ear pressure compared to 10% of CS patients (OR = 2.11, 95% CI: 0.18 to 25.35) at two-week follow-up.

Post-operative discomfort: The SR comparing HA to PRP or PRGF[37] included one RCT reporting AEs, assessing that 8% of patients receiving HA reported post-operative discomfort versus 76% of patients receiving PRP or PRGF.

Systemic Responses

An RCT included in a SR[36] reported slight chills at 1 week follow-up for HA compared to CS. Zero percent of CS patients reported chills versus 5.7% of patients receiving HA (OR=0.24, 95% CI: 0.01 to 5.90; p=0.36). Overall, the review found no relevant difference between the HA and CS treatment groups in terms of AEs.

Overall Quality of Evidence

Pain at injection site was reported by both SRs and in agreement with other indications for viscosupplementation (e.g., knee, shoulder, hand and ankle), so we rated the quality of evidence as low. For other local responses and systemic responses, the quality of evidence is very low.

Cartilage scaffold

3 human studies (1 RCT,[38] and 2 nonrandomized comparative studies[39,40]). For further information see Table 6 Appendix D.

Local Host Responses (human studies)

The RCT compared polyglycolic acid and hyaluronan matrix-augmented bone marrow stimulation (m-BMS) with Chondrotissue (BioTissue AG) after microfracture (MF) to MF alone in 24 patients with grade III/IV International Cartilage Repair Society cartilage degradation.[38] One patient in the m-BMS group reported an infected hematoma up to 108 weeks. Three patients in the m-BMS group reported mild swelling after 2 weeks, which resolved by 6 weeks; swelling did not occur in the MF group. There was 1 severe effusion after 6 weeks in the MF group, and none in the m-BMS group. Neither group had allergic reactions (moderate or severe).There were no events that were more likely in the group receiving HA (the m-BMS group).

Two nonrandomized comparative studies compared HA-based cell-free scaffold with Hyalofast (Anika Therapeutics) with a chitosan-glycerol phosphate/blood implant (BST-CarGel®, Piramal Life Sciences)[39] or MF alone[40] in patients with focal osteochondral lesions of the knee joint (Outerbridge grade III or IV).

The first study enrolled 21 patients in the Hyalofast scaffold group and 25 in the BST-CarGel implant group.[39] At mean 24 months follow-up, edema or cyst formation in the subchondral bone was detected in 8 (38%) knees with Hyalofast, and 10 (40%) knees with BST-CarGel). One patient from each group had persistent pain as well as early degenerative changes of the knee joint and planned to undergo replacement surgery at the latest follow-up. Deep venous thrombosis, septic arthritis, neurovascular complication, or intra-articular adhesion were not detected in any patients.

The second study enrolled 24 patients in the MF group (mean age 43±6.8 years) and 19 in the Hyalofast group (mean age 40±9.8 years), 62.8% female overall.[40] 1 patient from the HA scaffold group and 2 patients from the MF group had persistent pain as well as early degenerative changes of the knee joint up to mean 25 months.

Systemic Responses

We did not identify any studies investigating systemic responses to HA as cartilage scaffolds.

Overall Quality of Evidence

None of the three studies found any higher rates in groups receiving HA, but they may not have been large enough to detect effects. The evidence for swelling was reported in 1 high-quality study and in agreement with reporting with other HA categories (e.g., viscosupplementation-knee, and viscosupplementation-hand and ankle), so the quality of evidence is low. For other local responses/device events and systemic responses (no studies investigated), the quality of evidence is very low.

Bone putty/filler

Our literature searches did not identify any studies of these devices that met inclusion criteria.

ECRI Surveillance Data

Refer to Appendix F for a list of devices that guided our searches of ECRI Surveillance Data.

Patient Safety Organization

Search Results: ECRI PSO identified 115 reports that involved HA related to muscle/skeletal applications that occurred between April 2016 and November 2021. Seven of these involved pertinent events. The events included: 1) Wrong side procedure - 2 (28.5%), 2) Wrong product - 2 (28.5%), 3) Product expired - 2 (28.5%), 4) Wrong time – 1 (14.2%). Table 3 and Table 4 outline the complications and harm scores of these events, respectively.

All individual PSO event reports are redacted and included in Appendix F.

Table 3" Complications in HA-related PSO Event Reports – Muscle/Skeletal Applications

Complication	Viscosupplement	Bone Filler	Total
Wrong side procedure	**2**		**2**
Wrong product	**2**		**2**
Product expired	**1**	**1**	**2**
Wrong time	**1**		**1**
Total	**6**	**1**	**7**

Table 4: Harm Score Associated with HA-related PSO Event Reports – Muscle/Skeletal Applications

Harm Scores (NCC-MERP)	**Harm Scores (NCC-MERP)**	Viscosupplement	Bone Filler	**Total**
A	No Error			
B1	Error, No Harm			
B2	Error, No Harm			
C	Error, No Harm	4	1	5
D	Error, No Harm	1		1
E	Error, Harm	1		1
F	Error, Harm			
G	Error, Harm			
H	Error, Harm			
I	Error, Death			

Harm Scores (NCC-MERP)	Harm Scores (NCC-MERP)	Viscosupplement	Bone Filler	Total
NULL*				
Total		**6**	**1**	**7**

**Harm score was not reported*

Accident Investigations

Search Results: Zero investigations were recovered from the accident investigations database.

ECRI Problem Reports

Search Results: The search returned zero reports submitted by ECRI members.

Healthcare Technology Alerts

Search Results: The search returned 5 manufacturer issued alerts describing problems with adverse events, contamination, packaging issues, and impartially filled products, summarized in Table 5.

Table 5: Summary of Regulatory and Manufacturer Alerts - Muscle/Skeletal Applications

Device Type	# Alerts	Reported Problem
Viscosupplemenation: MOZ (Acid, Hyaluronic, Intraarticular)	2 manufacturer issued	• Reports of post-injection pain and swelling • Contaminated product may lead to infection
Bone Filler: MQV (Filler, Bone Void, Calcium Compound)	2 manufacturer issued	• Impartially filled tubes may delay surgery • Unsealed Tyvek packaging
Bone Filler: MQV (Filler, Bone Void, Calcium Compound); MBP (Filler, Bone Void, Osteoinduction (w/o Human Growth Factor)	1 manufacturer issued	• Incomplete outer packaging seal

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of Hyaluronic Acid. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

HA as a Material

There were no studies that met inclusion criteria for HA as a material indicating an area of future research.

Viscosupplementation

14 HA products were investigated in 36 studies addressing five various indications (knee, hip, hand/ankle, shoulder, and TMJ disorders). Hyalgan and Synvisc were investigated in 15 studies and 16 studies, respectively. 9 products (Monovisc, HYADD, Sinovial, Gel-One, Supartz, Go-On, Hanox M-XL, Ostenil, and Hyalubrix) were investigated in ≤3 studies. Most studies were high-quality and enrolled a large number of patients. In general, studies enrolled middle-aged women with mild-to-moderate OA. Several studies did not report important study characteristics (e.g., HA products investigated, HA dose), or details on clinical results (e.g., type of TRAE, number of events, number of patients experiencing events, timing of events).

Viscosupplementation – knee

26 studies (16 SRs, 10 RCTs) focused on knee viscosupplementation. Several outcomes such as swelling and pain at injection site were consistently reported across studies and in agreement with other HA categories (viscosupplementation in hands/ankles, shoulders, TMJ disorders; and scaffold), so we rated the quality of evidence as moderate. Other local responses (e.g., flare ups, edema) and all systemic responses (e.g., cellulitis, nervous system disorders) were rated low quality due to infrequent or rare reporting. Of 11 (42%) studies investigating systemic responses, 2 systemic skin responses (1 rash, 1 peeling of skin on hands and toes) were reported as device-related. Only 1 systemic response (GI disorders/complaints) was reported in more than 1 study, but this outcome occurred similarly versus placebo or usual care so in both instances, the association with HA is unclear.

Viscosupplementation – hip

4 SRs (n=2688) investigated HA products such as Durolane, Synvisc, Hyalbrix, Hyalgan, Adant. 3 SRs included placebo injections as comparators. Quality of evidence for local responses was rated low due to the high number of patients enrolled and similar reporting of outcomes (e.g., pain flare up, pain post-injection, hematoma) versus other categories. Systemic responses were not investigated resulting in a rating of very low quality.

Viscosupplementation – hand and ankle

2 SRs (n=1653) investigated HA products such as Euflexxa, Durolane, and Suplasyn. 1 study each examined viscosupplementation in hands and ankles, comparators were varied (e.g., PRP, methylprednisolone, botulinum toxin A, prolotherapy, corticosteroids, and placebo). 1 SR of 24 studies only included 9 (37%) studies with control groups and followup was as short as 1 month. Evidence for local responses such as swelling and pain at injection were rated low quality, while other local responses and systemic responses (not investigated) were rated very low quality.

Viscosupplementation – shoulder

2 SRs addressed this indication in patients with glenohumeral OA and adhesive capsulitis. 1 SR only included 5 (33%) studies with control groups. This SR pooled the AE rate for local and systemic events making it difficult to determine the AE rates separately. This same SR did not report data for several systemic responses including serious AEs such as cancer and chest pain, however study investigators deemed "most events" to not be product-related. The other SR reported intra-procedural pain in 12 patients however it was unclear whether the pain was a result of the capsular distension procedure, the IAHA injection, or both. Two local responses (musculoskeletal pain, pain at injection) were rated low quality. Other local responses and systemic responses were rated very low quality.

Viscosupplementation – TMJ disorders

2 SRs addressing this indication reported 3 local responses including pain at injection site, ear pressure, and post-operative discomfort. Studies reported events as occurring within 2 weeks of IAHA injections, however these responses were also reported after other types of IA injections (CS, PRP, and PRGF) making the association with HA unclear. Pain at injection site was reported by both SRs and in agreement with other indications for viscosupplementation (e.g., knee, shoulder, hand and ankle), so we rated the quality of evidence as low. For other local responses and systemic responses, the quality of evidence is very low.

Cartilage scaffold

Evidence for HA scaffolds was limited to 3 studies enrolling 75 patients in 2 (66%) scaffolds of interest. Evidence for Agili-C was lacking, and dose was NR for any study. 1 RCT reported the placement of an HA scaffold Chondrotissue in only 12 patients, while 2 nonrandomized comparative studies (led by the same investigator) reported on Hyalofast in 42 patients (possibly including duplicate patients). These latter 2 studies both reported persistent pain, which is inconsistent with reporting in other studies. The evidence for swelling however was reported in the RCT and was in agreement with reporting with other HA categories (e.g., viscosupplementation-knee, and viscosupplementation-hand and ankle), so the quality of evidence is low. For other local responses and systemic responses (no study investigating), the quality of evidence is very low.

Bone putty/filler

There were no studies that met inclusion criteria for HA bone putty/filler devices indicating an area of future research.

Safety Profile – Dermal, Facial and Eye Applications

Full Name: Hyaluronic Acid
CAS Registry Number: 9067-32-7

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of Hyaluronic Acid used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of Hyaluronic Acid. The devices in Table 6 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data.

Table 6: Medical Devices Containing HA for Dermal, Facial and Eye Applications provide by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Aid, Surgical, Viscoelastic. (Intraocular fluid)	LZP	3
Implant, Dermal, For Aesthetic Use	LMH	3
Implant, Dermal, For Aesthetic Use In the Hands	PKY	3
Products, Contact Lens Care, Rigid Gas Permeable	MRC	2
Accessories, Soft Lens Products	LPN	2

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of HA for dermal, facial and eye applications. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B2, and a flow diagram documenting

inclusion/exclusion of studies appears in Appendix C2. Summary evidence tables with individual study data appear in Appendix D2, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 7. We then turn to a detailed discussion of research on HA for dermal fillers, intraocular/ophthalmic viscoelastic solution/fluid, and eye drops.

In the discussion section, please note that a statement of "no difference" or "no significant difference" between devices/materials does not imply equivalence between devices/materials, as studies with low numbers of patients or events often lack sufficient statistical power to detect a difference between comparators. In addition, when we cite odds ratio(s), an odds ratio >1 means that the rate was higher in the HA group than in the non-HA group.

Table 7: Summary of Primary Findings from Systematic Review - Dermal, Facial and Eye Applications

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Dermal Fillers	Lumpiness, tenderness, pain, swelling, bruising, hematoma, edema, numbness, irregular surface, disfiguring surface, nodules, granuloma, necrosis, migration, vascular adverse events, infection, erythema, delayed inflammatory reactions, delayed-type hypersensitivity, partial or total vision loss, visual changes, brain infarcts or hemorrhage, capsular contraction, early resorption, embolism	Moderate	ASIA	Low
Intraocular/Ophthalmic Viscoelastic Solution/Fluid	IOP elevations, corneal or macular edema, ocular hypertension, inflammation, capsule break, Viscoat bubbles, layered hyphema, choroidal effusion, clogged tube shunt, TASS, Descemet membrane detachment	Moderate for IOP elevation and corneal/ macular edema Low for all other responses/events	Not evaluated	Very low
Eye Drops	Itching/stinging/irritation/ erythema/keratitis, eye pain, eye disorders/dry eye, hyperemia/hemorrhage,	Moderate	Not evaluated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	infection/viral conjunctivitis			

ASIA = autoimmune/inflammatory syndrome induced by adjuvants; IOP = intraoperative pressure; TASS = toxic anterior segment syndrome

Dermal Fillers

The literature search identified 33 relevant human studies (6 systematic reviews (SRs),[41-46] 11 randomized controlled trials (RCTs),[47-57] 4 comparative observational studies,[58-61] 12 single-arm[62-73]) and 1 comparative observational animal study.[74] For further information see Tables 1 and 2 in Appendix D.

The human studies examined over 70 different HA dermal fillers including Aesthefill, Allaxin, Bellast, Belotero, BioHyalux, a biphasic HA filler (NASHA), Captique, CPMHA, Dermalax implant plus, Dermicol-P35, DGE, DHF-001, DIVAVIVA, Elravie, Emervel Classic, HA (Titan) + Infrared, HA-biphasic, HA-G-monophasic, HA-monophasic, HA-P-biphasic, Hyacorp, Hylaform, hylan B plus, Juvederm, Juvina, Koken, Macrolane, Matridex (HA and dextranomer), Matrifill, Modelis, Neuramis, Perlane, PP-501-A/B, Prevelle SILK, Princess Volume, Puragen, Redensity II Eyes, Restylane, RHA 4, Surgiderm, Teosyal, Terafill, Uma Jeunesse, YVOIRE volume plus, and Zyplast. Non-HA fillers examined in these studies included calcium hydroxyapatite (CaHa; Radiesse), autologous fibroblast and keratin gel (AFKG), collagen-based fillers, Ial System Duo, polycaprolactone (PCL), autologous fat, lipofilling, polyalkymide, poly-L-lactic acid, and acrylamide.

The 1 animal study compared the HA filler Restylane with polymethyl methacrylate (PMMA).[74]

Local Responses/Device Events (human studies)

Comparisons of HA fillers to non-HA fillers: One SR[41] included 28 studies of various dermal fillers for treatment of tear trough deformity and reported adverse events for HA and non-HA fillers. Overall complication rates were statistically significantly different between HA and non-HA fillers ($p < 0.0001$), but the clinical significance is unclear since the complications are minor: HA (50.75%); calcium hydroxylapatite (CaHa, 19.95%); autologous fibroblast and keratin gel (AFKG, 11.43%); and collagen-based filler (90%). Prolonged edema was more likely to occur among patients receiving HA injections (11.2%) than in patients injected with the other materials (0 to 2.1%, $P < 0.00001$). The Tyndall effect and lumpiness were only reported in the HA group. Thirty of 31 patients who were noted to have product migration were in the HA group, an event rate of 1.96% (30/1585 patients) in the HA group. However, the number of patients who received AFKG or collagen-based filler was very low, so for these fillers some complications may not have been captured simply due to the low patient numbers. Most of the event rate comparisons were indirect (not compared within the same studies) and therefore could have been confounded by differences in patient characteristics across different studies.

Another SR[43] included 51 studies that evaluated dermal fillers (HA and non-HA) for treatment of nasolabial folds. Overall complication rates were 0.59 (95% CI: 0.46–0.72) for all HA fillers, 0.4 (95% CI: 0.12–0.7) for all collagen fillers, 0.82 (95% CI: 0.69–0.93) for Mesoglow, and 0.88 (95% CI: 0.72–0.99) for IAL-systems. However, the number of studies reporting on non-HA fillers was relatively small compared to the number of HA studies. The most common events associated with HA injections included lumpiness (43%), tenderness (39%), swelling (32%) and bruising (28%).

One RCT[57] with 37 patients compared HA (Juvederm Ultra 4) to CaHa for hand augmentation (randomization was by hand; all 37 patients received HA in one hand and CaHa in the other). While the HA hands experienced no adverse events, six patients experienced 11 adverse events in hands injected with CaHa. These events included edema (n = 4), pain (n = 3), impaired movement (n = 2) and loss of sensitivity/ touch-sensitivity (number of patients not reported). Most events resolved within 2 weeks, and no serious adverse events occurred.

One prospective controlled study[60] compared HA (Juvederm Voluma) to autologous fat for treatment of temporal hollowing. Early complications (within 2 weeks of injection) included bruising, pain and swelling which did not differ between Juvederm and autologous fat injection sites. Juvederm had more cases of irregular surface (5/22) compared to autologous fat (1/24). Among late complications (> 2 weeks post-injection), swelling occurred in 3/22 Juvederm sites and no autologous fat sites; it resolved within 12 months. Subcutaneous scarring occurred in 5/24 autologous fat sites and no Juvederm sites. Abdominal

pain occurred in 2 patients due to autologous fat harvest. Disfiguring surface occurred in 2/22 Juvederm sites and 1/24 autologous fat sites.

One retrospective controlled study[61] compared HA (Macrolane) to lipofilling for penile augmentation. Patients treated with Macrolane had no complications, while 8 patients treated with lipofilling developed granulomas. In 5 patients granulomas resolved spontaneously within 6 months with the help of massage, while 2 patients reported no relief from massage. After 20 days one patient experienced fat necrosis with progressive skin loss which was treated conservatively with weekly dressing, and secondary healing occurred after 3 months.

Comparisons of different HA fillers: One SR[43] reported that overall complication rates did not differ between monophasic (0.59, 95% CI: 0.36–0.8) and biphasic HA fillers (0.6, 95% CI: 0.43–0.76). Complications included redness, bruising, swelling, pruritus, skin induration, tenderness, skin discoloration, pain, nodulus, hematoma, infection, vascular adverse events, migration, numbness, and lumpiness. The most common complications included lumpiness, tenderness, swelling, and bruising.

Individual RCTs[48,50-52,54,56] did not report a difference in adverse event rates between different HA fillers. However, one retrospective comparative study[59] reported that delayed-onset nodules occurred at a higher rate among patients receiving Juvederm Volbella (1%) compared to Juvederm Vollure (0%), Juvederm Voluma (0%) and Restylane Silk (0.25%). The nodules developed 6 to 37 weeks after the last injection.

Single-arm studies of HA fillers: One SR[44] evaluated prospective and retrospective studies of HA fillers to estimate the incidence and prevalence of delayed inflammatory reactions and delayed-type hypersensitivity (DTH). Combined data from 35 prospective studies led to an estimated incidence of delayed inflammatory reactions of 1.1% per year, and that of possible DTH reaction was 0.06% per year. The majority of 7 retrospective studies estimated a percentage of delayed inflammatory reactions of less than 1% in 1 to 5.5 years. The incidence of DTH reaction cannot be determined from retrospective studies but would likely be similar to the rate calculated from the prospective studies. Only about 5% of all reported DTH cases were proven to be genuine DTH reactions. Two small single-arm case series[63,67] reported on delayed inflammatory reactions at HA filler injection sites following Covid-19 exposure (3 cases) or exposure to influenza-like illness (14 cases). Most cases occurred within 3 to 5 days of exposure for influenza, but the Covid-related cases showed a wider range (1 day to 2 weeks following exposure either to Covid or Covid vaccine).

One large retrospective single-arm cohort study[64] evaluated the rate of delayed adverse events (DAEs) among 4500 patients who received 9,324 treatments of HA filler (Juvederm Voluma). Forty-four patients experienced DAEs (incidence rate 0.98% per patient, 0.47% per treatment). The most common reactions were delayed swelling and nodule formation (29 each), along with erythema, warmth, and tenderness or pain. The median time to reaction was 4 months after the final HA injection. Fifteen of 44 cases (34.1%) had an identifiable immunologic stimulus such as flu-like illness, infection, or dental procedure immediately before DAE onset. Another large retrospective cohort study[68] reported that delayed-onset nodules occurred in 0.5% of Juvederm injections (23 cases out of 4,702 facial injections in 2,342 patients) with median time of onset 4 months post-injection.

One small retrospective study[66] evaluated 11 cases of delayed granuloma formation in the orofacial region 3 to 10 years after dermal filler orofacial injections (8 had received HA injections). All cases required surgical removal of granulomas.

One SR[45] included 26 studies reporting on 44 cases of vision loss following HA dermal filler injections. The symptoms included partial or complete loss of vision and periocular changes including ptosis, ophthalmoplegia and exotropia; 8/44 patients had CNS involvement in the form of brain infarcts or hemorrhage. Vision loss symptoms were almost always immediate; CNS involvement was 7 and 9 hours after injection in 2 cases. The most common injection sites associated with visual loss were the nose, forehead, and glabella, and the prognosis was better for patients with partial vision loss. No cases occurred following injections in the lower face. A recent case series[62] reported on 7 cases with similar symptoms due to periorbital vessel occlusion following HA facial injections.

Two single-arm studies reported complications related to use of Macrolane for breast enhancement. A retrospective case series[69] of 20 patients with Macrolane-related complications presented with breast lumpiness and noted rapid, asymmetric losses in breast volume. Cysts developed within 12 months of injection At least 85% of Macrolane filler was surgically removed from the breasts of all patients. A prospective study[70] reported complication rates among 194 patients who received Macrolane: minor adverse events 12.4% (24 patients), major adverse events 8.7% (17 patients), infection 0.5% (1 patient), capsular contraction 4.6% (9 patients), early resorption 3.1% (6 patients), and removal of product 0.5% (1 patient). Most events occurred within the first 6 months.

A large retrospective case series[65] of HA fillers used for non-surgical rhinoplasty reported that the only complication was persistent tip redness in 2% of patients that resolved spontaneously.

One prospective single-arm ultrasound study[58] of 63 female patients found alterations of the lacrimal, parotid, and submandibular glands after filler injection (86% of patients had HA injections) that suggest subclinical inflammatory responses to fillers. Further research would be needed to determine if ultrasound findings are clinically useful for preventing adverse events related to dermal fillers.

Local Responses/Device Events (animal studies)

One non-randomized animal study[74] evaluated the risk of embolism and necrosis of HA (Restylane) versus PMMA (Artecoll) injected intra-arterially in rabbit ears. With 0.1 ml injected volume, 5% of PMMA-injected ears had mild necrosis on day 7, while HA tended to form obvious transparent emboli and 60% of HA-injected ears showed necrosis on day 7. With 0.2 ml injected volume, 30% of PMMA-injected ears had necrosis and 100% of 0.2 ml HA-injected ears showed transparent emboli and necrosis. HA injection led to substantially increased areas of necrosis compared to PMMA group regardless of injection volume.

Systemic Responses

Two retrospective single-arm studies[72,73] reported on cases of patients suffering from late-onset, inflammatory, non-infectious adverse reactions related to dermal fillers/implants that could be totally or partially considered as autoimmune/ inflammatory syndrome induced by adjuvants (ASIA)-related disorders. The largest study (45 cases) included 7 cases who had received HA as the only filler, and the other study (15 cases) included 2 cases where HA was the only filler (and 1 case where HA was the second filler, following an earlier injection of silicone). Reported symptoms of HA cases in the larger study included 4 myalgia, 6 arthralgia/arthritis, 6 fatigue, 2 neurologic complaints, 2 cognitive features, 1 fever, 1 Sicca syndrome, 7 skin manifestations (3 facial nodules), 3 evolvement into autoimmune disease. The symptoms occurred between 6 and 317 months following exposure to dermal filler. These appear to be rare events but the rate of occurrence could not be determined because the total number of HA-treated patients was not reported in either study.

Overall Quality of Evidence

Several SRs and RCTs provided evidence concerning local responses/adverse events associated with HA dermal fillers, so the overall quality of evidence for local responses/events is moderate. Two small retrospective single-arm case series reported evidence of rare systemic responses in the form of autoimmune/inflammatory syndrome associated with HA fillers; the quality of evidence for systemic responses is therefore low.

Intraocular/Ophthalmic Viscoelastic Solution/Fluid

The literature search identified 10 human studies (1 SR,[75] 2 RCTs,[76,77] 3 observational comparative studies,[78-80] and 4 single-arm studies[81-84]). For further information see Table 3 in Appendix D.

The human studies examined ophthalmic viscoelastic devices (OVDs) including Healon, Healon5, Healon GV, 2% HPMC, Viscoat, OcuCoat, Provisc, Restylane-L, SKGEL, Soft Shell, DisCoVisc, Duovisc, and Twinvisc.

Local Host Responses (human studies)

All studies evaluated local responses/device events related to various ophthalmic viscoelastic (HA) solutions in human subjects.

Four studies compared intraoperative pressure (IOP) elevations following eye surgery and injection of HA solutions to other HA solutions or no HA solution. One SR[75] reported that Healon, Viscoat, Provisc, and Soft Shell were associated with statistically significant increases in IOP at 1 day post-surgery while other HA solutions (Healon GV, Healon5, 2%HPMC, OcuCoat, and Viscoat + Provisc showed either non-statistically significant increases or decreases in IOP. At 1-week follow-up, most HA solutions were associated with non-statistically significant reductions in IOP; only Healon GV and Healon5 were associated with statistically significant decreases in IOP. The remaining 3 studies (2 RCTs[76,77] and 1 retrospective comparative study[78]) showed no statistically significant difference in post-operative IOP levels between different HA solutions[76,77] or between HA and no HA.[78] These 3 studies did not evaluate Healon GV or Healon5. Overall, IOP tended to peak at 1 day post-surgery and decrease afterward.

Three studies (1 SR[75] and 2 RCTs[76,77]) reported cases of corneal and/or macular edema. These were rare events (the SR reported rates of corneal edema ranging from 0.6% to 2.5% across 4 studies, while macular edema rates were 0.6% and 0.9% in 2 studies, respectively) and there was no statistically significant difference in edema rates between groups of patients receiving different HA solutions.

One RCT[76] reported ocular hypertension in 12.6% of patients who received Twinvisc and 17.6% of patients who received Duovisc. This study also reported 1 case each of inflammation (0.9%), capsule break (0.9%) and Viscoat bubbles (0.9%), respectively.

One retrospective comparative study[78] reported that 20 of 95 (21.1%) of patients with HA fill (Provisc) had a layered hyphema compared with 2 of 45 (4.4%) in the control group (no HA fill) at 1 week post-surgery (P=0.01). One patient (1.0%) in the HA group and 1 patient (2.2%) in the non-HA group required drainage of choroidal effusions within the first postoperative month. Other complications included a retinal detachment in a patient without HA fill and a clogged tube shunt that occurred in a patient who received HA fill.

One prospective observational study[80] compared non-penetrating very deep sclerectomy (NPVDS) with the use of HA implant (SKGEL) to trabeculectomy (TB) in patients with medically uncontrolled glaucoma. The overall complication rate was higher in the TB group (79.5% vs 35.9%, p = 0.00011); whether the lower rate in the NPVDS group is related to HA or the sclerectomy procedure (or both) is unclear.

One retrospective single-arm study[82] reported on 34 patients who developed toxic anterior segment syndrome (TASS) after routine cataract surgery. The authors identified the source of TASS as HA (2.0% or 1.4%) derived from rooster comb; when they substituted with OVDs derived from bacterial fermentation no further cases of TASS were observed.

One retrospective single-arm study[83] with 115 patients (162 eyes) who received canaloplasty for glaucoma reported that 12 patients (7.4%) developed Descemet membrane detachment (DMD) with or without intracorneal hemorrhage. All cases resolved in 4 to 10 weeks (3 patients required additional surgery to resolve the DMD). Although the cause of DMD was unclear, the authors noted that "DMD could be related to excessive amounts of Healon GV injection into the Schlemm canal during the viscodilation portion of the surgery."

One retrospective study[79] compared a viscoelastic device with brilliant blue G (Visco-BBG) versus balanced salt solution with BBG (BSS-BBG) in patients who were receiving par plana vitrectomy (PPV) combined with internal limiting membrane (ILM) peeling. The authors reported no complications in the Visco-BBG group and only 1 complication (retinal perforation) in the BSS-BGG group.

Two single-arm observational studies[81,84] reported only complications that were considered to be unrelated to HA solutions.

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

The evidence regarding IOP came from 1 SR and 3 comparative studies (2 RCTs) and was of moderate quality, supporting an initial increase followed by decrease in IOP after 1 day post-surgery. Some HA solutions (Healon GV, Healon5) appeared to increase IOP less and decrease IOP sooner than others. Evidence that corneal and macular edema are rare events and have similar rates among different HA solutions was also moderate quality. Evidence for other outcomes were reported in fewer studies (mostly single studies, mostly observational) and the quality of evidence is low. Because no studies reported systemic responses, the quality of evidence regarding systemic responses is very low.

Eye Drops

The literature search identified 14 human RCTs. For further information see Table 4 in Appendix D. The studies examined HA-containing eye drops including Hylo Confort Plus/HydoGel, Lacure, Restasis, Tearin, Vislub®, Vismed®, Vismed® Multi, HA-trehalose (Thealoz Duo®/Thealose®). These products contained 0.1% to 0.2% HA.

Local Host Responses (human studies)

All 14 studies evaluated local responses/device events related to procedures utilizing HA eye drops in human subjects.

Eight studies[85-92] addressed general adverse events or complications related to HA. Four studies[85,88,90,92] reported no difference in adverse events between HA and a control or another treatment group. One study[89] found statistically significantly fewer adverse events when compared to another treatment group (p=0.0186). Three studies[86,87,91] found less than 10% of patients experienced adverse events where both groups contained HA.

Seven studies[85,93-98] addressed itching/stinging/irritation/pruritus. Two studies[85,98] showed a decrease in itching/stinging/irritation/erythema/keratitis when HA was compared to another treatment or a control. Four studies[93,95-97] showed no statistically significant difference in itching/stinging/irritation/erythema/keratitis when HA was compared to another treatment or a control. One study[94] showed less than 2% of patients experience itching/stinging/irritation/erythema/keratitis where both groups contained HA.

Six studies[85,94-98] addressed eye pain. Four studies[85,95,97,98] showed no statistically significant difference in pain when HA was compared to another treatment or a control. One study[94] showed less than 2% of patients experience pain where both groups contained HA. One study[96] showed an increase in pain when HA was compared to another treatment or a control.

Five studies[89,93,94,97,98] addressed eye disorders/dry eye. Two studies[93,94] showed 12% or fewer patients experienced eye disorders/dry eye where both groups contained HA. One study[97] showed no statistically significant difference in eye disorders/dry eye when HA was compared to another treatment or a control. Two studies[89,98] showed a decrease in eye disorders/dry eye when HA was compared to another treatment or a control.

Four studies[95-98] addressed hyperemia/hemorrhage. All 4 studies[95-98] showed no statistically significant difference in hyperemia/hemorrhage when HA was compared to another treatment or a control.

Three studies[94,95,98] addressed infection/viral conjunctivitis. Two studies[95,98] showed no statistically significant difference in infection/viral conjunctivitis when HA was compared to another treatment or a control. One study[94] showed less than 2% of patients experience infection/viral conjunctivitis where both groups contained HA.

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

The evidence base for human studies is large and includes 14 RCTs. The findings were mostly consistent in showing that HA did not play a large role in local host response or may have reduced the incidence of local host response. Some of the studies did not address the effects HA may have locally, as both experimental groups contained HA. Therefore, the quality of evidence for local host response is moderate. Because no studies reported on systemic responses, the quality of evidence for systemic responses is very low.

ECRI Surveillance Data

Patient Safety Organization

Search Results: ECRI PSO identified a total of 6 reports that involved HA materials that occurred between July 2016 and August 2021. One of these reports is pertinent to the topic of this report and it involved a hemorrhage/hematoma associated with a dermal implant. Table 8 and Table 9 outline the PSO event report complications and harm scores, respectively.

All individual PSO event reports are redacted and included in Appendix F.

Table 8: Complications in HA-related PSO Event Reports - Dermal, Facial and Eye Applications

Complication	Dermal implant	Total
Hemorrhage/Hematoma	**1**	**1**
Total	**1**	**1**

Table 9: Harm Score Associated with HA-related PSO Event Reports - Dermal, Facial, and Eye Applications

Harm Scores (NCC-MERP)	**Harm Scores (NCC-MERP)**	**Dermal implant**	**Total**
A	No Error		
B1	Error, No Harm		
B2	Error, No Harm		
C	Error, No Harm		
D	Error, No Harm		
E	Error, Harm		
F	Error, Harm		
G	Error, Harm		
H	Error, Harm		

Harm Scores (NCC-MERP)	Harm Scores (NCC-MERP)	Dermal implant	Total
I	Error, Death		
NULL*		1	
Total		**1**	**1**

**Harm score was not reported*

Accident Investigations

Search Results: The search returned zero accident investigations associated with HA for dermal, facial and eye applications.

ECRI Problem Reports

Search Results: The search returned zero reports submitted by ECRI members.

Healthcare Technology Alerts

Search Results: The search returned 7 manufacturer issued alerts describing problems with technique, updated IFU, discontinued use, clogged equipment, difficulty removing from body, contamination, leakage, and compromised sterility, summarized in Table 10.

Table 10: Summary of Regulatory and Manufacturer Alerts - Dermal, Facial and Eye Applications

Device Type	# Alerts	Reported Problem
LZP (Aid, Surgical Viscoelastic) – Intraocular Fluid	5 manufacturer issued	• Product is difficult to remove from the eye, increasing post-op intraocular pressure • Clogged phacoemulsification equipment can lead to ocular injury • Product may contain microscopic glass particles • Cannulae may leak viscoelastic material • Inadequately sealed syringes compromise sterility • Manufacturer reminds users of proper technique
Dermal Implant	2 manufacturer issued	• Updated IFU • Discontinued use for breast augmentation

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of Hyaluronic Acid. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

Across all device categories, the overall quality of evidence was low to very low for potential systemic responses.

For intraocular/ophthalmic/viscoelastic solution/fluids, other than IOP elevation and corneal/macular edema (moderate quality of evidence), all identified local host responses (e.g., ocular tension, inflammation) were of low quality of evidence.

There were no studies that addressed any particular cellular or molecular mechanisms for systemic manifestations.

Additionally, no studies addressed patient-related or material-related factors that could predict the likelihood and/or severity of immunological/systemic responses.

Safety Profile – Adhesion Barrier and Bulking Agent Applications

Full Name: Hyaluronic Acid
CAS Registry Number: 924474

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of Hyaluronic Acid used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of Hyaluronic Acid. The devices in Table 11 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data.

Table 11: Medical Devices Containing HA for Adhesion Barrier and Bulking Agent Applications provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Balloon, Epistaxis	EMX	1
Mesh, Surgical, Polymeric	FTL	2
Mesh, Surgical	FTM	2
Cuff, Nerve	JXI	2
Polymer, Ent Synthetic-Polyamide (Mesh or Foil Material	KHJ	2
Implant, Dermal, for Aesthetic Use	LMH	3
Agent, Bulking, Injectable for Gastro-Urology Use	LNM	3
Splint, Intranasal Septal	LYA	1
Barrier, Absorbable, Adhesion	MCN	3
Dressing, Wound and Burn, Hydrogel with Drug and/or Biologic	MGQ	Unclassified
System, Vocal Cord Medialization	MIX	2
Polymer, Ear, Nose and Throat, Synthetic, Absorbable	NHB	2

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of Hyaluronic Acid. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices below. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B3, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C3. Summary evidence tables with individual study data appear in Appendix D3, and a reference list of studies cited in the Safety Brief appears in Appendix E.

Hyaluronic acid (HA) is a natural polymer found in the extracellular matrix and in high concentrations in the skin and synovial fluid. HA suppresses immune responses and inflammation and aids wound healing. Based on these properties HA has been incorporated into a variety of medical products designed to reduce postsurgical inflammation.[99,100]

A summary of our primary findings is shown in Table 12. Even though the table mentions local host "responses" as well as systemic "responses", the events listed were not necessarily caused by the material. Only a few of these events were statistically significantly more likely with HA than without HA. Some listed events were actually statistically significantly less likely with vs without HA (in which case we write the word "less" next to the event). After the table, we present a detailed discussion of research on HA as a material as well as research on the various device categories. For three additional device categories, our searches identified no evidence (anti-adhesion protective oral gels, intravesical agents, and protective topical agents).

Table 12: Summary of Primary Findings from Systematic Review - Adhesion Barrier and Bulking Agent Applications

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Hyaluronic Acid as a material (1 human study, no animal studies)	Hematuria, nausea	Low	Urticaria	Low
Adhesion barrier (34 human studies, no animal studies)	Abdominal abscess, Acute pyelonephritis, Anastomotic fistula, Anastomotic leakage, Blood transfusion, Bowel injury, Cardiovascular complications, Changes in menstrual pattern, Hyperthermia, Ileus, Incision site abscess, Intestinal fistulas , Intra-abdominal abscess, Less Adhesion bowel obstruction, Less Post-operative intestinal obstruction , Paralytic ileus, Parietal abscess, Pelvic abscess, Peritonitis, Pleural effusion, Pneumonia, Postoperative biloma, Postoperative right portal vein embolization, Respiratory complications, Septic shock, Surgical-site infection, Suture failure, Transfusion, Urinary tract infection, Uterine dehiscence, Wound infection	High	Alanine aminotransferase, Albumin, Aspartate aminotransferase, Bilirubin, Blood urea nitrogen, C-reactive protein, Creatinine, Fever, Glucose, Hemoglobin, Liver enzymes, Liver function, Renal function, WBC count, White blood cell count	High
Anti-adhesion: Nasal packaging (5 human studies, no animal studies)	No events	Moderate	None investigated	Very Low
Barrier gel for oral lesions (3 human studies, no animal studies)	Less inflammation	Moderate	None investigated	Very Low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Bulking agents (3 human studies, no animal studies)	Urinary tract infection proctalgia, rectal hemorrhage, diarrhea, injection site complications, injection site sterile abscess, injection site mass, pseudo-cyst formation	Moderate	Fever	Moderate
Intravesical agents for bladder pain syndrome/interstitial cystitis therapy (2 human studies, no animal studies)	Less urinary tract infection	Low	None investigated	Very Low
Organ spacer (2 human studies, no animal studies)	Injection site pain, lower abdomen pain, hematuria	Low	Asthenia	Low
Protective topical agent for esophageal and gastric lesions in GERD (1 human study, no animal studies)	Cough, rhinitis, throat irritation	Low	Nervous system event (unspecified), vertigo, hypertension	Low
Vocal cord/fold medialization (1 human study, no animal studies)	Hematoma, edema of the aryteno-epiglottic fold and false vocal fold	Low	None investigated	Very Low

Hyaluronic Acid as a Material

One human study (one randomized controlled trial [RCT]), no animal studies. For more information, see Table 1 in Appendix D.

Local Responses (human studies)

One RCT of men (n = 49) undergoing radiotherapy for prostate cancer assessed using HA and chondroitin sulfate instilled into the bladder to prevent radiation-induced cystitis.[101] Patients also received oral HA and chondroitin sulfate. Control patients received no treatment. Mild to moderate drug-related adverse events were reported in 7 HA and chondroitin sulfate treated patients. Only 2 local adverse events were described, hematuria (blood in the urine) and nausea. Four of the seven adverse events were not described. There were no serious local drug-related adverse events or treatment-related withdrawals. No local adverse events were reported in control patients.

Because treated patients received HA as well as chondroitin sulfate, one cannot determine whether the reported adverse events were due to HA or chondroitin sulfate or other factors.

Systemic Responses

In the same RCT, only 1 systemic adverse event was described: a case of urticaria (skin rash due to an allergic reaction) in the treated group. There were no serious systemic drug-related adverse events or treatment-related withdrawals. As with local events, the study design does not permit a determination of the cause of this event.

Overall Quality of Evidence

The quality of the evidence is low for local responses and for systemic responses since the evidence comes from only one RCT with confounding factors that included multiple additional compounds administered to the treated patients and an unblinded control group that did not receive a placebo.

Adhesion barrier

34 human studies (14 SRs, 20 RCTs, no animal studies). For more information, see Table 2 in Appendix D.

Local Responses/Device Events (human studies)

Below, we discuss the evidence in five categories:

- Seprafilm (HA and carboxymethylcellulose)
- Sepraspray (HA and carboxymethylcellulose)
- Guardix-sol (HA + CMC gel)
- MateRegen (HA gel)
- Other HA gels

Seprafilm (HA and carboxymethylcellulose):

One SR examined SSI rate, anastomotic leak, ileus, intra-abdominal abscess, and small bowel obstruction in RCTs using HA and carboxymethylcellulose (CMC) barrier (Seprafilm) versus no treatment (control) during abdominal surgery.[102] The SR included 13 RCTs with 3,665 patients, of which 1,800 were in the Seprafilm group. Use of Seprafilm was associated with a significantly higher risk of anastomotic leak (3.1%) compared to control (1.6%), but a significantly lower incidence of small bowel obstruction (3.0%) compared to control (5.9%).

One SR examined complications in clinical studies using HA+CMC barrier (Seprafilm) versus control on rates of postoperative small bowel obstruction.[103] The SR included 4 RCTs and 5 clinical studies with 4,351 patients, of which 2,123 were in the Seprafilm group. No complications were related to Seprafilm. The SR reported "the risk of postoperative small bowel obstruction can be significantly decreased by the application of Seprafilm."

One SR examined postoperative complications including intra-abdominal infection, wound infection, anastomotic leakage, and postoperative hospital stay in clinical studies using HA+CMC barrier (Seprafilm) versus control after gastrointestinal neoplasms surgery.[104] The SR included 5 RCTs and 5 clinical studies with 2,937 patients, of which 1,334 were in the Seprafilm group. The incidence of postoperative intestinal obstruction was significantly lower in the Seprafilm group than the control (risk ratio, 0.52; 95% CI, 0.38–0.70; p<0.0001). Combined postoperative complications (intra-abdominal infection, wound infection, anastomotic leakage, and postoperative hospital stay) were also significantly lower in the Seprafilm group than the control (risk ratio 0.77; 95% CI, 0.61–0.97; p = .03). However, separate analysis of each postoperative complication did not find a significant difference.

One SR examined complications in RCTs using HA+CMC barrier (Seprafilm) versus control after gastrointestinal surgery.[105] The SR included 5 RCTs with 2,177 patients. The SR reported "As regards adverse effects, the use of Seprafilm has not been shown to result in a significant increase in morbidity, but…when Seprafilm was placed in direct contact with intestinal anastomoses, a significant increase in the rate of intestinal fistulas and their secondary morbidity was observed."

One RCT of 95 metastatic colorectal cancer patients requiring 2-stage hepatectomy compared HA+CMC barrier (Seprafilm) with no HA control.[106] There was no significant difference in complication rates between Seprafilm and control groups. Major complications included postoperative biloma that required percutaneous drainage and postoperative right portal vein embolization. Minor complications included urinary tract infections, minor pleural effusion, blood transfusion and parietal abscess.

One RCT of 345 patients undergoing elective colectomy compared HA+CMC barrier (Seprafilm) with no HA control.[107] No complications were related specifically to Seprafilm. Surgery-related complications seen equally in both groups included surgical-site infection, suture failure, and respiratory and cardiovascular complications.

One RCT of 753 females undergoing caesarean delivery compared HA+CMC barrier (Seprafilm) with no HA control.[108] No complications were related specifically to Seprafilm. Surgery-related complications seen equally in both groups included bowel injury, intraoperative transfusion, and uterine dehiscence.

One RCT of 488 patients undergoing colorectal surgery compared HA+CMC barrier (Seprafilm), HA+CMC gel (Guardix), and no HA control groups.[109] No complications were specifically related to Seprafilm or Guardix. Surgery-related complications seen equally in each group included pneumonia, surgical-site infection, anastomosis leakage, and intra-abdominal abscess.

Sepraspray (HA + CMC):

One RCT of 209 patients undergoing laparoscopic colorectal and/or small bowel surgery compared HA+CMC powder (Sepraspray Adhesion Barrier) with no HA control (n=104).[110] The Sepraspray group had significantly higher rates of adverse events (62.9%) and serious adverse events (27.6%) compared to control. Adverse events included hyperthermia (HA 5.7%, Control 2.9%), incision site abscess (HA 4.8%, Control 2.9%), urinary tract infection (HA 4.8%, Control 1.0%), and anastomotic fistula (HA 3.8%, Control 3.8%). Serious adverse events included pelvic abscess (HA 4.8%, Control 1.9%), abdominal abscess (HA 3.8%, Control 0%), septic shock (HA 1.0%, Control 1.9%), peritonitis (HA 1.9%, Control 2.9%), ileus (HA 2.9%, Control 0%), and anastomotic fistula (HA 2.9%, Control 3.8%).

One RCT of 41 females undergoing laparoscopic myomectomy compared HA+CMC powder (Sepraspray Adhesion Barrier) with no HA control.[111] No adverse events were specifically related to Sepraspray. Adverse events occurred in both groups but were not defined. The authors reported that surgical-site infections, intra-abdominal abscesses, and deep vein thrombosis did not occur in either group.

Guardix-sol (HA + CMC gel):

One RCT of 76 patients undergoing laparoscopic radical cystectomy compared HA+CMC gel (Guardix-sol) with no HA control.[112] Complication rates did not differ significantly in the Guardix-sol and control groups, "except for adhesive bowel obstruction, which occurred in zero and six patients, respectively ($p = 0.025$)." Reported complications included transfusion (HA 26.3%, Control 34.2%), paralytic ileus (HA 15.8%, Control 10.5%), wound disruption (HA 2.6%, Control 7.9%), and acute pyelonephritis (HA 5.3%, Control 7.9%).

One RCT of 43 males undergoing surgery for chronic epididymitis compared HA+CMC gel (Guardix-sol) with no HA control.[113] No complications occurred in either group (specifically looked for wound infection, wound hematoma, wound deadhesion, hematoma, cord injury, and testicular injury).

MateRegen (HA gel):

One RCT of 306 females with moderate to severe intrauterine adhesions (IUAs) undergoing operative hysteroscopy followed by embryo transfer compared intrauterine injection of HA gel (MateRegen) with no HA control.[114] No adverse events were observed in either group (authors did not specify what events they expected).

One RCT of 145 females with moderate to severe IUAs compared intrauterine injection of HA gel (MateRegen) with no HA control.[115] No surgical complications were reported in either group. After surgery, changes in menstrual pattern in the treatment group (87.7%, 107/122) were similar to the control group (76.4%, 97/123).

One RCT of 274 females undergoing dilation and curettage compared HA gel (MateRegen) with no HA control.[116] The authors noted that "no serious adverse events were observed during the study period, and there were no prolonged hospitalizations or reoperations owing to adverse events" in either group.

One RCT of 48 females undergoing curettage compared HA gel (MateRegen) with no HA control.[117] No complications or adverse events were related to MateRegen. No postoperative infections, prolong hospitalizations, or reoperations occurred in either group.

Other HA gels:

One RCT of 196 females undergoing laparoscopic surgery compared HA gel (HyaRegen NCH) with saline placebo.[118] No adverse events were related to HyaRegen NCH. The authors reported that adverse events were comparable between groups, mild and spontaneously resolved. No serious adverse events were observed in either group. The authors did not indicate what adverse events were expected.

One SR examined adverse events and abdominal complaints in RCTs using HA gel (Hyalobarrier Gel) versus control after endoscopic gynecologic surgery.[119] The SR included 5 RCTs with 335 females, of which 167 were in the Hyalobarrier Gel group. No adverse events were related to Hyalobarrier Gel. In gel-treated patients, two reported nausea and one reported vomiting. In control patients, one reported nausea.

One SR examined pain in clinical studies using HA gel (Hyalobarrier Gel) versus control after laparoscopic gynecologic surgery.[1] The SR included 1 RCT with 43 females, of which 25 were in the Hyalobarrier Gel group. The SR reported "Full conditioning with Hyalobarrier Gel placement resulted in decreased pain scores ($p < .001$) and faster recovery ($p < .0001$) compared with standard laparoscopy."

One SR examined adverse events and complications in RCTs using HA and HA+CMC barriers versus control after laparoscopic myomectomy (surgical procedure to remove uterine fibroids).[120] The SR included 8 RCTs with 748 patients, of which 392 were in the HA group. No serious adverse events or complications occurred in the included studies. The authors did not state what adverse events or complications they expected.

One SR examined complications in RCTs using HA and HA+CMC barriers versus control after gynecologic surgery.[121] The SR included 7 RCTs with 748 females. No complications were related to HA barriers.

One SR examined complications in clinical studies using HA and HA+CMC gels versus control after operative hysteroscopy.[122] The SR included 3 clinical studies with 262 females, of which 130 were in the HA groups. No complications were related to HA gels.

One SR, a Cochrane Review) examined adverse outcomes and pelvic pain in two SRs of RCTs comparing HA+CMC barrier versus control for adhesion prevention after gynecologic surgery.[123] The SR included 47 RCTs with between 59 and 127 females in HA+CMC and control groups. The available studies reported no adverse outcomes or pelvic pain related to HA+CMC barrier, but adverse event reporting occurred in only half of the studies.

One SR examined complications in RCTs using HA gel versus control after miscarriage.[124] The SR included 4 RCTs with 625 females, of which 290 were in the HA group. No complications were related to HA gel.

One SR examined complications in RCTs using HA gel versus control after intrauterine operation.[125] The SR included 7 RCTs with 952 females, of which 455 were in the HA group. No complications were related to HA gel. The authors reported that none of the included studies reported HA or surgery related complications, including hemorrhage, perforation or cervical laceration.

One SR examined complications in RCTs using HA gel versus control after hysteroscopic adhesiolysis.[126] The SR included 2 RCTs and 4 clinical studies with 394 females, of which 176 were in the HA group. No complications occurred in the HA gel group.

One SR examined complications in RCTs using HA gel versus control after gynecologic surgery.[127] The SR included 6 RCTs with 564 females, of which 286 were in the HA group. Only one RCT reported HA group complications, which were "patient discomfort and uterine perforation, with no statistically significant differences between the 2 [HA and control] groups."

One RCT of 65 females undergoing uterine septum resection compared intrauterine injection of HA with no HA control.[128] No complications, such as allergic reactions, occurred in the HA group. Menstrual patterns were not affected in either group.

One RCT of 143 females undergoing dilation and curettage compared HA gel with no HA control.[129] No complications occurred in the HA group. Menstrual patterns and pregnancy rates were not affected in either group.

One RCT of 149 females undergoing dilation and curettage compared HA gel with no HA control.[130] No complications were specifically related to HA gel. Cervix laceration was experienced by one patient in the HA group (1.3%) and no patients in the control group ($p=1.00$). Three patients in the HA group had excessive bleeding (3.9%) compared to one patient in the control group (1.4%) ($p=0.62$). Two patients in the HA group had postoperative infections (2.6%) compared to one patient in the control group (1.4%) ($p=1.00$). Four patients in the HA group had postoperative pain (5.2%) compared to three patients in the control group (4.2%) ($p=1.00$). Uterus perforation was experienced by one patient in the HA group (1.3%) and no patients in the control group ($p=1.00$).

One RCT of 124 females undergoing laparoscopic surgery for deep infiltrating endometriosis compared HA gel with sterile saline placebo.[131] No complications were related to HA gel. Patient pain was significantly reduced in the HA gel group after six months. HA treatment significantly reduced dysmenorrhea (painful menstruation), dyschezia (difficult or painful defecation), and dyspareunia (painful intercourse) at 3 and 6 months compared with control patients.

One RCT of 87 patients undergoing colorectal surgery compared HA gel, chitosan, and control groups and reported short-term (peristomal cutaneous infection, intra-abdominal hemorrhage, and abscess) and long-term (intestinal obstruction and anastomotic leakage) postoperative complications.[132] No complications were statistically significantly more likely in the HA gel

group. Short-term (30-day) complications were not seen in any patients. Long-term postoperative complications were similar among groups (10.5% of HA gel patients and 17.9% of control patients).

One RCT of 89 females undergoing operative hysteroscopy for intrauterine adhesions compared HA gel, intrauterine device (IUD), and HA gel+IUD groups.[133] No complications occurred in the HA gel group. None of the patients experienced excessive bleeding, infection, or other complications (not specified by the authors).

Systemic Responses

One SR examined systemic complications reported in 2 RCTs and 1 comparison study using Seprafilm (HA containing membrane) to prevent intestinal obstruction after gastrointestinal neoplasms surgery.[104] The SR reported aspartate aminotransferase, alanine aminotransferase (serum indicators of liver function), and blood urea nitrogen (indicator of kidney function) were not significantly different from controls five- and seven-days post-surgery. However, serum creatinine (another indicator of kidney function) was significantly higher in Seprafilm patients at 5 days but not at 7 days. The authors noted "that Seprafilm did not cause acute postoperative inflammation in short term, and had almost no effect on the liver and renal function of the patients."

One SR examined systemic complications in 5 RCTs comparing cross-linked HA gel with no treatment in patients undergoing endoscopic gynecological surgery.[119] Fever was reported in one of 167 HA patients and 2 of 168 control patients.

One RCT of 753 women undergoing caesarean delivery compared Seprafilm with no Seprafilm control.[108] Fever was reported in similar numbers of patients (4.5% Seprafilm, 3.0% control, risk ratio = 1.5 (95% CI of 0.7 to 3.3)).

One RCT of 196 women undergoing laparoscopic surgery compared a crosslinked hyaluronan gel with saline placebo.[118] The RCT examined blood chemistry (C-reactive protein, WBC count, hemoglobin, liver enzymes, albumin, blood urea nitrogen, creatinine, bilirubin, glucose, etc.) at 3 days, 30 days, and 9 weeks and found no clinically significant changes from baseline in the hyaluronan gel patients. Control patients had clinically significant elevations in white blood cell count and blood glucose from baseline at 9 weeks.

One RCT of 87 patients undergoing colorectal surgery compared HA gel with chitosan or no treatment.[132] White blood cell count, liver function, and renal function were comparable across groups at 2 weeks post-surgery.

Overall Quality of Evidence

The quality of evidence is high for local responses since the evidence comes from multiple SRs and RCTs reporting consistent results that there are few adverse events or complications related to HA-containing products. The quality of evidence is high for a lack of systemic responses since the evidence is from SRs with multiple RCTs and three individual RCTs.

Anti-adhesion: Nasal packaging

Five human studies (two SRs, three RCTs), no animal studies. For more information, see Table 3 in Appendix D.

Local Host Responses (human studies)

One SR examined complications reported in RCTs using Sepragel or MeroGel, both contain HA, as nasal packing after endoscopic sinus surgery.[134] The SR included four RCTs with 352 patients. According to the SRs, no adverse events or complications were reported in two of the included RCTs, and SR authors did not describe the other two RCTs results. No specifics were provided on what adverse events may have been expected.

One SR examined complications in studies evaluating endoscopic sinus surgery.[135] The SR included 13 studies with 501 patients (5 double-blind RCTs, 5 single-blind RCTs, and 3 prospective comparisons) that used HA as an absorbable packing, a non-absorbable packing impregnated with HA, or an HA spray. The SR reported "It is clear that hyaluronic acid in all preparations is safe and well-tolerated by patients, as evidenced by only one adverse event not related directly to hyaluronic acid, and the overall satisfaction with its use in absorbable nasal packs."

One RCT of patients (n = 205) undergoing tympanoplasty for adhesive otitis media reported that there were no complications or adverse events in the group receiving MeroGel (which contains HA).[136] The authors did not specify what complications were expected after surgery but did report that no patient suffered a sensorineural hearing loss or needed a reoperation.

One RCT of patients (n = 55) undergoing bilateral endoscopic sinus surgery compared an absorbable crosslinked HA hydrogel with a gelatin sponge control.[137] The authors reported that no adverse events related to the packing treatment occurred during the study but did not report what adverse events may have been expected.

One RCT of patients (n = 227) undergoing surgery for unilateral primary chronic dacryocystitis (an infection of the lacrimal sac, secondary to obstruction of the nasolacrimal duct) compared MeroGel with no MeroGel.[138] The authors did not report any adverse events related to MeroGel, but did not report what adverse events may have been expected.

Systemic Responses

No systemic responses were reported in the included studies.

Overall Quality of Evidence

The SRs and RCTs were consistent in observing that there are no adverse events or complications related to HA-containing products. The study authors noted that HA reduces local inflammatory responses and reduces scarring after surgery. The quality of the evidence is moderate for local responses since the majority of studies are RCTs and is very low for systemic responses (no studies investigated systemic effects).

Barrier gel for oral lesions

Three human studies (one SR, two RCTs), no animal studies. For more information, see Table 4 in Appendix D.

Local Responses/Device Events (human studies)

One SR examined HA as an adjunct treatment for chronic inflammatory disease.[99] The SR included 25 controlled studies with studies examining HA's effect on gingivitis, chronic periodontitis, dental surgery, and oral ulcers. No adverse events occurred with HA use. The authors noted that HA "suppresses the immune response preventing excessive exacerbations of inflammation." HA's effect on inflammation may be responsible for faster wound healing and reduction in postoperative discomfort.

One RCT using a split-mouth design (n = 24) examined HA's effect on moderate to severe chronic periodontitis.[139] No adverse events occurred in the HA group. Plaque index, gingival index, papillary bleeding index, and periodontal probing depth improved in HA-treated and control areas but was significantly better in HA-treated areas.

One RCT using a split-mouth design (n = 28) examined HA's effect on plaque-induced gingivitis.[140] The authors' reported "no adverse effects to the gel were observed on clinical examination and as reported by the patients." Plaque index, gingival index, and gingival bleeding were examined after treatment. Inflammation was reduced with all treatments, but the reduction was greater in HA-treated areas.

Systemic Responses

No systemic responses were reported in the included studies.

Overall Quality of Evidence

The SRs and RCTs were consistent in not observing any adverse events or complications related to HA containing products. The quality of the evidence is moderate for local response since all studies were RCTs or controlled studies and were consistent and is very low for systemic responses (no studies investigated).

Bulking agents

Three human studies (three RCTs), no animal studies. For more information, see Table 5 in Appendix D.

Local Host Responses (human studies)

One RCT of pediatric patients (n = 60) with grades III and IV primary vesicoureteral reflux used dextranomer HA to treat the condition as opposed to surgery.[141] Patients were followed for 1 year. Late local complications included 6 (20%) urinary tract infections in dextranomer HA patients and 5 (16.7%) in surgery patients.

One RCT of patients with fecal incontinence (n = 206) compared dextranomer HA with a sham injection procedure.[142] Patients were followed for 1 year. In this study proctalgia (14%, pain due to a spasm of the pelvic floor muscles, the muscles of the

anal sphincter, or the muscles of the rectum), rectal hemorrhage (7%), and diarrhea (5%) were seen in the treatment group but were not common in the sham control group (3% proctalgia, 1% rectal hemorrhage, and 4% diarrhea).

One RCT of women (n = 344) with urinary incontinence (reported in a SR) examined mid-urethral dextranomer HA (Zuidex) injections compared with collagen injections.[143] Patients were followed for 1 year. Dextranomer HA treated patients had higher rates of injection site complications (16% versus 0%). Injection site sterile abscess (8.4%), injection site mass (4.4%) and pseudo-cyst formation (2.2%) were only seen in Zuidex-treated women. Zuidex has been withdrawn from the market.

Systemic Responses

One RCT of pediatric patients (n = 60) with grades III and IV primary vesicoureteral reflux used dextranomer HA to treat the condition as opposed to surgery.[141] Fever was noted in several patients within 2 weeks of the procedure (3 dextranomer HA patients [10%] and 6 surgery patients [20%]).

One RCT of patients with fecal incontinence (n = 206) compared dextranomer HA with a sham injection procedure.[142] Patients were followed for 1 year. In this study, fever (8%) was seen in the treatment group but was not seen in the sham control group.

Overall Quality of Evidence

The quality of the evidence is moderate for local response and for systemic responses since all studies were RCTs and results were mostly consistent.

Intravesical agents for bladder pain syndrome/interstitial cystitis therapy

Two human studies (1 SR, 1 RCT), no animal studies. For more information, see Table 6 in Appendix D.

Local Host Responses (human studies)

One SR assessed HA and HA plus chondroitin sulphate for reducing the occurrence of recurrent bacterial cystitis.[144] The SR included 4 comparison studies (2 RCTs) with 143 patients. Bladder instillation of HA was well tolerated and reduced urinary tract infections.

One RCT of patients with bladder pain syndrome (n = 72) compared intravesical treatment with HA, chondroitin sulfate, and a combination of both and found there were no serious adverse events or patient withdrawals during the 24-month study in any patient.[145] The authors reported specifically looking for recurrent febrile urinary tract infections, symptomatic cardiac arrhythmias, significant nephrotoxicity, and hepatotoxicity that would require discontinuing treatment.

Systemic Responses

No systemic responses were reported in the included studies.

Overall Quality of Evidence

The quality of the evidence is low for local response since only 2 of the 4 studies in the SR were RCTs and the evidence base is small and is very low for systemic responses (no studies investigated).

Organ spacer

Two human studies (no RCTs, two case series), no animal studies. For more information, see Table 7 in Appendix D.

Local Host Responses (human studies)

One case series of patients (n = 60) undergoing high-dose-rate interstitial brachytherapy for prostate cancer reported that no adverse effects occurred after an HA injection into the perirectal fat prior to brachytherapy.[146] The authors did not report which adverse effects they may have expected.

One case series of patients (n = 36) undergoing hypofractionated radiation therapy for prostate cancer reported that injections of HA were well tolerated with one patient each experiencing persistent pain at the injection site, lower abdomen pain and hematuria (blood in the urine).[147]

Systemic Responses

One case series of patients (n = 36) undergoing hypofractionated radiation therapy for prostate cancer reported that injections of HA were well tolerated with one patient experiencing asthenia (abnormal physical weakness or lack of energy).[147]

Overall Quality of Evidence

The quality of the evidence is low for both local responses and systemic responses because the evidence base has only two small studies. Studies of this size are not sufficient to allow a full spectrum of adverse events to be seen.

Protective topical agent for esophageal and gastric lesions in GERD

One human study (one RCT), no animal studies. For more information, see Table 8 in Appendix D.

Local Host Responses (human studies)

One double-blind, placebo-controlled RCT of patients (n = 154) with non-erosive reflux disease treated with proton pump inhibitors reported no serious adverse events related to using an HA plus chondroitin sulphate formulation to coat the esophagus after a meal.[148] Mild gastrointestinal and respiratory (cough, rhinitis, throat irritation) adverse events were somewhat more common in HA-treated patients.

Systemic Responses

The same RCT reported some mild systemic adverse events occurring only in HA-treated patients: 3 nervous system, 1 vertigo, and 1 hypertension.

Overall Quality of Evidence

The quality of the evidence is low for both local responses and systemic responses because the evidence base has only one study but it was of medium size.

Vocal cord/fold medialization

One human study (1 SR), no animal studies. For more information, see Table 9 in Appendix D.

Local Host Responses

One SR with 14 case series (n = 442) assessed injection laryngoplasty with commercial preparations of HA to treat unilateral vocal fold paralysis.[149] The authors noted that HA was safe for this procedure and that one patient experienced hematoma and one patient experienced edema of the aryteno-epiglottic fold and false vocal fold. Some included studies reported local hypersensitivity and inflammation that the authors believe may have been reactions to proteins produced in the HA manufacturing process. Outcomes and adverse events will likely vary depending on injection technique and brand of product used.

Overall Quality of Evidence

The quality of the evidence is low for local responses and very low for systemic responses (no studies investigated). The SR included only case series and reported on only 442 patients.

ECRI Surveillance Data

There were no relevant reports found in ECRI's PSO, accident investigation, or PRN databases related to devices composed of SM-PFAS. Healthcare Technology Alerts search returned 4 manufacturer issued alerts describing problems including compromised sterility and off label use.

Refer to Appendix F for a list of devices that guided our searches of ECRI Surveillance Data.

Patient Safety Organization

Search Results: ECRI PSO identified 11 reports that involved adhesion barrier composed of HA that occurred between December 2016 and August 2021; however, none were pertinent to the topic of this report.

Accident Investigations

Search Results: Zero investigations were recovered from the accident investigations database.

ECRI Problem Reports

Search Results: The search returned zero reports submitted by ECRI members.

Healthcare Technology Alerts

Search Results: The search returned 4 manufacturer issued alerts describing problems with sterility, labeling, and off-label use, summarized in Table 13.

Table 13: Summary of Regulatory and Manufacturer Alerts - Adhesion Barrier and Bulking Agent Applications

Device Type	# Alerts	Reported Problem
MCN (Barrier, Absorbable, Adhesion)	2 manufacturer issued	• Defective packaging compromises sterility. • Recall; off-label use may lead to serious complications.
KHJ (Polymer, ENT Synthetic-Polyamide [Mesh or Foil Material])	1 manufacturer issued	• Mislabeled as sterile, when only syringe contents are sterile.
Adhesion Barrier	1 manufacturer issued	• Cannulae may not meet required sterility level.

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of Hyaluronic Acid. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

For 7 of 9 device categories, no local adverse events were statistically significantly more likely in patients receiving HA devices compared to patients receiving non-HA devices. This is predominantly because of a lack of studies with strong design that investigated these events. The exceptions were adhesion barrier and bulking agents.

For 7 of 9 device categories, no systemic adverse events were statistically significantly more likely in patients receiving HA device compared to patients received non-HA devices. This is predominantly because of a lack of studies with strong design that investigated these events. The exceptions were adhesion barrier and bulking agents.

Only one study related to HA as a material was identified. However, because treated patients received HA as well as chondroitin sulfate, one cannot determine whether the reported adverse events were due to HA or chondroitin sulfate or other factors

For 8 of 9 device categories, only study involving adhesion barriers investigated the cellular or molecular mechanisms for systemic manifestations.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1. English language publication
2. Published between January 2011 and August 2021
3. Human studies (animal studies that provide unique information will also be considered for inclusion)
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of HA or priority devices that include this material

Exclusion Criteria

1. Foreign language publication
2. Published before January 2011
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2. **Quantity of data** – number of systematic reviews and individual studies providing relevant data, as well as the proportion of included studies that reported a specific outcome.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. Magnitude of effect – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
6. Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

Appendix B1. Search Summary – Muscle/Skeletal Applications

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n=174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Material: Hyaluronic Acid (HA) - Muscle/Skeletal Applications

Set Number	Concept	Search Statement
Material		
1.	Hyaluronic acid (HA) and derivatives	'hyaluronic acid'/de OR 'hyaluronic acid derivative'/de OR hyaluronan?:ti,ab OR hyaluronate?:ti,ab OR hyaluronic:ti,ab
2.	HA viscosupplement devices	('adant' OR 'suprahyal' OR 'agili-c' OR 'artflex' OR 'arthrum' OR 'chondrotissue' OR 'cingal' OR 'crespine gel' OR 'curavisc' OR 'durolane' OR 'euflexxa' OR 'nuflexxa' OR 'gel-one' OR 'gel-syn' OR 'gelsyn' OR 'gel-syn-3' OR 'gelsyn-3' OR 'sinovial' OR 'genvisc 850' OR 'happycross' OR 'hyalgan' OR 'hyalofast' OR 'hyalograft-c' OR 'hyalone' OR 'hyalubrix' OR 'hyalonect' OR 'hyaluron hexal' OR 'hymovis' OR 'hyadd' OR 'monovisc' OR 'neovisc' OR 'orthovisc' OR 'ostenil' OR 'ostenil tendon' OR 'recosyn' OR 'recosyn forte' OR 'recosyn uno' OR 'recosyn md' OR 'sportvis' OR 'rheovital' OR 'rheo vital' OR 'spinevisc' OR 'supartz' OR 'supartz fx' OR 'synocrom' OR 'synocrom mini' OR 'synocrom forte' OR 'synocrom forte one' OR 'structovial' OR 'synojoynt' OR 'hyalrheuma' OR 'synvisc' OR 'synvisc-one' OR 'hylan g-f 20' OR 'triluron' OR 'hyalgen' OR 'trivisc' OR 'visco-3' OR 'viscoseal'):ti,ab,kw,de,tn,dn
3.	HA bone filler devices	('aft dbm' OR 'biosphere flex' OR '45s5 bg' OR '45s5 bioglass' OR 'bioglass 45s5' OR 'confirm dbm' OR 'confirm bioactive' OR (dbx AND bone) OR 'dbx inject' OR 'dbx strip' OR 'sygnal dbm' OR 'hyaloss' OR 'inqu paste mix' OR 'kinex' OR 'mtf new bone void filler' OR 'scs 17-01' OR 'tactoset'):ti,ab,kw,de,tn,dn

4.	HA other devices	('agili-c' OR 'biopoly' OR 'chondrotissue' OR 'hyalograft*'):ti,ab,kw,de,tn,dn
5.	HA + general device and musculoskeletal terms	#1 AND ('viscosupplementation'/exp OR 'intraarticular drug administration'/exp OR 'musculoskeletal system inflammation'/exp OR 'musculoskeletal injury'/exp/mj OR 'bone matrix'/exp OR 'joint'/exp/mj OR joint*:ti OR ((intra NEXT/1 articul*):ti) OR intraarticul*:ti OR osteoarthr*:ti OR 'arthritis':ti)
6.	Combine and Limit by language and publication date	(#2 OR #3 OR #4 OR #5) AND [english]/lim AND [2011-2021]/py
7.	Limit by publication type	#6 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

8.		**'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'**
9.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence
10.		Leachable* OR extractable*
11.		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail* OR fragment* OR debond*) NEAR/3 (hydrogel* OR implant* OR prosthes* OR prosthetic* OR injectable* OR putty OR putties OR graft OR device?)
12.		'mechanics'/exp
13.		'device material'/exp/mj
14.		'Biomedical and dental materials'/exp/mj
15.	Combine sets	#8 OR #9 OR #10 #11 OR #12 OR #13 OR #14
16.	**HA + Material Response**	**#7 AND #15**

Host Response

17.		**Host NEAR/2 (reaction* OR response*)**
18.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* OR 'carcinogenicity'/exp OR carcinogen*:ti

19.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
20.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
21.		'inflammation'/exp OR (inflamm* NEAR/3 (tissue OR macrophage* OR cytokine* OR react* OR respons* OR level* OR sign* OR effect* OR activat* OR local OR inhibit* OR alleviat* OR reduc* OR decreas* OR induce* OR synovial))
22.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab OR fouling OR 'anti-fouling' OR biofilm?
23.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis':de OR 'necrosis':ti,ab
24.		protrude* OR protrus* OR perforat*
25.		'fibrosis'/exp OR 'seroma'/exp OR 'hematoma'/exp OR 'seroma*' OR 'hematoma*' OR 'thrombosis'/exp OR 'thrombosis'/syn OR 'phlebitis'/exp OR 'phlebitis'/syn OR 'skin irritation'/exp OR 'pruritus'/exp OR 'pruritus' OR itch*:ti,ab
26.	Combine sets	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25

Other combinations

27.	**Combine sets HA + Material Response+ Host Response**	**#16 AND #26**
28.	**HA general devices + Host response**	#5 AND #7 AND #26
29.	**Combine sets**	#27 OR #28
30.	**HA systematic reviews**	#7 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
31.	**Final set**	**#29 OR #30**

Appendix B2. Search Summary – Dermal, Facial and Eye Applications

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Material: Hyaluronic Acid (HA) – Dermal, Facial and Eye Applications

Set Number	Concept	Search Statement
1.	**Hyaluronic acid (HA) and derivatives**	'hyaluronic acid'/de OR 'hyaluronic acid derivative'/de OR hyaluronan?:ti,ab OR hyaluronate?:ti,ab OR hyaluronic:ti,ab
2.	HA ophthalmic viscosurgical devices (OVDs)	(clearvisc OR healon OR healon5 OR endocoat OR vitrax OR staarvisc OR optivisc OR anikavisc OR nuvisc OR viscoat OR duovisc OR discovisc OR provisc OR amvisc OR biolon OR eyefill* OR 'eye fill' OR visthesia OR vcombivisc OR twinvisc OR 'z-hyalcoat' OR 'z-hyalin' OR 'z-hyalon' OR ophthalin OR 'bio-hyalur' OR biohyalur OR microvisc OR ivisc OR optheis OR rayvisc OR shellgan OR opelead OR opegan):ti,ab,kw,de,tn,dn
3.	HA dermal filler devices	(juvederm* OR restylane* OR perlane OR revanesse OR hydrelle OR elevess OR prevelle OR captique OR hylaform OR 'hylan b' OR teosyal OR 'rha 2' OR 'rha 3' OR 'rha 4' OR 'rha2' OR 'rha3' OR 'rha4' OR 'belotero' OR macrolane OR bagovit OR hyalorepair OR hyalsense OR ovita OR 'ovita fine' OR 'ovita hv' OR dermalax OR biohyalux OR elravie OR 'art filler' OR esthelis OR mesolis OR fortelis OR modelis OR hyaluderm OR succeev OR 'z-fill' OR zfill OR 'princess volume' OR 'saypha volume' OR profhilo OR aliaxin OR viscoderm OR dermalive OR surgiderm OR hydrafill):ti,ab,kw,de,tn,dn
4.	HA + general device and ocular terms	#1 AND ('eye disease'/exp OR 'vitrectomy'/exp OR 'ophthalmic viscosurgical device'/exp OR (eye OR eyes OR eyelid* OR ocular* OR periocular* OR opthalm* OR 'vitreous' OR vitrectom*):ti)

Set Number	Concept	Search Statement
5.	HA + general device and dermal terms	#1 AND ('face'/exp OR 'nose'/exp OR 'skin'/exp OR 'dermal implant'/exp OR 'injectable dermal implant'/exp OR 'plastic surgery implant'/exp OR (dermal OR skin OR face OR forehead OR eyelid* OR cheek* OR chin OR lips OR nasolabial):ti)
6.	**Combine sets**	**#2 OR #3 OR #4 OR #5**
7.	Limit by language and publication date	#6 AND [english]/lim AND [2011–2021]/py
8.	Limit by publication type	#7 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

9.		**'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'**
10.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence
11.		Leachable* OR extractable*
12.		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail* OR fragment* OR debond*) NEAR/3 (hydrogel* OR implant* OR prosthes* OR prosthetic* OR injectable* OR putty OR putties OR graft OR device?)
13		'mechanics'/exp [see Emtree explosions section at the end of the strategy]
14.		'device material'/exp/mj
15.		'Biomedical and dental materials'/exp/mj
16.	**Combine sets**	**#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15**

Host Response

17.		**Host NEAR/2 (reaction* OR response*)**
18.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
19.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj

20.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
21.		'inflammation'/exp OR (inflamm* NEAR/3 (tissue OR macrophage* OR cytokine* OR react* OR respons* OR level* OR sign* OR effect* OR activat* OR local OR inhibit* OR alleviat* OR reduc* OR decreas* OR induce* OR synovial))
22.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab OR fouling OR 'anti-fouling' OR biofilm?
23.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis':de OR 'necrosis':ti,ab
24.		protrude* OR protrus* OR perforat*
25.		'fibrosis'/exp OR 'seroma'/exp OR 'hematoma'/exp OR 'seroma*' OR 'hematoma*' OR 'thrombosis'/exp OR 'thrombosis'/syn OR 'phlebitis'/exp OR 'phlebitis'/syn OR 'skin irritation'/exp OR 'pruritus'/exp OR 'pruritus' OR itch*:ti,ab
26.	**Combine sets**	**#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25**

Other Combinations

27	**HA + Material Response + Host Response**	**#8 AND #15 AND #26**
28	**HA general devices + Host response**	(#4 OR #5) AND #8 AND #26
29	**Combine sets**	#27 OR #28
30.	**HA systematic reviews**	#8 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
31	**Combine all**	**#29 OR #30**

Appendix B3. Search Summary – Adhesion Barrier and Bulking Agent Applications

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Material: Hyaluronic Acid (HA) – Adhesion Barrier and Bulking Agent Applications

Set Number	Concept	Search Statement
1.	**Hyaluronic acid (HLA) and derivatives**	'hyaluronic acid'/de OR 'hyaluronic acid derivative'/de OR hyaluronan?:ti,ab OR hyaluronate?:ti,ab OR hyaluronic:ti,ab
2.	HLA adhesion barriers, packing	('acp gel' OR advacoat OR aftamed OR carbylan* OR 'endo gel' OR epidisc OR epifilm OR gelclair OR gengigel OR 'guardix sol' OR hyacorp OR hyalobarrier OR hyfence OR hylasine OR intergel OR 'incert ' OR 'incert-s' OR lubricoat OR merogel* OR meropack* OR pureregengel OR 'pureregen gel' OR sepracoat* OR seprafilm OR sepragel OR sepramesh OR sepraspray OR silsos OR versawrap* OR 'defehere' OR 'protahere' OR 'protad' OR 'singclean'):ti,ab,kw,de,tn,dn
3.	HLA vocal cord augmentation	('silkvoice' OR 'silk voice' OR 'hystem*'):ti,ab,kw,de,tn,dn
4.	HLA bulking/spacer	('barrigel' OR 'deflux' OR 'solesta' OR 'zuidex' OR 'dexell' OR 'urodex' OR 'vurdex'):ti,ab,kw,de,tn,dn
5.	HLA Devices: Adhesion barrier terms	#1 AND ('adhesion barrier'/exp OR 'adhesion barrier film'/exp OR 'adhesion barrier gel'/exp OR 'anti-adhesion solution'/exp OR 'adhesion'/exp OR 'peritoneum adhesion'/exp OR 'tissue adhesion'/exp OR 'uterus synechia'/exp OR 'anastomotic device'/exp OR 'surgical mesh'/exp OR 'adhes*':ti,ab OR

Set Number	Concept	Search Statement
		'adher*':ti,ab OR 'antiadhes*' OR 'anti-adhes*':ti,ab OR 'barrier*':ti,ab OR sealant*:ti,ab OR 'mesh':ti,ab OR 'nasal packing':ti,ab OR 'nasal splint*':ti,ab)
6.	HLA Devices: Vocal cord augmentation terms	#1 AND ('vocal cord paralysis'/exp OR 'vocal cord disorder'/exp OR 'vocal cord'/exp OR 'vocal fold scarring'/exp OR 'vocal fold atrophy'/exp OR 'dysphonia'/exp OR (vocal NEAR/3 (fold* OR cord* OR inject* OR augment* OR laryngoplasty OR medialization OR bulk*)) OR 'injection laryngoplasty' OR 'medialization laryngoplasty')
7.	HLA Devices: Bulking agent terms	#1 AND ('anti vesicoureteral reflux gel'/exp OR 'feces incontinence device'/exp OR 'injectable incontinence implant'/exp OR 'feces incontinence'/exp OR 'urine incontinence'/exp OR 'hydrogel organ spacer'/exp OR 'prostate immobilization device'/exp OR 'spacer balloon'/exp OR (bulking NEAR/3 (agent* OR material* OR substance* OR inject* OR procedure* OR treatment* OR therapy)) OR 'vesico-ureteral reflux' OR 'vesicoureteral reflux' OR 'anti-vesico-ureteral reflux' OR 'anti-vesicoureteral reflux' OR (spacer OR spacers):ti,ab)
8.	**Combine sets**	**#2 OR #3 OR #4 OR #5 OR #6 OR #7**
9.	Limit by language and publication date	#8 AND [english]/lim AND [2011–2021]/py
10.	Limit by publication type	#9 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

11.		**'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'**
12.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence
13		Leachable* OR extractable*
14.		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail* OR fragment* OR debond*) NEAR/3 (hydrogel* OR implant* OR prosthes* OR prosthetic* OR injectable* OR packing OR splint? OR device?)
15.		'mechanics'/exp [see Emtree explosions section at the end of the strategy]
16.		'device material'/exp/mj
17.		'Biomedical and dental materials'/exp/mj
18.	**Combine sets**	**#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**

Host Response

19.		**Host NEAR/2 (reaction* OR response*)**
20.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
21.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
22.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
23.		'inflammation'/exp OR (inflamm* NEAR/3 (tissue OR macrophage* OR cytokine* OR react* OR respons* OR level* OR sign* OR effect* OR activat* OR local OR inhibit* OR alleviat* OR reduc* OR decreas* OR induce* OR synovial))
24.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab OR fouling OR 'anti-fouling' OR biofilm?
25.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis':de OR 'necrosis':ti,ab
26.		protrude* OR protrus* OR perforat*
27.		'fibrosis'/exp OR 'seroma'/exp OR 'hematoma'/exp OR 'seroma*' OR 'hematoma*' OR 'thrombosis'/exp OR 'thrombosis'/syn OR 'phlebitis'/exp OR 'phlebitis'/syn OR 'skin irritation'/exp OR 'pruritus'/exp OR 'pruritus' OR itch*:ti,ab
28.	**Combine sets**	**#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27**

Other Combinations

29	**HLA + Material Response + Host Response**	**#10 AND #18 AND #28**
30	**HLA general devices + Host response**	(#6 OR #7) AND #10 AND #28
31	**Combine sets**	#29 OR #30
32.	**HLA systematic reviews**	#10 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
33	**Combine all**	**#31 OR #32**

Example Embase Explosion

Mechanics/exp

- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight
                            - Extremely low birth weight
            - Body weight change
                - Body weight fluctuation
                - Body weight gain
                    - Gestational weight gain
                - Body weight loss
                    - Emaciation
                - Body weight control
                - Fetus weight
                - Ideal body weight
                - Lean body weight
                - Live weight gain
            - Dry weight
            - Fresh weight
            - Molecular weight
            - Organ weight
                - Brain weight
                - Ear weight
                - Heart weight

        - Liver weight
        - Lung weight
        - Placenta weight
        - Spleen weight
        - Testis weight
        - Thyroid weight
        - Uterus weight
      - Seed weight
      - Tablet weight
      - Thrombus weight
    - Weightlessness
- Hydrodynamics
  - Hypertonic solution
  - Hypotonic solution
  - Isotonic solution
  - Osmolality
    - Hyperosmolality
    - Hypoosmolality
    - Plasma osmolality
    - Serum osmolality
    - Urine osmolality
  - Osmolarity
    - Blood osmolarity
    - Hyperosmolarity
    - Hypoosmolarity
    - Plasma osmolarity
    - Serum osmolarity
    - Tear osmolarity
    - Urine osmolarity
  - Osmosis
    - Electroosmotic
    - Osmotic stress
      - Hyperosmotic stress
      - Hypoosmotic stress
- Photodynamics
  - Photoactivation
    - Photoreactivation
  - Photodegradation
  - Photoreactivity
    - Photocytotoxicity
    - Photosensitivity
    - Photosensitization
    - Phototaxis
    - Phototoxicity
  - Photostimulation
- Proton motive force
- Shock wave
  - High-energy shock wave
- Stress strain relationship
- Thermodynamics
  - Adiabaticity
  - Enthalpy
  - Entropy

- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed
        - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress

    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity
- Viscoelasticity

Appendix C1. Study Flow Diagram – Muscle/Skeletal Applications

I. 1,795 Citations were identified by searches, of which:

1. 991 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.)

2. The remaining 804 citations were screened for potential inclusion at title/abstract level (529 citations were selected by text mining in Distiller (30%); and 275 additional citations were selected - 89 by logistic regression (5%) and 186 for including "random" or "systematic" in the title or abstract)

a. 377 citations were excluded at the title/abstract level. Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

b. The remaining 427 full length citations were reviewed, of which:

i. 189 citations were excluded at 1st pass full article level, Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest, or were not available.

ii. The remaining 238 citations were reviewed, of which:

1. 199 citations were excluded at the prioritization level. Citations excluded at this level were animal, single-arm or nonrandomized comparative studies; or were individual studies already represented in a systematic review; or were systematic reviews superseded by a more comprehensive systematic review.

2. 39 citations were included.

Appendix C2. Study Flow Diagram – Dermal, Facial and Eye Applications

1,401 Citations were identified by searches, of which:

1. 862 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.)

2. The remaining 539 citations were screened for potential inclusion at title/abstract level (420 citations were selected by text mining in Distiller (30%); and 119 additional citations were selected – 70 by logistic regression (5%) and 49 for including "random" or "systematic" in the title or abstract)

    a. 297 citations were excluded at the title/abstract level. Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

    b. The remaining 242 full length citations were reviewed, of which:

        i. 80 citations were excluded at 1st pass full article level, Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest, or were not available.

        ii. The remaining 162 citations were reviewed, of which:

            1. 104 citations were excluded at the prioritization level. Citations excluded at this level were animal, single-arm or nonrandomized comparative studies; or were individual studies already represented in a systematic review; or were systematic reviews superseded by a more comprehensive systematic review.

            2. 58 citations were included.

Appendix C3. Study Flow Diagram – Adhesion Barrier and Bulking Agent Applications

1,217 Citations were identified by searches, of which:

1. 718 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.)

2. The remaining 499 citations were screened for potential inclusion at title/abstract level (365 citations were selected by text mining in Distiller (30%); and 134 additional citations were selected – 61 by logistic regression (5%) and 73 for including "random" or "systematic" in the title or abstract)

    a. 167 citations were excluded at the title/abstract level. Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

    b. The remaining 332 full length citations were reviewed, of which:

        i. 77 citations were excluded at 1st pass full article level, Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest, or were not available.

        ii. The remaining 255 citations were reviewed, of which:

1. 204 citations were excluded at the prioritization level. Citations excluded at this level were animal, single-arm or nonrandomized comparative studies; or were individual studies already represented in a systematic review; or were systematic reviews superseded by a more comprehensive systematic review.

2. 52 citations were included.

Appendix D1. Evidence Tables – Muscle/Skeletal Applications

Table 14: Viscosupplementation – knee: Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Hyaluronic acid (HA) injections

Source Citation: Carico et al. 2021[2]

Study Design: SR - MAUDE

Device or Material: HA injection

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Pain after injection, Purulent aspirate, Swelling

Patient characteristics (gender, mean age): NR

Number per group: 63 total unique fatalities. Knee viscosupplementation when reported.

Observed adverse effects: 8 fatalities possibly related to HA injection: Patient developed pain after injection and a purulent aspirate before dying. Patient had swelling that led to incision of the knee and subsequent death. Patient had pain and swelling after injection, died for unreported reasons after admission. Suicide following worsening pain.

Timing of adverse effects: Timing NR for fatalities associated with local adverse events.

Factors that predict response: Patients with risk factors for infections, such as immunocompromised patients since most fatalities were often associated with infectious processes vs. the effects of the HA.

Source Citation: Sedrak et al. 2021[3]

Study Design: SR; Case Report

Device or Material: HA for IA injection (89% receiving Synvisc [HA] Sanofi-Aventis)

Contact Duration: SR: up to 6 months Case report: 4 weeks

Dose: NR

Frequency/Duration: SR: 2 to 4+ administrations; Case report: single administration

Response: Pseudoseptic arthritis presenting with: Effusion Pain, acute, Synovial leucocyte elevation

Patient characteristics (gender, mean age): 85.2% female, 60.8 years (31-79).

Number per group: SR (11 studies: 5 single arm studies, 6 case reports), 28 knees (27 patients) with acute pseudoseptic arthritis after HA injection for knee OA.

Case report: 1 knee (1 patient).

Observed adverse effects: SR: All patients presented with acute pain and joint effusion. 24 of 28 cases underwent arthrocentesis, with 3 cases (12.5%) having synovial leucocyte elevation in the range typically concerning

for septic arthritis, and another 16 cases (66.7%) with elevations in an inflammatory cell count range of 5,000 to 50,000. Case report: progressive and increasing pain with obvious suprapatellar effusion.

Timing of adverse effects: SR: 22 cases (78.6%) of pseudoseptic arthritis presented within 24 hours of injection; 15 of the 22 cases (68.2%) presented within the first 12 hours. Time from injection to presentation ranged from 1 hour to 9 days. 7 cases (25%) occurred after 2nd injection, 5 cases (17.9%) occurred after 3rd injection, and 13 cases (46.4%) occurred after fourth or greater injection. 16 of 17 cases (57.1%) reported significant improvement in clinical and laboratory tests within 3 weeks. 2 cases (7.1%) did not mention improvement by 6 months. Case report: symptoms at 12 hours post-injection with significant improvement in acute flare of pain and swelling by week 1. By week 4, complete resolution of acute inflammatory symptoms.

Factors that predict response: NR

Source Citation: Park et al. 2020[18]

Study Design: RCT

Device or Material: Hyaluronic acid injections (HA; not specified) vs. PRP injections

Contact Duration: 6 months

Dose: NR

Frequency/Duration: Single administration

Response: Musculoskeletal pain, Swelling and tenderness of knee joint

Patient characteristics (gender, mean age): 78% female; 62.3 years HA, 60.6 years PRP.

Number per group: 55 each arm, mild-to-moderate knee OA.

Observed adverse effects: No serious AEs were reported, and no significant differences were reported for mild-to-moderate AEs. Musculoskeletal pain (3 HA, 1 PRP), and mild tenderness and mild swelling of knee joint occurred in both arms – see below for timing and N.

Timing of adverse effects: Mild swelling: At 6 weeks: HA: 28 mild, 27 moderate (100%); PRP: 30 mild, 25 moderate (100%)). At 3 months (HA: 28 mild, 19 moderate (85%); PRP: 29 mild, 24 moderate (96%)). At 6 months (HA: 30 mild, 18 moderate (87%); PRP: 28 mild, 22 moderate (91%)). Mild tenderness: Baseline and 6 weeks: 2 HA (baseline and 6 weeks) and 1 PRP (baseline).

Factors that predict response: NR

Source Citation: Raeissadat et al. 2020[19]

Study Design: RCT

Device or Material: Hyalgan® injections (FidiaFarmaceutici S.p.A, Abano Terme, Italy) vs. PRP-derived growth factor (PRGF) injections

Contact Duration: 12 months

Dose: NR

Frequency/Duration: 3 weekly injections of Hyalgan, 2 PRGF injections 3 weeks apart

Response: Heaviness of injection site, Stiffness

Patient characteristics (gender, mean age): 58.63±7.09 HA, 57.08±7.3 PRGF, 71% female.

Number per group: 119 patients (59 HA, 60 PRGF) with mild-to-moderate knee OA (Kellgren and Lawrence grade 2 to 3); at 12 months 52 HA, 50 PRGF.

Observed adverse effects: Minor complications including swelling (0 HA), stiffness, and heaviness of injection site occurred in 3 (5.9%) Hyalgan, 10 (19.6%) PRGF

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Di et al. 2018[4]

Study Design: Systematic review

Device or Material: HA injections (unspecified) vs. PRP (4 frozen, 3 fresh; 4 leukocyte-poor PRP, 3 leukocyte-rich PRP)

Contact Duration: mean 9 months (6 months to 12 months)

Dose: NR

Frequency/Duration: HA (NR), PRP (2 to 4 injections)

Response: Post-injection pain, Swelling

Patient characteristics (gender, mean age): 56% females, 59.8 years

Number per group: 7 RCTs, 908 patients with mild knee OA. Sample size 55 to 183; mean 128.

Observed adverse effects: 2 studies reported no AEs. 1 study reported significantly more post injection pain with PRP (p=0.039). 1 study reported no significant difference in AEs with 92% of AEs in the HA arm not related to treatment. 1 study reported no significant difference in AEs. 16 AEs (8 per arm) were all related to pain associated with infiltration. 1 study reported severe pain and swelling with HA, but significantly more post-injection swelling and pain overall with PRP. 1 study reported no significant differences in infiltration-related AEs which were infrequent, mild and appeared immediately after injection.

Timing of adverse effects: AEs immediately after injection.

Factors that predict response: NR

Source Citation: Li et al. 2018[5]

Study Design: Systematic review

Device or Material: Intra-articular HA (IAHA; unspecified) vs intra-articular oxygen-ozone (manufacturer NR)

Contact Duration: mean 9 months (range 6 to 12 months)

Dose: HA dose: 10 mg/ml x 2.0 ml (3 studies), 10 mg/ml x 2.5 ml (1 study); Ozone dose: 30 ug/ml (3 studies), 35 ug/ml (1 study)

Frequency/Duration: NR

Response: Bleeding, Local skin reaction

Patient characteristics (gender, mean age): 75% female, 60 to 71 years.

Number per group: 4 RCTs (sample size 42 to 141). 298 (151 HA, 147 oxygen-ozone) patients with end-staged knee OA.

Observed adverse effects: Included local skin reaction and bleeding. No significant difference in incidence rate of AEs (risk difference 0.006, 95% CI: -0.047 to 0.058; p=0.837).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Altman et al. 2016[6]

Study Design: Systematic review

Device or Material: IAHA injections of various molecular weights (HMW ≥3000 kDa, MMW <3000 and >1500 kDa, LMW ≤1500 kDa); biological fermentation derived HA (Bio-HA) or avian-derived HA (AD-HA); included Euflexxa, Synvisc, Supartz, Orthovisc, and Durolane

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Effusion after injection, Flare ups

Patient characteristics (gender, mean age): NR

Number per group: 30 RCTs. 11 RCTs (n=2094) addressed HMW. 4 RCTs (n=621) addressed MMW. 15 RCTs (n=2639) addressed LMW. 1776 patients received Bio-HA treatment, while 3070 received AD-HA treatment.

Observed adverse effects: Significantly lower incidence of acute flare ups at the injection site with AD-HA (54 (3.04%) Bio-HA vs. 405 (13.19%); p<0.05). HMW products had the highest rate of injection site flare-ups. Significantly more injection flare ups with HMW vs. MMW (13.73% vs. 3.31%; p<0.001) and HMW vs. LMW (13.73% vs. 10.73%; p<0.001). Significantly more flare ups with LMW vs. MMW (10.73% vs. 3.31%; p=0.007). No significant difference in effusion after injection based on molecular weights (1.9% HMW, 1.7% MMW, 1.8% LMW), but significantly higher incidence of effusion with AD-HA (3.44% AD-HA, 0.54% Bio-HA; p<0.001).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Zhao et al. 2016[7]

Study Design: Systematic review

Device or Material: Hylan G-F 20 (Synvisc, relatively higher molecular weight) vs. LMWHAs (Artzal, Orthovisc, Bio-HA, Hyalgan, Sinovial, Variofil, Hydros)

Contact Duration: mean 26.8 weeks (range 3 to 54 weeks)

Dose: average molecular weight (kd): range 500 to 3600

Frequency/Duration: 1 injection (2 RCTs), 2 injections (1 RCT), and 3 injections (17 RCTs)

Response: Treatment-related adverse events

Patient characteristics (gender, mean age): gender NR, mean 62.8 years.

Number per group: 10 RCTs (n=2616, 2711 knees) were included in the safety analysis. Synvisc: n=1,203 (1,249 knees), LMWHA: n=1,413 (1,462 knees). Knee OA.

Observed adverse effects: No significant difference in patients with TRAEs (14.7% Synvisc vs. 11.6% LMWHA; risk difference 0.02, 95% CI: -0.01 to 0.05; p=0.13) or number of TRAEs (23.2% Synvisc vs. 16.3% LMWHA; risk difference 0.03, 95% CI: -0.01 to 0.07; p=0.14).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Miller et al. 2020[8]

Study Design: Systematic review

Device or Material: IAHA (Synvisc, Hyalgan, Suplasyn, Suvenyl, Durolane) vs. oral NSAIDs (naproxen, diclofenac, loxoprofen, etoricoxib)

Contact Duration: mean 17.8 weeks (range 5 to 26 weeks)

Dose: NR

Frequency/Duration: HA: 1 injection (1 study of Durolane), 3 weekly (3 studies of Synvisc, and Suplasyn), and 5 weekly (2 studies of Hyalgan and Suvenyl); NSAIDS: naproxen 500 mg bid, diclofenac 100 mg qd and 75 mg bid, loxoprofen 60 mg tid, etoricoxib 60 mg qd

Response: Arthralgia, Effusion, Injection site pain

Patient characteristics (gender, mean age): 36% to 72% females; 57 to 69 years.

Number per group: 6 RCTs (sample size 60 to 327 patients). 831 patients with mild-to-moderate knee OA; 414 HA, 417 NSAIDs.

Observed adverse effects: Significantly lower risk of AEs with HA (5 studies, 19.8% vs. 29%; risk ratio 0.74, 95% CI: 0.59 to 0.94; p=0.01. Significantly higher risk of arthralgia (8.1% vs. 2.9%; p=0.001) with HA. No significant difference in risk of serious AE (5 studies, 1.2% vs. 0.9%, RR 1.37, 95% CI: 0.26 to 7.14; p=0.71). Lower leg effusion rarely occurred (1 (0.3%) HA, 2 (0.5%) NSAIDs).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: He et al. 2017[10]

Study Design: Systematic review

Device or Material: IAHA (Hyalgan, Orthovisc, Synvisc, Ostenil, NASHA, Hylastan SGL-80, HYADD 4, sodium hyaluronate, HA) vs. intraarticular corticosteroids (CS; triamcinolone hexacetonide, methylprednisolone acetate, 6-methylprednisolone acetate, triamcinolone acetonide)

Contact Duration: mean 4.8 months (range 1 to 6 months)

Dose: 16 mg (Synvisc, HA), 20 mg (Hyalgan, Ostenil), 25 mg (sodium hyaluronate, 30 mg (Orthovisc), 60 mg (NASHA)

Frequency/Duration: Single injection of NASHA , Synvisc, and HA; 1 or 2 weekly injections of Hyalston; 2 weekly injections of HYADD 4; 3 weekly injections of Orthovisc and Synvisc; 5 weekly injections of Hyalgan, sodium hyaluronate, and Ostenil

Response: Joint stiffness, Joint swelling, Knee pain

Patient characteristics (gender, mean age): 62% females, range 49 to 71 years.

Number per group: 12 RCTs (n=1794), sample size: 41 to 391 patients with knee OA. 971 HA, 823 CS; 6 RCTs (n=1352) reported TRAEs

Observed adverse effects: Significantly more TRAEs with HA (746 events vs. 606 events; risk ratio 1.66, 95% CI: 1.34 to 2.06; p<0.00001) which may have been caused by higher injection frequency of HA.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Bannuru et al. 2014[11]

Study Design: Systematic review

Device or Material: IAHA injections including Synvisc (Genzyme, Ridgefield, NJ), Hyalgan (Fidia Pharmaceutical Corporation, Abano Terme, Italy), Suplaysn (Bioniche Life Sciences Inc., Belleville, Ontario), and Suvenyl (Chugai Pharmaceutical Corp., Tokyo, Japan) vs. NSAIDs including diclofenac, naproxen, loxoprofen

Contact Duration: mean 10.4 weeks (range 4 to 12 weeks)

Dose: HA (NR)

Frequency/Duration: 3 or 5 weekly injections pf IAHA

Response: None reported

Patient characteristics (gender, mean age): females range 36% to 68%, range 61 to 67 years.

Number per group: 5 RCTs (n=712), sample size 51 to 325. Knee OA. 357 HA, 355 NSAID.

Observed adverse effects: 3 SAEs (2 myocardial infarctions, 1 transient ischemic attack) but unrelated to IAHA. 1 SAE (related GI bleed) with NSAIDs

Timing of adverse effects: N/A

Factors that predict response: NR

Source Citation: Ke et al. 2021[20]

Study Design: RCT

Device or Material: Hylan G-F 20 injections (Synvisc, Sanofi) vs. saline injections

Contact Duration: 26 weeks

Dose: 6 ml, 48 mg hylan polymer

Frequency/Duration: Single injection

Response: Arthralgia, Edema, peripheral, Injection-site edema, joint pain, pain, swelling, Joint swelling, peripheral

Patient characteristics (gender, mean age): 78% female, 61.5 years (All East Asian ethnicity)

Number per group: 440 (220 each arm). Mostly mild-to-moderate knee OA.

Observed adverse effects: No difference in treatment-emergent adverse events (TEAEs (61.5% Synvisc, 64.5% placebo). AEs later considered treatment-related were mostly musculoskeletal and connective tissue disorders (e.g., arthralgia, peripheral joint swelling). TEAEs more commonly reported with Synvisc included injection site pain (1 (0.5%) vs. 0), joint swelling (8 (3.7%) vs. 2 (0.9%), injection site edema (1 (0.5%) vs. 0), injection site swelling (1 (0.5%) vs. 0), and edema peripheral (1 (0.5%) vs 0). Arthralgia (7 (3.2%) each arm) and injection site joint pain (1 (0.5%) occurred similarly. Injection site joint swelling only occurred with placebo (1 (0.5%)). No serious TRAEs were reported.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Miller et al. 2019[12]

Study Design: Systematic review

Device or Material: IAHA (Hyalgan, Durolane, Euflexxa, Hya-Ject, Orthovisc, Artzal, Monovisc, Kartilage Cross, Go-On, Suplasyn, NRD101, Gel-One) vs. intraarticular saline injections

Contact Duration: median 6 months (range 5 weeks to 2 years)

Dose: molecular weight (kd) ≥6000 (7 studies), <1500 to <6000 (6 studies), ≤1500 (9 studies)

Frequency/Duration: injections: 1 (7 studies), 3 (13 studies), 4 (3 studies), 5 (11 studies), 11 (1 study)

Response: Arthralgia, Injection site pain, Joint effusion, Joint swelling

Patient characteristics (gender, mean age): female range 22 to 100% overall, age range 53 to 72 overall

Number per group: 35 RCTs (n=8078), sample size <100 per arm (12 studies), ≥100 per arm (13 studies) 4295 IAHA, 3783 saline.

Observed adverse effects: No difference in risk of AEs (42.4% vs. 39.7%; Risk ratio 1.01, 95% CI: 0.96 to 1.07; p=0.61), SAEs (1.8% vs. 1.2%; RR 1.44, 95% CI: 0.91 to 2.26, p=0.12). Significantly more local non-serious AEs with IAHA (14.5% vs. 11.7%; RR 1.21, 95% CI: 1.07 to 1.36; p=0.003). Most common local reactions were injection site pain, arthralgia, joint swelling, and joint effusion which mostly subsided within 2 to 3 days.

Timing of adverse effects: Up to 3 days post-injection for injection site pain, arthralgia, joint swelling, and joint effusion.

Factors that predict response:NR

Source Citation: Honvo et al. 2019[13]

Study Design: Systematic review

Device or Material: Injections of hyaluronic acid, sodium hyaluronate, and Hyalgan vs. intraarticular saline injections

Contact Duration: 25 to 29 weeks (8 RCTs), 52 weeks (1 RCT)

Dose: 20 mg, 25 mg, 60 mg, 1 ml, 2 ml, 30 mg/2 ml

Frequency/Duration: 1 cycle; number of injections per cycle was 1 (1 study), 3 (3 studies), 5 (4 studies), and 11 (1 study)

Response: Treatment-related serious AEs, Treatment-related severe AEs

Patient characteristics (gender, mean age): gender NR, range 62 to 66 years.

Number per group: 9 RCTs (n=1967), 6 RCTs on knee OA, 3 RCTs on ankle OA; for safety analysis. 991 IAHA, 976 saline/placebo.

Observed adverse effects: All TRAEs Significantly increased odds of treatment-related serious AEs with IAHA (80 HA, 42 placebo; OR 1.78, 95% CI: 1.21 to 2.63), but no significant differences in any severe AEs (25 HA, 26 placebo; OR 1.08, 95% CI: 0.50 to 2.31; p=0.270).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Petterson and Plancher 2019[21]

Study Design: RCT

Device or Material: Lightly cross-linked IAHA (Monovisc™) vs. intraarticular saline injections

Contact Duration: 2 to 26 weeks

Dose: 88 mg

Frequency/Duration: Single administration

Response: Arthralgia, Joint stiffness, Joint swelling

Patient characteristics (gender, mean age): 58% female, 59 years.

Number per group: 369 patients (184 Monovisc, 185 saline) with mild-to-moderate knee OA (Kellgren Lawrence grade II and III).

Observed adverse effects: No significant difference in incidence of arthralgia (7 (3.8%) in each arm), joint swelling (2 (1.1%) Monovisc, 1 (0.5%) saline), joint stiffness (1 (0.5%) Monovisc, 2 (1.1%) saline). Device-related AEs occurred in 13 (7.1%) patients with Monovisc, and 10 (5.4%) patients with saline. 24 events (not specified) occurred with Monovisc, and 14 events with placebo.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Hangody et al. 2018[22]

Study Design: RCT

Device or Material: Monovisc (Anika Therapeutics) vs. saline injections

Contact Duration: 26 weeks

Dose: 4 mL, 88 mg HA

Frequency/Duration: Single administration

Response: Arthralgia

Patient characteristics (gender, mean age): 66% female with Monovisc, 74% female with saline; 59.2 years Monovisc, 58.0 saline.

Number per group: 219 (150 Monovisc, 69 saline) patients with Kellgren-Lawrence grade I to III knee OA.

Observed adverse effects: Device-related AEs included arthralgia (2 Monovisc). No serious AEs occurred with Monovisc. 2 SAEs occurred with saline.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Concoff et al. 2017[14]

Study Design: Systematic review

Device or Material: IAHA of various molecular weights (including Durolane, Euflexxa, Orthovisc, Synvisc, Hyalgan, Artzal, Gel-ONE, BioHY, NRD101 HA, Fermathron plus) vs. intraarticular saline injections

Contact Duration: mean 26 weeks (range 4 to 52 weeks)

Dose: 10 mg/2 ml to 30 mg/3 ml

Frequency/Duration: Single injections (4 RCTs, n=1196), 2 to 4 injections (16 RCTs, n=2865), ≥5 injections (11 RCTs, n=1847); 1 study administering 1-11 injections was included in 2 subgroups (2-4, and ≥5)

Response: Treatment-related adverse events (unspecified)

Patient characteristics (gender, mean age): NR

Number per group: 30 RCTs (n=5848).

Observed adverse effects: Significantly more TRAEs with IAHA in studies using ≥5 injections (risk ratio (RR) 1.70, 95% CI: 1.12 to 2.59; p=0.01). No significant difference in TRAEs in studies using single injection IA-HA (RR 1.11, 95% CI: 0.93 to 1.32; p= 0.26), or 2 to 4 injections (RR 0.98, 95% CI: 0.87 to 1.09; p=0.67). No significant difference in number of patients experiencing a TRAE (RR 1.13, 95% CI: 0.95 to 1.35; p=0.16).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: O'Hanlon et al. 2016[15]

Study Design: Systematic review

Device or Material: HA injections (Hyalgan, Adant, Orthovisc, Synvisc, hyaluronic acid, Suplasyn, NRD101, Bio-Hy) vs. placebo injections

Contact Duration: 26 weeks

Dose: 20 mg/2 ml; 2 mL, 15 mg/mL; 2 ml, 20 mg/ml; 0.2 mg/2 ml; 2.5 ml 1% hyaluronan; 2 ml 0.8%; single 6 ml; 16 mg/2ml

Frequency/Duration: 1-10 total treatments, time between treatments: 1 day, 1 to 3 weeks

Response: Arthralgia, Cutaneous vasculitis, Effusion, Knee pain, Knee swelling, Knee tenderness

Patient characteristics (gender, mean age): % female range 46 to 80, age range 39 to 92 years.

Number per group: All Kellgren Lawrence grades included. 8 studies (1056 HA, 1017 placebo) included in meta-analysis on all serious AEs. 10 studies (1645 HA, 1564 placebo) included in meta-analysis on all non-serious AEs.

Observed adverse effects: No significant difference in serious AEs (27 events HA, 16 events placebo; relative risk 1.39, 95% CI: 0.78 to 2.47) or non-serious AEs (415 events HA, 375 events placebo; RR 1.03, 95% CI: 0.93 to 1.15). 1 non-serious local reaction attributed to HA was cutaneous vasculitis in 1 patient. Other non-serious AEs were arthralgia, effusion, transient increase in pain, swelling, and tenderness in treated knee.

Timing of adverse effects: Cutaneous vasculitis during 1st week post HA injection. Responses immediately post-injection were arthralgia, effusion, transient increase in pain, swelling, and tenderness in treated knee.

Factors that predict response: NR

Source Citation: Petrella et al. 2011[23]

Study Design: RCT

Device or Material: HA injections of DMW (combined HA different molecular weights and concentrations), HMW, LMW vs. saline injections

Contact Duration: 104 weeks

Dose: DMW: 0.7 ml of sterile 2.2% LMW (0.58-0.78 x 10^6 Daltons) sodium hyaluronate and 0.7 ml of sterile 1% HMW (1.2-2.0 x 10^6 Daltons) sodium hyaluronate. LMW: sodium hyaluronate of 500-730 kDa, 20 mg/2 mL. HMW: sodium hyaluronate of 6000 kDa, 16 mg/2 mL

Frequency/Duration: Weekly for 3 weeks

Response: Erythema at injection site, Local swelling, Pain, Stiffness in index knee

Patient characteristics (gender, mean age): 47% female, range 68 to 71 years.

Number per group: 200 (50 DMW, 50 HMW, 50 LMW, 50 saline) with K-L grade I to III.

Observed adverse effects: Non-serious AEs associated with the injection procedure included pain and local swelling at injection site (21%), erythema at injection site (12%), and stiffness in the index knee (7%). There were no serious AEs.

Timing of adverse effects: Immediately post-injection all HA injections. 2 reactions at 52 weeks and 1 reaction at 104 weeks with HMW.

Factors that predict response: NR

Source Citation: Chen et al. 2020[24]

Study Design: RCT

Device or Material: Synvisc-One ([HA] Sanofi-Aventis) vs. cooled radiofrequency ablation (CRFA) with COOLIEF ([non-HA] Avanos Medical)

Contact Duration: 6 months

Dose: 6 mL

Frequency/Duration: Single administration

Response: Baker cyst, Pain during and after procedure

Patient characteristics (gender, mean age): Subjects presenting signs and symptoms of knee OA (84% moderate-to-severe OA). Synvisc-One: 54% female, 63.1 years. COOLIEF: 52% female, 63.3 years.

Number per group: Synvisc-One: 88; COOLIEF: 89.

Observed adverse effects: Of 157 events (63 HA, 94 CRFA), 27 events were deemed related to treatment. In the HA group, 9 (14%) events in 9 patients were noted as being related to treatment, versus 18 (19%) events in 13 patients in the CRFA group. Adverse-event profiles were deemed similar. Events occurring with both treatments included: Pain during procedure: Synvisc-One 3 (3%), COOLIEF 3 (3%). Post-procedure pain: Synvisc-One 3 (3%), COOLIEF 7 (8%). AEs only occurring with Synvisc-One: Baker's cyst in 2 (2%) patients, and an unspecified event in 1 patient. AEs only occurring with COOLIEF: numbness (2 (2%)), stiffness/tightness (1 (1%)), bruising/swelling (1 (1%)), skin issue (1 (1%)).

Timing of adverse effects: Recorded at 6-month follow-up.

Factors that predict response: NR

Source Citation: Rezasoltani et al. 2020[25]

Study Design: RCT

Device or Material: Hyalgan ([HA] Fidia Farmaceutici) vs. PT, dextrose prolotherapy, botulinum neurotoxin

Contact Duration: 3 months

Dose: 2 mL

Frequency/Duration: 3 injections, 1 week apart

Response: No device-related responses

Patient characteristics (gender, mean age): Overall: 62.5% females, 67.1 years (range 50 to 83 years). PT: 60% female, 70 years. Botulinum neurotoxin: 73% female, 67.7 years. HA: 53% female, 66.1 years. Dextrose prolotherapy: 63% female, 64.8 years.

Number per group: 28 patients per group (total n = 112). At least moderate knee OA.

Observed adverse effects: After HA or toxin injection, patients remained under observation at the clinic for at least 30 minutes for possible short-term side effects including hypersensitivity and bleeding, none recorded. None of the participants showed or reported serious side effects for the treatments.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Ting et al. 2020[16]

Study Design: Systematic review

Device or Material: HA vs. acupotomy

Contact Duration: 3 to 5 week duration; 3 and 6 months followup

Dose: 2 mL

Frequency/Duration: Single and multiple administration

Response: Redness and swelling after injection

Patient characteristics (gender, mean age): 44% to 72% female, 40 to 78 years.

Number per group: 4 RCTs in meta-analysis. 30 to 50 each arm (total 153 HA, 156 acupotomy).

Observed adverse effects: Four RCTs reported AE incidence at 2.2% for the HA group and 4.3% in the acupotomy group. Results for HA (2 RCTs) included no AEs, and redness and swelling post-injection in 3 patients. Results for acupotomy (2 RCTs) included palpitation, chest tightness, and cold sweat in 4 patients; and pain, bleeding, hematoma, and swelling in 3 patients.

Timing of adverse effects: Pain and swelling shortly after injection.

Factors that predict response: NR

Source Citation: Hermans et al. 2019[26]

Study Design: RCT

Device or Material: HMW-HA (Hylan G-F 20 (Synvisc, Sanofi, S.A. Paris, France) plus usual care (UC) vs. UC

Contact Duration: Up to 52 weeks

Dose: 6000 kDa

Frequency/Duration: 3 weekly injections

Response: Knee flare up, Other AEs unspecified

Patient characteristics (gender, mean age): 50% female, 54 years.

Number per group: 156 patients with mild-to-moderate knee OA. 77 HMW-HA, 79 UC.

Observed adverse effects: 156 TRAEs occurred (77 Synvisc, 79 controls). 6 weeks: total patients experiencing a TRAE was higher with Synvisc (40 (45%) Synvisc, 23 (18%) UC) and due to knee flare up (36% Synvisc, 10% UC), other (11% Synvisc vs. 10% UC); and were GI-related (see systemic responses below).13 weeks: total patients experiencing a TRAE was higher with UC (15% Synvisc, 27% UC) and due to knee flare up (8% Synvisc, 16% UC), other (8% Synvisc, 9% UC); and were GI-related (see systemic responses below). 26 weeks: total patients experiencing a TRAE was similar (16% Synvisc, 15% UC) and due to knee flare up (8% Synvisc, 8% UC), other (5% Synvisc, 7% UC); and were GI-related (see systemic responses below). 39

weeks: total patients experiencing a TRAE was similar (13% Synvisc, 11% UC) and due to knee flare up (8% Synvisc, 7% UC), other (4% Synvisc, 1% UC); and were GI-related (see systemic responses below). 52 weeks: total patients experiencing a TRAE was lower with Synvisc (12% Synvisc, 20% UC) and due to knee flare up (6% Synvisc, 11% UC), other (4% Synvisc, 16% UC); and were GI-related (see systemic responses below).

Timing of adverse effects: At 6, 13, 26, 29, and 52 weeks.

Factors that predict response: NR

Source Citation: Kim et al. 2019[17]

Study Design: Systematic review

Device or Material: HA vs. PDRN injections

Contact Duration: 4 to 12 months

Dose: 2 mL (8 to 30 mg/mL)

Frequency/Duration: 3 to 5 injections, 1 week apart

Response: General AEs

Patient characteristics (gender, mean age): 57.5% female. 60 to 67 years.

Number per group: 5 RCTs. Sample size 14 to 50 (total 290 patients in the meta-analysis, n = 145 each for HA and PDRN groups). Diagnosis NR.

Observed adverse effects: The incidence of attributable AEs was low in the HA and PDRN groups, and the difference in events between the groups was not significant (relative risk 2.15, 95% CI: 0.17 to 26.67; p=0.55).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Saeed et al. 2015[27]

Study Design: RCT

Device or Material: IAHA injection vs. arthroscopic debridement

Contact Duration: 6 months

Dose: NR

Frequency/Duration: Weekly for 5 weeks

Response: Pain at injection site

Patient characteristics (gender, mean age): 83.3% females, range 40 to 60 years (66%), >60 years (34%).

Number per group: 120 (60 each arm) with knee OA K-L grade II and III.

Observed adverse effects: Pain at injection site in 8 (13.4%) patients with IAHA vs. pain and mild effusion in 13 (26%) patients after debridement. No serious AEs were reported.

Timing of adverse effects: Immediately post-injection/postoperative and subsided within 4 to 5 days.

Factors that predict response: NR

Systemic Response/Toxicity

HA intra-articular injections

Source Citation: Carico et al. 2021[2]

Study Design: SR - MAUDE

Device or Material: HA intraarticular injection

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Cellulitis, Death, Paralysis, Septic shock, Septicemia

Patient characteristics (gender, mean age): NR

Number per group: 63 total unique fatalities. Knee viscosupplementation when reported

Observed adverse effects: 8 fatalities possibly related to HA injection. Patient received HA injection, hospitalized with septic shock, developed paralysis, and died after 4 months. Patient developed necrotizing fasciitis after starting chemotherapy and receiving an HA injection. Patient developed septicemia, cause of death unknown. Patient developed cellulitis following HA injection.

Timing of adverse effects: One MAUDE report detailed a patient hospitalized with septic shock who developed paralysis and died after four months. Timing NR for other fatalities associated with systemic adverse events.

Factors that predict response: Patients with risk factors for infections, such as immunocompromised patients

Source Citation: Sedrak et al. 2021[3]

Study Design: SR; Case Report

Device or Material: HA for intraarticular injection (89% receiving Synvisc [HA] Sanofi-Aventis)

Contact Duration: SR: up to 6 months Case report: 4 weeks

Dose: NR

Frequency/Duration: SR: 1 to 4+ administrations; Case report: single administration

Response: Pseudoseptic arthritis presenting with: Elevated CRP above 50, Elevated ESR above 5,000, Elevated PMN above 75% Fever, Leukocytosis above 10,000

Patient characteristics (gender, mean age):

Number per group: 85.2% female, 60.8 years (31-79).

Observed adverse effects: SR (11 studies: 5 single arm studies, 6 case reports), 28 knees (27 patients) with acute pseudoseptic arthritis after HA injection for knee OA. Case report: 1 knee (1 patient). SR: 6 patients (22.2%) were reported to have fevers on presentation with other reported symptoms. 8 of 28 cases reported the results of blood work, with a leukocytosis above 10000 noted in 4 cases (50%), and a white blood cell count above 12,500 in one case (12.5%). Five of seven studies (71.4%) reporting CRP and ESR reported elevated CRP above 50, and 6 of those studies (85.7%) reported having elevated ESR. 10 out of 25 cases (40%) reported leucocyte differentials with elevated PMNs above 75%.

Timing of adverse effects: SR: 22 cases (78.6%) presented within 24 hours of injection; 15 of the 22 cases (68.2%) presented within the first 12 hours. Time from injection to presentation ranged from 1 hour to 9 days. 3 cases (10.7%) occurred after the 1st injection, 7 cases (25%) occurred after 2nd injection, 5 cases (17.9%) occurred after 3rd injection, and 13 cases (46.4%) occurred after fourth or greater injection. Case report: Arthrocentesis revealed cell count of 123,260 and WBC count of 15.5. 8 mL of serosanguinous fluid aspirated at repeat aspiration 20 hours post-injection, with cell count of 175,960.

Factors that predict response: The pathophysiological response for pseudoseptic arthritis has yet to be fully described, though literature suggests that the accumulation of viscous material (e.g., phagocytised HA) may contribute to the adverse event. Significantly more reactions occurred in patients receiving more than a single administration. Time to onset of symptoms is faster than patients with septic arthritis following IA injection (11.9 days versus 72 hours). Composition of HA injected (82.8% of cases) involved Synvisc (including the case report) with literature suggesting these avian-derived HA preparations may have a higher incidence of acute flare-ups and effusions in comparison to biologically fermented preparations.

Source Citation: Park et al. 2020[18]

Study Design: RCT

Device or Material: HA injections (not specified) vs. PRP

Contact Duration: 6 months

Dose: NR

Frequency/Duration: Single administration

Response: Backache, Headache, Nasopharyngitis

Patient characteristics (gender, mean age): 78% female; 62.3 years HA, 60.6 years PRP

Number per group: 55 each arm, mild-to-moderate knee OA

Observed adverse effects: Nasopharyngitis occurred in both arms (2 HA, 1 PRP). 2 AEs only occurred with HA (backache: 2 HA, 0 PRP; headache: 1 HA, 0 PRP).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Di et al. 2018[4]

Study Design: Systematic review

Device or Material: HA injections (unspecified) vs. PRP (4 frozen, 3 fresh; 4 leukocyte-poor PRP, 3 leukocyte-rich PRP)

Contact Duration: up to 52 weeks

Dose: NR

Frequency/Duration: HA (NR), PRP (2 to 4 injections)

Response: None reported

Patient characteristics (gender, mean age): 56% females, 59.8 years

Number per group: 7 RCTs, 908 patients with mild knee OA. Sample size 55 to 183; mean 128.

Observed adverse effects: None reported.

Timing of adverse effects: N/A

Factors that predict response: N/A

Source Citation: Miller et al. 2020[8]

Study Design: Systematic review

Device or Material: Intraarticular HA (Synvisc, Hyalgan, Suplasyn, Suvenyl, Durolane) vs. oral NSAIDs (naproxen, diclofenac, loxoprofen, etoricoxib)

Contact Duration: mean 17.8 weeks (range 5 to 26 weeks)

Dose: NR

Frequency/Duration: HA: single course of 1- (1 study of Durolane), 3- (3 studies including Synvisc, Suplasyn), and 5- (2 studies including Hyalgan and Suvenyl); NSAIDS: naproxen 500 mg bid, diclofenac 100 mg qd and 75 mg bid, loxoprofen 60 mg tid, etoricoxib 60 mg qd

Response: Cardiac-related complications, Headache

Patient characteristics (gender, mean age): 36% to 72% females; 57 to 69 years.

Number per group: 6 RCTs (sample size 60 to 327 patients). 831 patients with mild-to-moderate knee OA; 414 HA, 417 NSAIDs,

Observed adverse effects: Significantly higher risk of headache (8.4% vs. 4.4%; p=0.03) with HA. Rarely occurring AEs were cardiac-related complications (1 (0.3%) HA, 0 NSAID). Drug allergies/intolerance occurred in 4 (1%) NSAID.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Ran et al. 2018[9]

Study Design: Systematic review

Device or Material: Intraarticular HA vs. intra-articular methylprednisolone (MPA)

Contact Duration: mean 30.4 weeks (range 24 to 52 weeks)

Dose: NR

Frequency/Duration: HA: 2 ml once a week for 5 weeks or 3 weeks, single injections of 3 ml or 4 ml, single injection of 4 ml once a week for 2 weeks

Response: Headache, Nausea, Vomiting

Patient characteristics (gender, mean age): range 53% to 66% female; range 49 years to 72 years

Number per group: 5 RCTs (n=1004); sample size: 60 to 433 patients with knee OA.

Observed adverse effects: AEs in 4 RCTs included nausea, vomiting and headache. No significant difference in AE incidence (Risk difference = -0.042, 95% CI: -0.092 to 0.009; p=0.107)

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: He et al. 2017[10]

Study Design: Systematic review

Device or Material: Intraarticular HA (Hyalgan, Orthovisc, Synvisc, Ostenil, NASHA, Hylastan SGL-80, HYADD 4, sodium hyaluronate, hyaluronic acid) vs. intraarticular corticosteroids (CS; triamcinolone hexacetonide, methylprednisolone acetate, 6-methylprednisolone acetate, triamcinolone acetonide)

Contact Duration: mean 4.8 months (range 1 to 6 months)

Dose: 16 mg (Synvisc, hyaluronic acid), 20 mg (Hyalgan, Ostenil), 25 mg (sodium hyaluronate, 30 mg (Orthovisc), 60 mg (NASHA)

Frequency/Duration: Single injection of NASHA , Synvisc, and hyaluronic acid; 1 or 2 weekly injections of Hyalston; 2 weekly injections of HYADD 4; 3 weekly injections of Orthovisc and Synvisc; 5 weekly injections of Hyalgan, sodium hyaluronate, and Ostenil

Response: No treatment-related systemic responses

Patient characteristics (gender, mean age): 62% females, range 49 to 71 years

Number per group: 12 RCTs (n=1794), sample size range 41 to 391. 971 HA, 823 CS; 6 RCTs (n=1352) reported treatment-related AEs.

Observed adverse effects: 3 RCTs reported serious systemic responses in either IAHA or intraarticular CS group, but none were related to treatment or procedure.

Timing of adverse effects: NR

Factors that predict response: NR

HA vs. saline/placebo

Source Citation: Honvo et al. 2019[13]

Study Design: Systematic review

Device or Material: Injections of hyaluronic acid, or sodium hyaluronate, Hyalgan vs. placebo

Contact Duration: 25 to 29 weeks (8 RCTs), 52 weeks (1 RCT)

Dose: 20 mg, 25 mg, 60 mg, 1 ml, 2 ml, 30 mg/2 ml

Frequency/Duration: 1 cycle; number of injections per cycle was 1 (1 study), 3 (3 studies), 5 (4 studies), and 11 (1 study)

Response: System-organ class-related AEs (cardiac, GI, musculoskeletal and connective tissue, nervous system, renal and urinary disorders; respiratory, thoracic and mediastinal; skin and subcutaneous tissue, and vascular)

Patient characteristics (gender, mean age): gender NR, range 62 to 66 years.

Number per group: 9 RCTs (n=1967), 6 RCTs on knee OA, 3 RCTs on ankle OA; for safety analysis. 991 IAHA, 976 saline/placebo.

Observed adverse effects: All treatment-related adverse events No significant differences in any system-organ class(SOC)-related AEs (GI, cardiac, vascular, respiratory, nervous system, skin and subcutaneous tissue disorders, musculoskeletal, renal and urinary disorders, infections and infestations, and hypersensitivity reaction). GI disorders: 69 HA, 83 placebo; OR 0.81, 95% CI: 0.52 to 1.27; p=0.344. Cardiac disorders: 5 HA, 4 placebo; OR 1.25, 95% CI: 0.36 to 4.41; p=0.639. Vascular disorders: 5 HA, 3 placebo; OR 1.70, 95% CI: 0.39 to 7.29; p=0.650. Respiratory, thoracic and mediastinal disorders: 71 HA, 52 placebo; OR 1.21, 95% CI: 0.82 to 1.78; p=0.764. Nervous system disorders: 66 HA, 55 placebo; OR 1.15, 95% CI: 0.77 to 1.70; p=0.79. Skin and subcutaneous tissue disorders: 22 HA, 10 placebo; OR 1.71, 95% CI: 0.52 to 5.63; p=0.173. Musculoskeletal and connective tissue disorders: 145 HA, 149 placebo; OR 0.99, 95% CI: 0.71 to 1.39; p=0.225. Renal and urinary disorders: 6 HA, 12 placebo; OR 0.54, 95% CI: 0.21 to 1.41; p=0.75. Hypersensitivity reaction: 23 HA, 19 placebo; OR 0.64, 95% CI: 0.05 to 7.94; p=0.081.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Hangody et al. 2018[22]

Study Design: RCT

Device or Material: Monovisc (Anika Therapeutics) vs. saline injections

Contact Duration: 26 weeks

Dose: 4 mL, 88 mg HA

Frequency/Duration: Single administration

Response: Rash

Patient characteristics (gender, mean age): 66% female with Monovisc, 74% female with saline; 59.2 years Synvisc, 58.0 saline.

Number per group: 219 (150 Monovisc, 69 saline) patients with Kellgren-Lawrence grade I to III knee OA.

Observed adverse effects: Device-related AEs included rash (1 Monovisc).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: O'Hanlon et al. 2016[15]

Study Design: Systematic review

Device or Material: HA injections (Hyalgan, Adant, Orthovisc, Synvisc, hyaluronic acid, Suplasyn, NRD101, Bio-Hy) vs. Placebo

Contact Duration: 26 weeks

Dose: 20 mg/2 ml; 2 mL, 15 mg/mL; 2 ml, 20 mg/ml; 0.2 mg/2 ml; 2.5 ml 1% hyaluronan; 2 ml 0.8%; single 6 ml; 16 mg/2ml

Frequency/Duration: 1-10 total treatments, time between treatments: 1 day, 1 to 3 weeks

Response: Skin reaction

Patient characteristics (gender, mean age): % female range 46 to 80, age range 39 to 92 years

Number per group: Kellgren Lawrence all grades included. 8 studies (1056 HA, 1017 placebo) included in metaanalysis on all serious AEs.

Observed adverse effects: 1 serious AE attributed to HA was skin reaction characterized by peeling of skin on hands and toes occurring in 1 patient.

Timing of adverse effects: Skin reaction occurred 8 days post HA injection.

Factors that predict response: NR

HA vs. miscellaneous treatments

Source Citation: Hermans et al. 2019[26]

Study Design: RCT

Device or Material: HMW-HA (Hylan G-F 20 (Synvisc, Sanofi, S.A. Paris, France) plus usual care (UC) vs. UC

Contact Duration: Up to 52 weeks

Dose: 6000 kDa

Frequency/Duration: 3 weekly injections

Response: GI complaints

Patient characteristics (gender, mean age): 50% female, 54 years.

Number per group: 156 patients with mild-to-moderate knee OA. 77 HMW-HA, 79 UC.

Observed adverse effects: Systemic TRAEs included GI complaints. 6 weeks: 7% Synvisc, 6% UC, 13 weeks: 3% Synvisc, 12% UC, 26 weeks: 5% Synvisc, 3% UC , 39 weeks: 5% Synvisc, 4% UC, 52 weeks: 4% Synvisc, 3% UC

Timing of adverse effects: At 6, 13, 26, 29, and 52 weeks.

Factors that predict response: NR

AE: adverse event; bid: twice a day; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; HA: hyaluronic acid: HMW: high molecular weight; IA: intraarticular; IAHA: intraarticular hyaluronic acid; kd: kilodalton; kDa: kilodalton; K-L: Kellgren and Lawrence; LMW: low molecular weight; LMWHAs: low molecular weight hyaluronic acids; MAUDE: manufacturer and user facility device experience FDA database; ml: milliliter; MMW: medium molecular weight; NR: not reported; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; qd: 4 times a day; tid: 3 times a day; PDRN: polydeoxyribonucleotide; PMN: polymorphonuclear leukocytes; RCT: randomized controlled trial; SR: systematic review; TRAE: treatment-related adverse events; WBC: white blood cell.

Table 15: Viscosupplementation – hip: Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Liao et al. 2019[28]

Study Design: Systematic review of 5 RCTs comparing HA to placebo

Device or Material: HA solution (Durolane, hylan G-F 20, Hyalubrix, Hyalgan, Adant)

Contact Duration: Final follow-up at 56 to 182 days post-procedure

Dose: HA: 2.5 ml, 3 ml, 6 ml (2 studies), 8 ml

Frequency/Duration: 1 to 3 injections

Response: Hematoma, Pain flare, Pruritus

Patient characteristics (gender, mean age): 67% female. Mean age 60 to 70. Characteristics not reported by treatment group.

Number per group: HA (n = 298); placebo (n = 293). Note: 39% of the patients in this SR were in studies that are also included in [31].

Observed adverse effects: Hematoma: 1 (HA), 0 (placebo). Pain flare: 7% (HA), 2.4% (placebo). Pruritus: 1 (HA), 0 (placebo). Statistical tests of between-group differences in AEs were not performed.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Leite et al. 2018[29]

Study Design: Systematic review of 9 RCTs comparing HA to placebo or other intra-articular treatments

Device or Material: HA solution (Durolane, Hyalubrix, Synvisc-One, Hyalgan, Adant, Hylan G-F 20), corticosteroid, PRP, mepivacaine, placebo

Contact Duration: 2 to 12 months

Dose: HA: 2 to 8 ml

Frequency/Duration: 1 to 3 injections

Response: Overall AEs

Patient characteristics (gender, mean age): Gender of patients was available for 8 of the 9 studies (508/885 = 57% female). Mean age was given in 8 of the 9 studies (overall mean 60.9 years).

Number per group: HA (n = 558), CS (n = 201), PRP (n = 115), mepivacaine (n = 20), placebo (n = 270). Note: 1 study (n = 357) is also in Liao et al., 1 study (n = 312) is also in Wu et al., 4 studies (n = 284) are also in both, and 3 studies (n = 223) are also in Ye et al.

Observed adverse effects: HA: 29.0% overall AE rate across 9 studies (range: 0% to 49.7%). Placebo: 23.7% rate across 4 studies (range: 0% to 34.9%). PRP: 8.7% rate across 3 studies (range: 0% to 20%). Corticosteroid: 38.3% rate across 3 studies (range: 0% to 48.7%). Mepivacaine: 5% in 1 study. Meta-analysis of overall AEs was performed for comparisons of HA with placebo and methylprednisolone; no statistically significant differences were found.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Ye et al. 2018[30]

Study Design: Systematic review of 4 RCTs comparing HA to PRP

Device or Material: HA solution, PRP (products not specified)

Contact Duration: 12 months

Dose: HA: 1 ml – 2 ml

Frequency/Duration: NR

Response: Nausea, Post-injective pain

Patient characteristics (gender, mean age): In 3 studies reporting: HA 50.0% female; PRP 56.5% female; combined 53.4% female. Mean age: HA, 59.8; PRP, 59.0; combined, 59.4.

Number per group: HA (n = 148), PRP (n = 155).

Observed adverse effects: Nausea: RR = 1.15, 95% CI: 0.34 to 3.93. One included study reported significantly higher post-injective pain for PRP than for HA (p = 0.043).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Wu et al. 2017[31]

Study Design: Systematic review of 6 RCTs comparing HA to placebo and conservative treatment (Depomedrol)

Device or Material: HA solution (hylan G-F 20, Hyalubrix, Ostenil, Durolane, Adant, Hyalgan)

Contact Duration: Final follow-up at 56 to 180 days post-procedure

Dose: HA: 2 ml (2 studies), 2.5 ml, 3 ml, 6 ml, 8 ml

Frequency/Duration: 1 to 3 injections

Response: Overall AEs

Patient characteristics (gender, mean age): Gender NR. Mean age 59.5-70 years. Characteristics not reported for treatment group.

Number per group: HA (n=291); placebo (n=114); Depomedrol (n=207). Note: 44% of the patients in this SR were in studies that are also included in Liao et al. 2019[28].

Observed adverse effects: No significant differences between HA and "control group" (placebo and conservative treatment combined) in overall AEs ("including transient post injection pain, superficial infection and hematoma"); RR 0.94; 95% CI 0.41 to 2.20; p > 0.05.

Timing of adverse effects: NR

Factors that predict response: NR

AE: adverse event; CS: corticosteroid; HA: hyaluronic acid; ml: milliliter; NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; SR: systematic review

Table 16: Viscosupplementation – hand and ankle: Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Boffa et al. 2021[32]

Study Design: Systematic review of 24 studies of intra-articular injective treatments for ankle lesions. 18 studies included HA.

Device or Material: HA solution (Euflexxa, Durolane, Suplasyn, Hanox-M-XL, Hyalgan, Synvisc, Supartz, Orthovisc, Adant, sodium hyaluronate), PRP, corticosteroid, botulinum toxin type A, prolotherapy, mesenchymal stem cells, placebo/saline

Contact Duration: Final follow-up at 1 to 45.5 months

Dose: HA: 1 ml to 12.5 ml

Frequency/Duration: 1 to 5 injections

Response: Enlarged lymph nodes, Pain, Pseudogout, Swelling

Patient characteristics (gender, mean age): 55% male. Mean age 35.5 to 63.9 years.

Number per group: HA (n=581), PRP (n=83), corticosteroid (n=48), botulinum toxin type A (n=38), prolotherapy (n=27), exercise therapy (n=15), mesenchymal stem cells (n=6), saline (n=46). Of the 24 studies, 8 were RCTs, 1 was a nonrandomized comparative study, and 15 were single-arm studies.

Observed adverse effects: One patient each in the HA group reported enlarged lymph node in ipsilateral groin, osteochondritis dissecans (not considered treatment-related), and pseudogout. "In some cases, pain and swelling were reported at the injection site soon after the injection."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kroon et al. 2016[33]

Study Design: Systematic review of 13 RCTs and "quasi-RCTs" of intra-articular therapies for hand OA. 9 studies included HA.

Device or Material: HA solution (hylan G-F 20, sodium hyaluronate), corticosteroid, dextrose, infliximab, placebo (saline, lidocaine, bupivacaine)

Contact Duration: 24 weeks

Dose: HA: 1 ml – 3 ml

Frequency/Duration: HA: 1-3 injections

Response: Overall AEs

Patient characteristics (gender, mean age): 87% female. Mean age 62.8 years.

Number per group: HA (n=360), corticosteroid (n=280), dextrose (n=30), infliximab (n=10), placebo (n=172). Note: Two studies (one comparing HA with placebo, one comparing infliximab with placebo) were within-subject. Each patient in those 2 studies (33 HA/placebo, 10 infliximab/placebo) is counted as being in both groups in the numbers given here.

Observed adverse effects: Of the nine studies including HA, one did not report numbers of patients experiencing AEs. In the 8 remaining studies, AE rates were as follows: HA, 11.5%; corticosteroid, 9.0%; placebo, 2.7%. Numbers of patients with specific types of AE were not reported, either overall or by group; AEs were described as minor, and included surgeries unrelated to study medication, pain and local swelling, skin and nail abnormalities, heat and/or redness, and unspecified "local AEs."

Timing of adverse effects: NR

Factors that predict response: NR

AE: adverse event; HA: hyaluronic acid; ml: milliliter; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma: RCT: randomized controlled trial

Table 17: Viscosupplementation – shoulder: Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Zhang et al. 2019[34]

Study Design: Systematic review of 15 studies

Device or Material: HA (Orthovisc, sodium hyaluronate, Hylan G-F 20, Euflexxa) vs anesthetic + corticosteroid, 6-methylprednisolone, or phosphate-buffered saline. HA dose vs HA dose. 7 studies had no control.

Contact Duration: 12 weeks to 3 years

Dose: 2 mL to 8 mL

Frequency/Duration: Single injection to five weekly injections

Response: Abscess, Musculoskeletal pain, Pain at injection site

Patient characteristics (gender, mean age): Gender NR in 5 studies, range 50.5% to 76% male per arm in 10 studies; all patients older than 18 years.

Number per group: 15 studies (5 RCTs, 10 single arm), sample size for HA: range 15 to 265.

Observed adverse effects: Thirteen studies recorded adverse events after intra-articular administration of HA and found a pooled adverse event rate of 33.92% (406 of 1197) and a serious adverse event rate of 5.35% (64 of 1197). Almost all of these events were deemed by the study investigators to not be product-related. Common AEs from IAHA were musculoskeletal pain, and pain at injection site. Serious AEs such as severe musculoskeletal pain and abscess were also reported. Similar findings were present in control groups receiving intra-articular injection of corticosteroids or phosphate-buffered saline, with a reported pooled adverse event rate of 48.88% (240 of 491) and a serious adverse event rate of 2.24% (11 of 491).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Lee et al. 2015[35]

Study Design: Systematic review of 4 RCTs

Device or Material: HA vs intraarticular corticosteroid injection or physical therapy

Contact Duration: 2 weeks to 6 months

Dose: 20 to 30 mg

Frequency/Duration: Weekly for 2-3 weeks (2 studies), every 2 weeks for 6 weeks (1 study); 15-day intervals for the first month, then monthly for 6 months (1 study); total injections 2 to 8

Response: Pain

Patient characteristics (gender, mean age): 69% female; 54.5 to 64.2 years.

Number per group: NR

Observed adverse effects: Rovetta and Monteforte reported no major adverse events and adverse event data could not be obtained for 2 other included trials (Callis et al., Hsieh et al). Park et al. reported that 12 out of 45 participants undergoing capsular distension combined with intra-articular HA injection experienced pain during the procedure, and the pain may be a result of the capsular distension procedure, the intra-articular HA injection, or both.

Timing of adverse effects: Intra-procedural.

Factors that predict response: NR

Systemic Response/Toxicity

Source Citation: Zhang et al. 2019[34]

Study Design: Systematic review of 15 studies

Device or Material: HA (Orthovisc, sodium hyaluronate, Hylan G-F 20, Euflexxa) vs anesthetic + corticosteroid, 6-methylprednisolone, or phosphate-buffered saline. HA dose vs HA dose. 7 studies had no control.

Contact Duration: 12 weeks to 3 years

Dose: 2 mL to 8 mL

Frequency/Duration: Single injection to five weekly injections

Response: Cancer, Chest pain, Diarrhea, Flu symptoms, Headache

Patient characteristics (gender, mean age): Gender NR in 5 studies, range 50.5% to 76% male per arm in 10 studies; all patients older than 18 years.

Number per group: 15 studies (5 RCTs, 10 single arm), sample size for HA: range 15 to 265.

Observed adverse effects: Diarrhea, flu symptoms, and headache were commonly reported (data not provided). Serious AEs such as chest pain and cancer were also reported (data not provided).

Timing of adverse effects: NR

Factors that predict response: NR

HA: hyaluronic acid; IAHA: intraarticular hyaluronic acid; ml: milliliter

Table 18: Viscosupplementation – temporomandibular joint disorders: Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Liu et al. 2019[36]

Study Design: Systematic review

Device or Material: Hyaluronate vs. corticosteroid or placebo

Contact Duration: 1 week to 8 years

Dose: 0.5 to 1 mL

Frequency/Duration: Single administration

Response: Ear pressure, Pain after injection

Patient characteristics (gender, mean age): 50% to 88% female, 25.6 to 50.1 years.

Number per group: 14 to 102. 8 studies included.

Observed adverse effects: No relevant difference between CS and HA groups in the occurrence of adverse events. In three studies reporting adverse events, 4 (20%), 13 (37%), and 0% of patients receiving HA injection reported TMJ pain after injection, compared to 0%, 14 (50%), and 28 (70%) patients receiving CS injection

– odds ratio 2.98, 95% CI: 0.08 to 111.17; p=0.55. Ear pressure (reported in Bjornland et al. 2007): 1 (5%) HA; 2 (10%) CS – odds ratio 2.11, 95% CI: 0.18 to 25.35; p=0.56.

Timing of adverse effects: Ear pressure reported at 2 week follow up.

Factors that predict response: NR

Source Citation: Haigler et al. 2018[37]

Study Design: Systematic review

Device or Material: HA vs. PRP or PRGF injection

Contact Duration: 12 months

Dose: 1 mL to 5mL

Frequency/Duration: Single administration; 1x/week for 3 consecutive weeks

Response: Discomfort post-op, Pain at injection site

Patient characteristics (gender, mean age): 56%-96% female; 28.1 to 38.2 years

Number per group: 13 to 50. 3 relevant RCTs.

Observed adverse effects: One of three relevant studies (an RCT) reviewed reported adverse events. Pain during injection: 15 (60%) HA, 22 (88%) PRP or PRGF. Post-operative discomfort: 2 (8%) HA, 19 (76%) PRP or PRGF

Timing of adverse effects: Post-injection; Immediate post-op

Factors that predict response: NR

Source Citation: Liu et al. 2019[36]

Study Design: Systematic review

Device or Material: Hyaluronate vs. corticosteroid or placebo

Contact Duration: 1 week to 8 years

Dose: 0.5 to 1 mL

Frequency/Duration: Single administration

Response: Chills

Patient characteristics (gender, mean age): 50% to 88% female, 25.6 to 50.1 years.

Number per group: 14 to 102. 8 studies included.

Observed adverse effects: No relevant difference between CS and HA groups in the occurrence of adverse events. Slight chill (reported in Shi et al. 2002): 2 (5.7%) HA; 0% CS – odds ratio 0.24, 95% CI: 0.01 to 5.90; p=0.36. General rash (reported in Bjornland et al. 2007): 0% HA; 2 (10%) CS – odds ratio 5.54, 95% CI: 0.25 to 123.08; p=0.28.

Timing of adverse effects: 1 week (sourced in abstract of Shi et al. 2002).

Factors that predict response: NR

CS: corticosteroid; HA: hyaluronic acid; mL: milliliter; NR: not reported; PRP: platelet-rich plasma; PRPG: platelet-rich growth factor; TMJ: temporomandibular joint

Table 19: Scaffold - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Glasbrenner et al. 2020[38]

Study Design: RCT

Device or Material: Polyglycolic acid and hyaluronan matrix-augmented bone marrow stimulation (m-BMS; Chondrotissue [BioTissue AG]) after microfracture (MF) vs. MF

Contact Duration: 108 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Infected hematoma, Mild swelling

Patient characteristics (gender, mean age): 37.5% female, 46.0 years m-BMS, 40.5 years MF.

Number per group: 12 each arm, grade III/IV International Cartilage Repair Society (ICRS) cartilage degradation.

Observed adverse effects: Infected hematoma in 1 patient and mild swelling in 3 patients in m-BMS group. There was only 1 severe effusion after 6 weeks in the MF group. Moderate or severe allergic reactions were not observed in either group.

Timing of adverse effects: Infected hematoma: NR; mild swelling 2 weeks after surgery in m-BMS group, resolved after 6 weeks.

Factors that predict response: NR

Source Citation: Sofu et al. 2019[39]

Study Design: Nonrandomized comparative

Device or Material: HA-based cell-free scaffold (Hyalofast®, Anika Therapeutics Inc.) vs. chitosan-glycerol phosphate/blood implant (BST-CarGel®, Piramal Life Sciences)

Contact Duration: Mean: 24.4±5 months

Dose: NR

Frequency/Duration: Single administration

Response: Cyst formation, Early degenerative changes, Edema, Persistent pain

Patient characteristics (gender, mean age): 52% female; 39±10 years Hyalofast, 42±11 years BST-CarGel.

Number per group: Hyalofast, n=21, BST-CarGel, n=25; focal osteochondral lesion of the knee joint (Outerbridge grade III or IV). Both groups underwent MF.

Observed adverse effects: Edema or cyst formation in the subchondral bone was detected in 8 (38%) knees with Hyalofast and 10 (40%) knees with BST-CarGel. One patient in both groups had persistent pain as well as early degenerative changes of the knee joint and planned to undergo replacement surgery at the latest follow-up. Deep venous thrombosis, septic arthritis, neurovascular complication, or intra-articular adhesion was not detected in any patient.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Sofu et al. 2017[40]

Study Design: Nonrandomized comparative

Device or Material: HA based cell-free scaffold (Hyalofast, Hyalofast; Anika Therapeutics) + MF vs MF

Contact Duration: Mean 25.7 ± 2.5 months

Dose: NR

Frequency/Duration: Single administration

Response: Early degenerative changes, Persistent pain

Patient characteristics (gender, mean age): 62.8% female; 40 ± 9.8 years HA scaffold, 43 ± 6.8 years MF.

Number per group: HA scaffold=19, MF=24; focal osteochondral lesion of the knee joint.

Observed adverse effects: One patient from group 1 (HA scaffold) and 2 patients from group 2 (MF) had persistent pain as well as early degenerative changes of the knee joint.

Timing of adverse effects: NR

Factors that predict response: NR

HA: hyaluronic acid; NR: not reported; RCT: randomized controlled trial

Appendix D2. Evidence Tables – Dermal, Facial and Eye Applications

Table 20: Dermal Fillers - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Gorbea et al. 2021[41]

Study Design: Systematic Review

Device or Material: HA fillers included Restylane (Galderma Laboratories, Lausanne, Switzerland), Teosyal Pure (Teoxane Laboratories, Geneva, Switzerland), and Juvederm Ultra XC (Allergan, Dublin, Ireland); and Juvederm Voluma XC, Perlane, Belotero Balance, Redensity II Eyes, unspecified CL-HA, Uma Jeunesse, Matrifill, and Juvederm Volbella (manufacturers NR) vs. calcium hydroxyapatite (CaHa), autologous fibroblast and keratin gel (AFKG), and collagen-based fillers

Contact Duration: 1 month, and >6 months

Dose: Volume per tear trough: ranged from 0.2 to 0.58 mL, Average Volume HA per patient was 1.16mL

Frequency/Duration: Single administration

Response: Discomfort, Ecchymosis, Edema, Erythema, Fluid collection, Infection, , Itching, Lumpiness, Migraine, Migration, Tyndall effect

Patient characteristics (gender, mean age): 28 studies; 1956 patients; 1535 (78.5%) of the patients were injected with hyaluronic acid filler; patient ages ranged from 18 to 89 years with a mean of 44.9 years; large female majority (1456/1956, 74.4%)

Number per group: 1535 HA (839 Restylane, 151 Teosyal Pure, 150 Juvederm Ultra XC, 101 Juvederm Voluma XC, 100 Perlane, 52 Belotero Balance, 52 Redensity II Eyes, 40 unspecified CL-HA, 22 Uma Jeunesse, 18 Matrifill, 10 Juvederm Volbella), 376 CaHa, 35 AFKG, and 10 collagen-based

Observed adverse effects: For HA: Ecchymosis 125 (14.01); Erythema 33 (2.15); Edema 172 (11.21); Lumpiness 127 (8.27); Tyndall effect 88 (5.41); Product migration 30 (1.95); Hyaluronidase 77 (5.02); Infection 2 (0.13); Fluid collection 18 (1.17); Itching 5 (0.33); Migraine 1 (0.07); Discomfort 16 (1.04) Overall complication rates were significantly different between HA and non-HA fillers ($p < 0.0001$), but the clinical significance is unclear: HA: 50.75%; CaHa, 19.95%; AFKG, 11.43%; and collagen-based filler, 90%. Prolonged edema was more likely to occur among patients receiving HA injections than in patients injected with the other materials ($P < 0.00001$). The Tyndall effect and lumpiness were only reported in the HA group. Thirty of 31 patients who were noted to have product migration were in the HA group. However, the number of patients who received AFKG or collagen-based filler was very low, so for these fillers some complications may not have been captured simply due to the low patient numbers.

Timing of adverse effects: NR

Factors that predict response: Patients on whom cannulas were used were less likely to develop ecchymosis; use of sharp needle tips may result in more traumatic injury to the orbicularis, regional vasculature, and lymphatic structures.

Source Citation: Kumar et al. 2021[42]

Study Design: Systematic Review

Device or Material: HA fillers included Teosyal® PureSense Ultra Deep (Teoxane Lab, Switzerland), Juvéderm VOLUMA (Allergan plc, Dublin, Ireland), YVOIRE volume plus (LG Life Sciences, Seoul, Korea), VYC−20 or VYC−17.5 from the Vycross range of HA-based products (Allergan, Dublin, Ireland), and 1 of 5 brands of HA fillers used in some studies – Allergan, Dublin, Ireland; NyumaPharma, Arona, Italy; Merz Aesthetics, Raleigh, NC; Neauvia, Lugano, Switzerland; and Teoxane, Geneva, Switzerland

Contact Duration: NR

Dose: Different formulations of hyaluronic acid filler were used among the studies with a volume of injection ranging from 0.1 to 1.5 ml

Frequency/Duration: Single administration

Response: Bruising, Erythema, Hematoma, Post-injection pain, Transient edema, Vascular impairments

Patient characteristics (gender, mean age): 11 studies; 1101 patients; majority female; ranging from 18 to 68 years of age

Number per group: Ranged from 29 patients to 280 patients across 11 studies

Observed adverse effects: Transient edema and erythema, post-injection pain, and bruising were some temporary complications. Rare complications that were reported were vascular impairments and hematoma

Timing of adverse effects: Varied by study

Factors that predict response: Different formulations of HA filler were used among the studies with a volume of injection ranging from 0.1 to 1.5 ml. Various techniques were used for the purpose of injection.

Source Citation: Stefura et al. 2021[43]

Study Design: Systematic Review

Device or Material: HA fillers included Aesthefill, Belotero Basic/Balance, BioHyalux, biphasic HA filler (NASHA), Captique, CPMHA, Dermalax implant plus, Dermicol-P35, DGE, DHF-001, Elravie, Emervel Classic, HA (Titan) + Infrared, HA-biphasic, HA-G-monophasic, HA-monophasic, HA-P-biphasic, Hylaform/Hyalform Plus, hylan B plus, Juvederm 30/Ultra 3/Ultra Plus, Ultra, Koken, Matrifill, Neuramis, Perlane PER, Perlane-L, Perlane—LGP, PP-501-A/B, Prevelle SILK, Puragen, Restylane, Restylane Defyne, Restylane Refyne, Restylane Sub-Q, Revanesse Versa, Teosyal, Terafill, Uma Jeunesse Classic, Uma Jeunesse Ultra, Uma Jeunesse, VYC-17.5L (HA+lidocaine), Zyplast versus Ial System Duo, polycaprolactone (PCL), porcine collagen, bovine collagen, CaHA (Radiesse) + lidocaine, CaHA (Radiesse), human-based collagen (Cosmoplast)

Contact Duration: Up to 1 year

Dose: Mean injected volume varied by study from a low of 0.62 mL to a high of 2.4 mL

Frequency/Duration: Single administration

Response: Redness, Bruising, Swelling, Pruritus, Skin induration, Tenderness, Skin discoloration, Pain, Nodulus, Hematoma, Infection, Vascular adverse events, Migration, Numbness, Lumpiness

Patient characteristics (gender, mean age): 51 studies with a total of 4,097 patients in multiple countries; 35 studies including 3388 patients were conducted in multiple centers, and 16 single-center studies including 709 patients. The quality of the analyzed studies, according to the Cochrane RoB tool, is low. All studies evaluated dermal filler injections in nasolabial folds. Mean age range 40 to 56 years.

Number per group: HA fillers (n=3623), non-HA fillers (n=474)

Observed adverse effects: Redness, bruising, swelling, pruritus, skin induration, tenderness, skin discoloration, pain, nodulus, hematoma, infection, vascular adverse events, migration, numbness, and lumpiness. Most

common events included lumpiness, tenderness, swelling and bruising. Overall complication rates were 0.59 (95% CI: 0.46–0.72) for all HA fillers, 0.59 (95% CI: 0.36–0.8) for monophasic HA fillers, 0.6 (95% CI: 0.43–0.76) for biphasic HA fillers. For non-HA fillers, complication rates were 0.4 (95% CI: 0.12–0.7) for all Collagen fillers, 0.82 (95% CI: 0.69–0.93) for Mesoglow, and 0.88 (95% CI: 0.72–0.99) for IAL-systems.

Timing of adverse effects: Up to 1 year

Factors that predict response: Variation in injection techniques including injected volume, HA concentration, depth of injection, needle, eventual touch-up injections and the method of injection; Risk of vascular occlusion seems higher in patients with history of cosmetic rhinoplasty; Vascular adverse events associated with potential skin necrosis can occur.

Source Citation: Chung et al. 2020[44]

Study Design: Systematic Review

Device or Material: HA dermal fillers included Restylane (Q-Med AB, Galderma, Uppsala, Sweden), Juvederm (Allergen, Irvine, CA) and Belotero (Merz, Greensboro, NC)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Delayed inflammatory response, Delayed-type hypersensitivity (DTH)

Patient characteristics (gender, mean age): 35 prospective studies (4043 patients); 2 prospective studies with histological examinations (438 patients); 7 retrospective studies (size of population ranged from 320 to 406,000); 15 case studies (20 patients)

Number per group: Restylane (26 articles), Juvéderm (12 articles), and Belotero (1 article)

Observed adverse effects: Delayed inflammatory response; DTH. The incidence of delayed inflammatory reactions calculated from the prospective studies was 1.1% per year, and that of possible DTH reaction was 0.06% per year. Most retrospective studies estimated a percentage of delayed inflammatory reactions of less than 1% in 1 to 5.5 years. The incidence of DTH reaction would be lower than that. Among all the DTH cases reported, only about 5% of them were proven to be genuine DTH reactions.

Timing of adverse effects: NR

Factors that predict response: Previous adverse reactions to HA implants; Pretreatment skin tests are useful for preventing potential DTH reaction; adverse events after the injection of non-FDA-approved fillers may be higher than those seen after utilizing the FDA-approved products.

Source Citation: Kapoor et al. 2020[45]

Study Design: Systematic review

Device or Material: HA dermal fillers included Bellast, Belotero, Hyacorp Modelis, Restylane

Contact Duration: NR

Dose: Data show that in a vast majority of cases (n = 17/19; 89.5%), the volume of HA filler used was less than or equal to 2.0 ml

Frequency/Duration: Single administration

Response: Vision loss, CNS involvement, Ptosis, Ophthalmoplegia, Exotropia

Patient characteristics (gender, mean age): 26 articles reporting 44 cases of vision loss; female (n=40; 90.9%); male (n=4; 9.1%); age range 20-61 years

Number per group: 44

Observed adverse effects: Partial and complete loss of vision; periocular changes including ptosis, ophthalmoplegia and exotropia; 8/44 patients had CNS involvement in the form of brain infarcts or hemorrhage.

Timing of adverse effects: Vision loss symptoms were almost always immediate; CNS involvement was 7 and 9 hours after injection

Factors that predict response: Nose, glabella, and forehead were the common dangerous areas for injections; HA filler volumes as low as 0.2 ml can cause permanent, complete vision loss; 'Partial' vision loss after HA filler was found to have a better prognosis than the 'complete' vision loss. Branch retinal artery occlusion was found to be the most favorable pattern for better prognosis after HA filler-related vision loss, while central retinal artery occlusion and ophthalmic artery occlusion patterns were associated with the poorest prognosis.

Source Citation: Stojanovi et al. 2019[46]

Study Design: Systematic review

Device or Material: HA dermal fillers included Belotero, Emervel, Hyamax Kiss, Juvederm Ultra, Juvederm Ultra Plus, Juvederm Volbella, Perfectha Derm, Perlane, Restylane, Restylane Kysse

Contact Duration: 1 month to 6 years

Dose: NR

Frequency/Duration: Single administration

Response: Bruising, Contusion, Itching, Pain, Redness, Swelling

Patient characteristics (gender, mean age): 22 studies of 3965 subjects; average age between 40 and 55 years; majority of patients were women. All received HA fillers to enhance lip fullness.

Number per group: Sample size ranged from 10 to 400 patients.

Observed adverse effects: Local reactions at the injection sites (swelling, contusion, bruising, pain, redness, and itching); serious AEs are uncommon. Most resolved in less than 60 days (majority in 2 weeks)

Timing of adverse effects: NR

Factors that predict response: Number and volume of HA-based gel injections, the nature of the product injected as well as possible individual factors

Source Citation: Beer et al. 2021[47]

Study Design: Multicenter RCT

Device or Material: HA injectable filler, VYC-20L (Juvederm Voluma XC)

Contact Duration: Visits occurred at months 1, 3, 6, 9, and 12 after the last treatment

Dose: Median total initial injection volume was 2.2 mL (range, 0.7–4.0 mL) for the treatment group (initial treatment and touch-up combined) and 2.8 mL (range, 1.3–4.0 mL) for the treated control group (initial treatment and touch-up combined) Median total injection volume for repeat treatment was 1.2 mL (range, 0.2–4.0 mL)

Frequency/Duration: 1 or 2 injections

Response: Injection site abscess, Gingival pain, Cystic acne, injection site cellulitis, injection site inflammation, injection site induration

Patient characteristics (gender, mean age): Enrolled participants desired chin augmentation. The majority were women (88.5%) and White (81.8%), with a median age at study entry of 52 years (range, 22–80) and mean body mass index of 25.0 kg/m^2. Fitzpatrick skin types were I/II (34.9%), III/IV (52.1%), and V/VI (13.0%).

Number per group: 192 participants were randomized resulting in 144 in the treatment group and 48 in the control group (which received HA injection 6 months after the treatment group).

Observed adverse effects: Common treatment-related AEs included injection site abscess, gingival pain, cystic acne, injection site cellulitis, and injection site inflammation. For initial/touch-up treatment, 14 treated participants (7.7%) had 20 treatment-related AEs while 3 (4.1%) had 7 treatment-related AEs after repeat treatment. Most treatment-related AEs were mild or moderate in severity. For initial/touch-up treatment, 2.7% (5/182) of participants had mild treatment-related AEs and 4.4% (8/182) had moderate AEs. For repeat treatment, 4.1% (3/74) of participants had mild and 1.4% (1/74) moderate AEs. Two participants (1.1%) had 3 severe treatment-related AEs, including injection site inflammation and cellulitis in one participant and injection site induration in another participant. Overall, 167 treated participants (92.3%) reported at least 1 ISR after initial treatment, 86 (82.7%) after touch-up treatment, and 55 (75.3%) after repeat treatment. The most frequently reported ISRs after initial treatment included tenderness to touch (81.8%), firmness (75.1%), and swelling (68.5%). Similar results were seen after repeat treatment, where the most common ISRs were also tenderness to touch (71.2%), firmness (69.9%), and swelling (58.9%).

Timing of adverse effects: Injection site abscess (onset 6 days), gingival pain (onset 1 day), acne cystic (onset 6 days), injection site cellulitis (onset 7 days), and injection site inflammation (onset 7 days)

Factors that predict response: A lower incidence of ISRs was observed for injections with a cannula than without a cannula after initial touch-up and repeat treatments. There was an overall decrease in the number of AEs with repeat treatment compared with initial/touch-up treatment. One possibility is the lower volume injected during repeat treatment.

Source Citation: Cheon et al. 2021[48]

Study Design: Multicenter RCT (split-face design)

Device or Material: DIVAVIVA medium and Restylane Perlane Lidocaine

Contact Duration: **Study 1:** 24 weeks from baseline. **Study 2** (Extension): 25 to 52 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Bruise, Edema, Erythema, Pain, Pruritis

Patient characteristics (gender, mean age): Majority female, 107 subjects with bilateral symmetric moderate to severe nasolabial folds with grade 3 or 4 on a Wrinkle Severity Rating Scale. In the full analysis set, age ranged from 32 to 65 years.

Number per group: **Study 1**: 107 enrolled/106 completed; **Study 2:** 87 enrolled/82 completed

Observed adverse effects: **Study 1:** # of injection site-related adverse events (pain, edema, bruise, pruritis, and erythema) was 40 in DIVAVIVA group, 36 in Restylane Perlane Lidocaine group, there were no severe injection site-related adverse events. They were all mild. **Study 2:** The number of adverse events occurring during extension study was 13 cases. All adverse events were mild. One case, injection site mass, was considered to be possibly related to the device.

Timing of adverse effects: **Study 1:** All cases recovered within 10 days without treatments. **Study 2:** Cases recovered during the extension study.

Factors that predict response: Not reported

Source Citation: Lee et al. 2021[62]

Study Design: Single center retrospective single-arm study

Device or Material: Facial fillers (not specified)

Contact Duration: Followed up for 6 months or longer

Dose: NR

Frequency/Duration: Single administration

Response: Purpura/blister, Ptosis/ophthalmoplegia, Subconjunctival hemorrhage, Focal skin discoloration, Purpura

Patient characteristics (gender, mean age): 10 consecutive patients who presented with occluded periorbital vessels after facial injection.

Number per group: 7 injected with HA, 1 with collagen, 1 with poly-L-lactic acid, and 1 with a local anesthetic of 2% lidocaine with 1:100,000 epinephrine.

Observed adverse effects: Purpura/blister or purpura occurred in 6/7 (85%) patients with HA. Ptosis/ophthalmoplegia or ophthalmoplegia occurred in 4/7 (57%). Additional complications included subconjunctival hemorrhage (5) and facial discoloration (1).

Timing of adverse effects: Time to symptom after injection included immediately (n = 6), within 30 min (n = 2), within 2 h (n = 1), and within 2 days (n = 1). Time to presenting after vascular accident included within 6 h (n = 5), 1 day (n = 1), 2 days (n = 2), and 3 days (n = 2).

Factors that predict response: Clinical features are diverse according to the site and extent of vascular occlusion and injection materials. Visual prognosis was associated with the site of vascular occlusion and initial visual acuity.

Source Citation: Munavalli et al. 2021[63]

Study Design: Case series of 4 cases

Device or Material: Types of HA fillers included Restylane Lyft, Restylane L, Juvederm Volbella, Juvederm Voluma, and Juvederm Ultra

Contact Duration: 1 to 2.5 years

Dose: NR

Frequency/Duration: Varied by case

Response: Edema, Erythema, Swelling, Tenderness

Patient characteristics (gender, mean age): Four (4) female patients ages 50, 51, 36, and 43. All had h/o receiving HA filler injections. (HA filler for Case 4 not identified). Timing of last HA filler injections varied and was identified as previous 12 months, previous 18 months, 2019, and 2.5 years ago.Confirmed or potential exposure to COVID-19 varied and was identified as positive COVID-19 diagnosis, receipt of first blinded injection in an mRNA-1273 clinical phase III trial, injection of first dose of Moderna vaccine, and injection of 2nd dose of Pfizer vaccine.

Number per group: 4 cases/4 patients

Observed adverse effects: **Case 1:** severe periorbital swelling, followed by worsening facial edema, erythema, and tenderness. **Case 2:** facial edema, erythema, tenderness and pain *Note: Case 2 was eliminated from the study. Two subsequent COVID-19 antibody tests were negative and unblinding revealed that this patient received the saline injection.* **Case 3:** Increased tenderness in the right tear trough, followed by worsening of unilateral infraorbital edema and development of perioral edema. Also noted that the face remained persistently swollen in areas of previous filler injection. **Case 4:** Mild tenderness underneath the right eye, followed by swelling under the left eye

Timing of adverse effects: **Case 1:** Onset 2 weeks after positive COVID-19 diagnosis. **Case 2:** Onset 8 days after blinded injection. **Case 3:** Onset 12 h after vaccination. **Case 4:** Onset 24-hours after 2nd vaccination

Factors that predict response: The authors hypothesize that a COVID-19 spike protein triggers inflammatory reactions to dermal HA filler.

Source Citation: Humphrey et al. 2020[64]

Study Design: Retrospective single-arm study

Device or Material: Juvederm Voluma (HA-V)

Contact Duration: 9-year period

Dose: Average cumulative volume before the first reported DAE was 5.1 mL (clinic 1) and 4.5 mL (clinic 2), for a combined cumulative volume of 5.0 mL.

Frequency/Duration: Single administration

Response: Erythema, Nodule formation, Pain, Swelling, Tenderness, Warmth

Patient characteristics (gender, mean age): 9324 treatments in 4500 patients (3908 women, 592 men)

Number per group: 44 patients (1 man, 43 women) aged 27 to 79 years (average, 59 years) who experienced DAEs, for a combined incidence rate of 0.98% per patient, 0.47% per treatment, and 0.23% per 1-mL syringe

Observed adverse effects: Delayed swelling and nodule formation (29 each) were the most common reactions, along with erythema, warmth, and tenderness or pain. Two patients experienced a single DAE comprising more than 1 episode.

Timing of adverse effects: The median time to onset of DAE from the most recent injection of HA-V was 4 months (range, 1-13 months). Of 22 patients who received multiple injections of HA-V, the median time of onset from first injection was 15.5 months (range, 3-65 months).

Factors that predict response: Patients who experienced DAEs received 0.5 to 13.3 mL of HA-V in multiple locations, most commonly in the mid and lower face. Nearly half of the patients (21/44) received more than 1 treatment with HA-V before DAE onset. The average cumulative volume of HA-V before the first reported DAE was 5.1 mL (clinic 1) and 4.5 mL (clinic 2), for a combined cumulative volume of 5.0 mL. Of 44 cases of DAEs, 41 occurred in patients with HA-V that had been blended/admixed with variable volumes of lidocaine with epinephrine and/or normal saline. More than half of the reactions (23/44) occurred between October and January. A review of cases to identify potential immunologic triggers showed that 15 of 44 (34.1%) had an identifiable immunologic stimulus such as flu-like illness, infection, or dental procedure immediately before DAE onset.

Source Citation: Kassir et al. 2020[65]

Study Design: Retrospective single-arm study

Device or Material: Fillers for non-surgical rhinoplasty including HA (Restylane) and Calcium hydroxyapatite

Contact Duration: NR

Dose: Average injection volume varied by location: Nasal tip 0.1–0.2cc, Columellar base 0.1–0.2cc, Dorsum 0.1–0.4cc, Radix 0.1–0.2cc

Frequency/Duration: Single administration

Response: Persistent redness

Patient characteristics (gender, mean age): Since 2006, 2130 patients older than 18 who underwent non-surgical rhinoplasty; 2023 patients were female (95%), and 107 were male (5%)

Number per group: Yearly distribution began with 35 cases in 2006 and increased each year with the highest number of 342 cases in 2019, the last year of the study. Each of the nose regions was injected in the following percentage of patients: Tip 95%, Columella 58%, Dorsum 83%, and Radix 62%.

Observed adverse effects: Two percent of patients had persistent tip redness which was observed suspecting possible necrosis. However, this recovered spontaneously, suggesting external vascular compression in the tip rather than intraarterial occlusion. There was no skin necrosis or ocular complications.

Timing of adverse effects: The duration of redness lasted from 5 to 60 min.

Factors that predict response: NR

Source Citation: Ogilvie et al. 2020[49]

Study Design: RCT

Device or Material: HA injectable filler VYC-25L (Juvederm Volux)

Contact Duration: Month 1 and 3, 12, 18 and 1 month after retreatment

Dose: Median range volume injected, mL **Treatment group** (Initial/Touchup): 3.43 (1.2-4.1), n = 90; After repeat treatment: 3.00 (0.5-5.0), n = 65 **Control group** (Initial/Touchup): 3.55 (1.7-4.0), n = 29; After repeat treatment: 2.50 (0.8-4.0), n = 24

Frequency/Duration: Single administration

Response: Bruising, Firmness, Injection-site pain, Swelling, Tenderness, Unclear pronunciation

Patient characteristics (gender, mean age): The mean age was 46.2 [13.3] years (range, 20-75 years), most subjects were female (92%, n = 110; the remaining 8% were men, n = 10), and the population was predominantly white (85.8%). At baseline, the mean glabella-subnasale-pogonion angles were 160.6° [4.2°] for the Volux group and 161.3° [2.8°] for controls.

Number per group: A total of 120 subjects were randomized (90 in the Volux group, 30 in the control group); of these, 119 subjects received initial/touch-up Volux treatment (90 Volux, 29 control) and 89 subjects (65 Volux, 24 control) received repeat treatment.

Observed adverse effects: The mean pain score as assessed by all treated subjects immediately after initial and touch-up treatment (n = 119) was 2.6 [1.8]; almost identical to that after repeat treatment (n = 87; 2.6 [2.2]). Most subjects who received treatment reported at least 1 ISR; 96.6% for initial and touch-up treatment combined and 95.5% for repeat treatment. The most commonly reported ISRs with initial/touch-up and repeat treatments were firmness (95.8% vs 94.4%) and tenderness to touch (95.8% vs 94.4%), respectively. Severe ISRs of bruising and firmness occurred at higher-than-expected rates after initial/touch-up treatment, but at typical rates for a HA soft tissue filler after repeat treatment (statistical significance testing was not performed). Most ISRs had a duration of 1 week. A total of 53 TEAEs occurred in 18 (20.2%) subjects. All TEAEs were at the injection site. Three TEAEs were reported more than 1 year after initial/touch-up treatments; 2 subjects reported swelling and 1 subject reported pain. All 3 events were of mild or moderate severity and resolved within 2 days without treatment or sequelae. The most common TEAEs following repeat treatment were the same as TEAEs following initial/touch-up treatments, although rates were more variable: injection site mass (14.6% vs 21.8%), injection site induration (13.5% vs

12.6%), and injection site pain (7.9% vs 12.6%), respectively. Nearly all TEAEs were related to ongoing ISRs. No serious TEAEs (related or unrelated to treatment) were reported, and no subject discontinued the study because of a TEAE after repeat treatment. Four subjects experienced speech disorder (specifically, unclear pronunciation) following initial and touch-up treatments, and 1 subject experienced unclear pronunciation following repeat treatment.

Timing of adverse effects: Pain: At initial treatment and touch-up treatment ISRs: At initial treatment, touch-up treatment, and repeat treatment TEAEs: Reported more than 1 year after initial/touch-up treatments and repeat treatments

Factors that predict response: Volux was chosen for this study because it has the highest concentration of HA (25 mg/mL), which was anticipated to provide the strong volumizing and lift properties necessary to sculpt, shape, and contour the high-mobility chin and jaw areas.

Source Citation: Wortsman et al. 2020[58]

Study Design: Prospective comparative study

Device or Material: Cosmetic fillers (CFs): HA (not specified), silicone oil, polymethylmethacrylate, polycaprolactone, calcium hydroxyapatite, and poly acrylamide

Contact Duration: ≥4 months after the last filler injection in ≥50%

Dose: NR

Frequency/Duration: Administration in >one facial location or in >two facial locations

Response: Ultrasound alterations of the lacrimal, parotid, and submandibular glands after filler injection

Patient characteristics (gender, mean age): 63 female patients (mean age: 53 years; SD 12.9) with h/o cosmetic filler injection in the nasolabial, periocular, or labial-peribuccual regions of the face.

Number per group: **Location of fillers % (CI 95%)**: Nasolabial 85.7 (77–94.3), Periocular 66.7 (55.1–78.3), Labial-peribuccal 82.5 (73.1–91.9) **Distribution of fillers % (CI 95%):** >One facial location 85.7 (77.1–94.3), >Two facial locations 71.4 (60.3–82.6) **Fillers identified in the sample:** HA in 86%, silicone oil in 48%, polymethylmethacrylate in 40%, polycaprolactone in 19%, calcium hydroxyapatite in 4.8%, and polyacrylamide in 1.6% of cases

Observed adverse effects: **Ultrasound Alterations of the Glands % (95% CI):** Lacrimal gland echostructure of the parenchyma 58.7 (46.5–70.9), Lacrimal gland hypervascularity 38.1 (26.1–50.1), Parotid gland echostructure of the parenchyma 87.3 (79.1–95.5), Parotid gland hypervascularity 14.3 (5.7–22.9), Submandibular gland echostructure of the parenchyma 88.9 (81.1–96.6), Submandibular gland hypervascularity 34.9 (23.1–46.7).

Timing of adverse effects: Ultrasound examination took place ≥4 months after the last filler injection in most cases (≥ 50%)

Factors that predict response: The presence of filler deposits close to the glands increased the chance of alterations in these glands. HA, by itself or with hyaluronidase, presented a high percentage of abnormalities in the glands. The mix of HA and other CFs had 20.8 more times the risk of alterations in the parotid gland (CI 1.8–240.9) compared to HA alone. The presence of more than 2 types of CFs and 2 or multiple facial locations presented a higher risk of abnormality of the glands.

Source Citation: Zhang et al. 2020[66]

Study Design: Retrospective single-arm study

Device or Material: HA fillers including Juvina, Allaxin, Perlane, Juvederm, Restylane, Juvederm Voluma XC, Matridex (HA and dextranomer), Juvederm Ultra

Contact Duration: 10 year period

Dose: NR

Frequency/Duration: Single administration

Response: Delayed granuloma reactions in the orofacial region following HA filler injections

Patient characteristics (gender, mean age): All patients were female, with a mean age of 38.5 years, who had developed delayed granulomatous reactions after receiving HA injections and underwent surgical resections in the authors' hospital.

Number per group: 11 patients (8 had been injected with HA fillers).

Observed adverse effects: Palpable nodules with/without growth and with/without pain

Timing of adverse effects: The nodules had developed 3 months to 6 years before surgical resections, and roughly 3 to 10 years following filler injection.

Factors that predict response: Different brands of dermal fillers, HA and non-HA, were injected into the same anatomical location. In one case a non-absorbable non-HA filler was injected.

Source Citation: Dai et al. 2019[50]

Study Design: RCT (split-face design)

Device or Material: Princess® VOLUME (PV) vs Restylane

Contact Duration: 24 weeks

Dose: 1 mL median injection volume

Frequency/Duration: Most received 1 injection (only 2 patients had a follow-up injection)

Response: Injection site hemorrhage, Injection site nodules, Pain, Swelling

Patient characteristics (gender, mean age): 96.67% female, mean age of 43 years (range 29–64 years)

Number per group: 120 patients total (120 received Restylane in one nasolabial fold and PV in the other), 115 patients completed the study.

Observed adverse effects: 58 subjects (48.33%) reported at least one AE for PV, and 53 (44.17%) reported at least one AE for Restylane. Overall, the most frequently reported AEs for PV and Restylane were swelling (30.83% and 29.17%, respectively) and pain (21.67% and 23.33%, respectively). Although more patients in the PV group had injection site nodules (16.67% vs 10.83%), the difference was not statistically significant. Overall, the incidence rates of AEs were similar in both groups. No severe AEs were reported.

Timing of adverse effects: Most AEs lasted for 14 days or less in 98.28% and 96.23% of subjects who had a treatment site response to PV or Restylane, respectively.

Factors that predict response: NR

Source Citation: Kaufman-Janette et al. 2019[51]

Study Design: RCT (split-face design)

Device or Material: RHA® 4 (RHA4) and Restylane® Lyft

Contact Duration: 1 year up to 15 months

Dose: Volumes (initial + touch up): 1.79 (±0.87) mL for RHA4 vs 1.75 (±0.90) mL for Lyft, (P = .48, NS).

Frequency/Duration: Single administration

Response: Bruising, Discoloration, Firmness, Itching, Lumps/bumps, Pain, Redness, Swelling, Tenderness

Patient characteristics (gender, mean age): The per-protocol (PP) analysis group included 81 women and 7 men and had a mean (±SD) age of 57 (±9) years. Fitzpatrick skin types: 61.4% of subjects had skin types I- to-III and 38.6% had skin types IV-VI.

Number per group: 88 subjects were included in the PP population; 18 subjects were in the untreated control group. All subjects who received treatment were considered for the safety analysis: n = 120 for the SAFT population.

Observed adverse effects: **CTRs:** bruising, discoloration, firmness, itching, lump/bumps, pain, redness, swelling, and tenderness. **TRAEs:** Frequencies of TRAEs were consistent with expected incidence rates and similar between treatment groups. Seventy-one (59%) and 62 (52%) subjects experienced a TRAE related to RHA4 and Lyft, respectively. All TRAEs were mild-to-moderate (no severe TRAE), and 334 of 364 events reported (92%) were administration site conditions. Overall, most frequent TRAEs were injection lumps/bumps (n = 55/120, 45.8% of subjects), injection site firmness (n = 49/120, 40.8%), injection site swelling (n = 27/120, 22.5%), and tenderness (n = 21/120, 17.5%). There were no reports of late-onset TRAEs or granulomas with either filler.

Timing of adverse effects: **CTRs:** Injection pain was virtually absent 5 minutes postinjection, and there were no clinically meaningful differences between devices regarding pain. Proportions of subjects experiencing at least one CTR were comparable between treatment groups and the majority had resolved by Day 14. **TRAEs:** Any CTR extending past 14 days was recorded as a TRAE. No late-onset TRAEs or granulomas were reported. Three subjects experienced a serious AE (arthralgia, diverticulitis, and lung infection), but none was deemed to be related to the study treatment.

Factors that predict response: The global incidence of TRAEs was higher in subjects with Fitzpatrick skin types I-III (n = 48, 71.6%) than in those with types IV-VI (n = 29, 54.7%).

Source Citation: Li et al. 2019[52]

Study Design: RCT (split-face design)

Device or Material: Restylane Lyft vs Restylane

Contact Duration: 12 months

Dose: 1.1 mL mean injection volume

Frequency/Duration: 1 or 2 injections

Response: Transient bruising

Patient characteristics (gender, mean age): 98% female, mean age 43.6 ± 8.1 years

Number per group: 100 per group (each cheek randomized to a different treatment) (100 total patients, 95 completed the study)

Observed adverse effects: Two subjects (2%) experienced AEs related to the study product and/or injection procedure: transient bruising after treatment (mild intensity with Restylane and moderate intensity with Restylane Lyft). Both AEs spontaneously resolved within the following week, and no treatment-related serious AEs were reported.

Timing of adverse effects: Within 1 week of injection

Factors that predict response: NR

Source Citation: Sadeghpour et al. 2019[59]

Study Design: Retrospective comparative study

Device or Material: Juvederm Volbella (VOB), Juvederm Vollure (VLR), Juvederm Voluma (VOL), Restylane Silk

Contact Duration: Up to 54 weeks

Dose: 0.5 mL per injection

Frequency/Duration: 1 to 3 injections

Response: Delayed-onset nodules

Patient characteristics (gender, mean age): Across groups, 91.1% to 97.6% were female, mean age ranged from 58.6 to 62.7 years

Number per group: 315 VOL, 219 VLR, 495 VOB, 385 Restylane Silk

Observed adverse effects: Five patients (1.0%) developed delayed nodules after VOB injection. No nodules were observed in patients who received VLR or VOL. One patient (0.25%) developed delayed nodules after Restylane Silk injection. All nodules were treated successfully using a combination of intralesional triamcinolone and hyaluronidase. No patient developed systemic symptoms.

Timing of adverse effects: 20 to 54 weeks after first VOB injection, 6 to 37 weeks after last VOB injection.

Factors that predict response: NR

Source Citation: Turkmani et al. 2019[67]

Study Design: Retrospective single-arm study

Device or Material: Several HA dermal fillers (Belotero, Hylaform, Juvederm, Restylane, Surgiderm, Teosyal)

Contact Duration: 2 to 10 months

Dose: NR

Frequency/Duration: 2 to 8 injections

Response: Delayed hypersensitivity reaction to HA fillers following influenza-like illness

Patient characteristics (gender, mean age): 100% female, age range 22 to 65 years

Number per group: 14 females who experienced delayed hypersensitivity reactions

Observed adverse effects: All 14 patients experienced delayed hypersensitivity reactions at HA filler sites 3-5 days following an influenza-like illness. The most common sites of the reactions were the cheeks (n=9), tear trough (n=8), and lips (n=3). Patients were treated with oral prednisolone 20–30 mg or Methyl prednisolone 16–24 mg daily for 5 days, followed by tempering of the dose for another 5 days. After a 2 week follow up, there was a complete resolution of the symptoms in 10 patients following the oral steroid therapy. The remaining 4 patients still presented minimal swelling that was treated with hyaluronidase 1 month after the onset of symptoms.

Timing of adverse effects: 2 to 10 months following last filler injection.

Factors that predict response: NR

Source Citation: Ueland et al. 2019[60]

Study Design: Prospective comparative study

Device or Material: Juvederm Voluma vs autologous fat (AF)

Contact Duration: 24 months

Dose: Juvederm median injection volume 0.9 (0.2 to 2) mL, AF median volume 3.1 (0.5–9.6) mL

Frequency/Duration: 1 to 5 injections (median 1 for Juvederm, 2 for AF)

Response: Bruising, Disfiguring surface, Pain, Swelling

Patient characteristics (gender, mean age): 93% female, mean age 62 (range 33 to 77) years

Number per group: 17 patients were treated bilaterally and 12 unilaterally (5 received Juvederm and 7 AF) for temporal hollowing. Patients treated bilaterally received injections of Juvederm in the right temple and AF in the left temple. Additional injections were given when needed at follow-up after 6, 12, 18, and 24 months.

Observed adverse effects: *Early complications* included bruising, pain and swelling which did not differ between Juvederm and AF injection sites. Juvederm had more cases of irregular surface (5/22) compared to AF (1/24). *Late complications*: Swelling occurred in 3/22 Juvederm sites and no AF sites; it resolved within 12 months. Subcutaneous scarring occurred only in 5/24 AF sites (no Juvederm sites developed this event). Abdominal pain occurred in 2 patients due to AF harvest. Disfiguring surface occurred in 2/22 Juvederm sites and 1/24 AF sites.

Timing of adverse effects: Early complications occurred within first 2 weeks of injection, late complications occurred after 2 weeks and up to 12 months.

Factors that predict response: NR

Source Citation: Wu et al. 2019[53]

Study Design: RCT (split-hand design, no- treatment control)

Device or Material: HA filler, Restylane® Vital (RESv)

Contact Duration: Injection on day 1, at 1 month, and at 2 months

Dose: 0.5-1 mL RESV per injection

Frequency/Duration: Single administration

Response: Bruising, Injection-site discoloration, Injection-site pain, Injection-site swelling, Redness, Swelling

Patient characteristics (gender, mean age): 96 females, 4 males; 49 years of age on average (ranging from 23 to 74 years); 93% were of Han Chinese background; 71% had Hand Grading Scale (HGS) score of 2 (moderate) and the rest had a score of 3 (severe).

Number per group: 100 subjects enrolled, 7 withdrawn from study; Subjects were randomly assigned to have one hand be treated and the opposite hand to no treatment.

Observed adverse effects: Local tolerability reactions included redness, bruising, and swelling. 27 treatment-related AEs were reported by 12 (12%) subjects, and the most common were injection site swelling (6%), injection site pain (4%), and injection site discoloration (4%). Most related AEs were mild or moderate.

Timing of adverse effects: Most AEs occurred at time of treatment. Five subjects reported related AEs with delayed onset (>21 days after last treatment) after the third treatment, such as injection/implant site pruritus, swelling, and discoloration.

Factors that predict response: Frequent hand washing was determined to be an occupational risk factor for developing hand skin irritation associated with report of AEs with delayed onset.

Source Citation: Prager et al. 2017[54]

Study Design: RCT (split-face design)

Device or Material: Belotero Volume vs Juvederm Voluma

Contact Duration: 18 months

Dose: 2 mL per injection

Frequency/Duration: Single injection of each filler (different sides of the face)

Response: Swelling, Pain, Redness, Bruising, Firmness, Itching, Discoloration

Patient characteristics (gender, mean age): 96% female, mean age 50.3 years

Number per group: 46 patients total (each received a different injection on each side of their face)

Observed adverse effects: 39 and 40 patients reported at least 1 injection site reaction for Belotero and Juvederm, respectively. Pain, redness, swelling, bruising, firmness/induration, itching and coloration/discoloration, did not show a statistically significant difference between treatments. One case of headache was considered possibly related to the injections.

Timing of adverse effects: Day 0 to 18 months.

Factors that predict response: NR

Source Citation: Weiss et al. 2016[55]

Study Design: RCT (control group had no treatment)

Device or Material: Restylane Lyft

Contact Duration: 15 months

Dose: Mean 6.23 mL (range, 2.00– 14.00 mL) at initial injection, mean 3.80 mL (range, 0.30–10.10 mL) at the 12-month retreatment.

Frequency/Duration: 1 to 2 injections

Response: Swelling, Pain, Hematoma, Infection, Late onset inflammation

Patient characteristics (gender, mean age): 92% female, mean age 52.9 ± 7.6 years

Number per group: 150 patients received midface injections of Restylane, 50 patients received no treatment

Observed adverse effects: TEAEs were more often related to injection procedure than to device and were mostly mild and transient; the most common were implant site hematoma, implant site pain, and implant site swelling. Four serious AEs in 2 subjects were considered to be related to the procedure or device; one subject reported implant site inflammation (late onset inflammatory reactions) in both cheeks at separate times. The other subject experienced implant site hematoma and implant site infection in the right cheek. All events resolved.

Timing of adverse effects: Most events occurred within 1 day of injection.

Factors that predict response: NR

Source Citation: Beleznay et al. 2015[68]

Study Design: Retrospective single-arm study

Device or Material: Juvederm Voluma

Contact Duration: Median 4 months

Dose: Median 3 mL (range 1 to 12.3 mL)

Frequency/Duration: 1 or 2 injections

Response: Delayed-onset nodules

Patient characteristics (gender, mean age): Gender NR, mean age 54 years in cases.

Number per group: 23 cases of delayed-onset nodules out of 4,702 total Juvederm facial injections in 2,342 patients

Observed adverse effects: Delayed-onset nodules occurred in 0.5% of Juvederm injections. No systemic symptoms were reported.

Timing of adverse effects: Median 4 months after injection, range 1 to 13 months. The median time to resolution of the nodule's following treatment was 6 weeks (range, 1 to 36 weeks).

Factors that predict response: Nine of the 23 (39%) had an immunologic stimulus such as flu-like illness or dental procedure immediately preceding the reaction.

Source Citation: Butterwick et al. 2015[56]

Study Design: RCT

Device or Material: Juvederm Ultra XC vs Belotero Balance

Contact Duration: 6 months

Dose: Mean 1.25 mL

Frequency/Duration: 1 or 2 injections

Response: Swelling, Induration, Nodules, Bruising, Tyndall effect

Patient characteristics (gender, mean age): 99% female, mean age 58.2 ± 8.4 years

Number per group: 69 per group (138 total)

Observed adverse effects: Adverse events related to the procedure were reported for 10 (15%) subjects in each arm. Severe injection site bruising was reported for 1 (1%) subject in each arm. Adverse events deemed related to the device were reported for 3 (4%) subjects in the Juvederm arm (induration, swelling, nodules) and 1 (1%) subject in the Belotero arm (Tyndall effect). There were no statistically significant differences in incidence or severity of injection site reactions.

Timing of adverse effects: One day to 6 months, most occurred within the first month.

Factors that predict response: NR

Source Citation: Sattler et al. 2014[57]

Study Design: RCT

Device or Material: Juvederm Ultra 4 vs calcium hydroxylapatite (Radiesse)

Contact Duration: 12 months

Dose: Bolus per injection: 0.1 to 0.2 mL interdigitally

Frequency/Duration: 3 to 4 injections initially, some patients received 1 to 3 touch-up injections

Response: None

Patient characteristics (gender, mean age): 100% female, median age 56 (range 45 to 65 years)

Number per group: 37 patients (each hand received a different filler)

Observed adverse effects: In total, 11 adverse events were documented in 6 patients. All adverse events were related to the injection with calcium hydroxylapatite.

Timing of adverse effects: Within first 2 weeks of injection.

Factors that predict response: NR

Source Citation: Trignano et al. 2015[69]

Study Design: Retrospective single-arm study

Device or Material: Macrolane

Contact Duration: 12 months

Dose: NR

Frequency/Duration: NR

Response: Intramammary and intramuscular cysts

Patient characteristics (gender, mean age): 100% female, mean age 35.75 years

Number per group: 20 patients who had experienced complications following Macrolane breast enhancement.

Observed adverse effects: All 20 patients presented with breast lumpiness and noted rapid, asymmetric losses in breast volume. Six of these patients were concerned about existing breast ptosis that had been worsening in association with the rapid resorption of HA. At least 85% of Macrolane filler was surgically removed from the breasts of all patients.

Timing of adverse effects: Cysts developed within 12 months of injection.

Factors that predict response: NR

Source Citation: Sito et al. 2013[61]

Study Design: Retrospective comparative study

Device or Material: HA (Macrolane) vs lipofilling

Contact Duration: Mean 24 months

Dose: Macrolane 30 to 40 mL, lipofilling unclear

Frequency/Duration: Single injection

Response: None

Patient characteristics (gender, mean age): 100% male, mean 33 years (range 26 to 42 years). All patients underwent penile augmentation.

Number per group: Macrolane (n = 56), lipofilling (n = 27)

Observed adverse effects: No complications were observed in patients treated with Macrolane, but a granuloma formed in 8 patients treated with lipofilling. The symptoms of 5 of these patients resolved spontaneously within 6 months with the help of massage; 2 patients reported no relief of symptoms from massage, and fat necrosis with progressive skin loss occurred in 1 patient after 20 days. That patient's wounds were treated conservatively with weekly dressing, and secondary healing occurred after 3 months.

Timing of adverse effects: Timing of granulomas unclear but average follow-up was 24 months.

Factors that predict response: NR

Source Citation: Inglefield 2011[70]

Study Design: Prospective single-arm study

Device or Material: Macrolane

Contact Duration: Mean 13.3 months

Dose: Mean 136 mL (range 20 to 200 mL)

Frequency/Duration: Single injection

Response: Capsular contraction, Early resorption, Infection, Removal of product

Patient characteristics (gender, mean age): 100% female, mean age 35 years (range: 19 to 62 years)

Number per group: 194 patients who received Macrolane for breast enhancement.

Observed adverse effects: Minor adverse events 12.4% (24 patients), major adverse events 8.7% (17 patients), infection 0.5% (1 patient), capsular contraction 4.6% (9 patients), early resorption 3.1% (6 patients), removal of product 0.5% (1 patient).

Timing of adverse effects: Most events occurred within the first 6 months

Factors that predict response: NR

Source Citation: Park et al. 2011[71]

Study Design: Retrospective single-arm study

Device or Material: HA fillers (brand NR)

Contact Duration: Mean 5.3 months

Dose: NR

Frequency/Duration: NR

Response: Dyspigmentation, Inflammatory symptoms, Nodules, Tissue necrosis

Patient characteristics (gender, mean age): 82.1% female, mean age 33.7 ± 10.1 years

Number per group: 28 cases of HA filler-related facial complications

Observed adverse effects: 12 patients (42.9%) with a nodularity or palpable mass, 10 patients (35.7%) with inflammatory symptoms such as swelling, tenderness and redness, three patients (10.7%) with tissue necrosis, including one case of alar rim involvement and three patients (10.7%) with dyspigmentation.

Timing of adverse effects: Mean 5.3 months post-injection

Factors that predict response: NR

Systemic Response/Toxicity

Source Citation: Alijotas-Reig et al. 2018[72]

Study Design: Retrospective single-arm study

Device or Material: Dermal fillers/implants

Contact Duration: Onset 6 months or longer after bioimplant injection (mean 70.7 months)

Dose: NA

Frequency/Duration: Single administration

Response: Autoimmune/ inflammatory syndrome induced by adjuvants (ASIA) - see list of specific symptoms under observed adverse events

Patient characteristics (gender, mean age): 88.9% female, mean age NR

Number per group: 45 cases of patients suffering from late-onset, inflammatory, non-infectious adverse reactions related to dermal fillers/implants. Only 7/45 patients received HA as the sole injected material. The biomaterials in other cases were: polyalkylamide, poly-L-lactic acid, HA plus methacrylate, silicone medical grade, and unknown filler.

Observed adverse effects: *Symptoms*: Of the 7 cases who received HA alone, the following symptoms were reported: 4 myalgia, 6 arthralgia/arthritis, 6 fatigue, 2 neurologic complaints, 2 cognitive features, 1 fever, 1 Sicca syndrome, 7 skin manifestations (3 facial nodules), 3 evolvement into autoimmune disease. Similar symptoms/manifestations were reported for other biomaterials. *Clinical findings*: Of the 7 cases who received HA alone: 1 had livedo reticular and systemic lupus erythematosus. 1 had panniculitis, undifferentiated connective tissue disease, multiple sclerosis-like. 1 had panniculitis, angioedema, and autoimmune thyroiditis. 1 had cutaneous vasculitis and autoimmune thyroiditis. 1 had angioedema, panniculitis, facial nodules, Chron's disease. 1 had angioedema, facial nodules, myositis, skin induration. 1 had angioedema, facial nodules, skin induration

Timing of adverse effects: 6 to 317 months following exposure to biomaterial (mean 70.7 months)

Factors that predict response: NR

Source Citation: Alijotas-Reig et al. 2012[73]

Study Design: Retrospective single-arm study

Device or Material: Biomaterials injections including HA, acrylamides, or methacrylate compounds

Contact Duration: Onset 12 months or longer after bioimplant injection

Dose: NA

Frequency/Duration: Single administration

Response: Local and Systemic reactions (possible ASIA-related disorders) following injection of different fillers

Patient characteristics (gender, mean age): 15 patients; 14 females/1 male with late-onset inflammatory adverse reactions related to fillers other than silicone that could be totally or partially considered as ASIA-related disorders.

Number per group: 15

Observed adverse effects: **Local and Systemic Complaints by filler:** *Polyalkymide (6/15),* Local: Thigh & buttock panniculitis, facial nodules, skin indurations; Systemic: Monoclonal gammopathy, fatigue, arthralgia, livedo reticularis in legs, arthritis, malaise; pain in jaw, primary biliary cirrhosis, sicca syndrome, hands erythema (vasculitis-like), multiple buttock nodules, feverish, myalgia, rash (vasculitis-like), angioedema, lymphadenopathy, pneumonitis; *Poly-L-lactic acid (1/15),* Local: facial nodules; Systemic: Malaise, feverish, cutaneous sarcoidosis *HA/methacrylate (2/15*), Local: facial nodules, indurations; Systemic: Skin rash, liquen, sicca syndrome, cutaneous sarcoidosis *Polyacrylamide (1/15*), Local: extensive facial nodules; Systemic: Malaise, lymphadenopathy, arthritis, rash, *HA (3/15),* Local: None; Systemic: Generalized cutaneous vasculitis, arthritis, fever, lymphadenopathy, anti-neutrophil citoplasmic antibodies (ANCA), recurrent angioedema, skin rash, Sjogren's syndrome, *Unknown filler (1/15)*, Local: nodules in low back/buttocks; Systemic: Muscle pain and weakness, fatigue, inflammatory polyradiculopathy, *Acrylamide (1/15),* Local: None; Systemic: sicca syndrome, morphea, polyarthritis

Timing of adverse effects: The mean latency between filler or most recent filler injection and appearance of symptoms was 15.9 months (range one to 48 months).

Factors that predict response: **Possible conditions or triggering events:** Seven out of the 15 patients had previously undergone injected procedures using other biomaterials. Two out of 15 patients had had silicone breast enlargement. In all but four cases, inflammatory signs at the implantation site preceded the distant or systemic manifestations. Only two patients experienced infectious history as a possible triggering event, but in both cases the infections were not directly associated with the point of bioimplant injection.

AE = adverse event; AF = autologous fat; AFKG = autologous fibroblast and keratin gel; ASIA = autoimmune/inflammatory syndrome induced by adjuvants; CaHa = calcium hydroxyapatite; CF = cosmetic filler; CNS = central nervous system; CTR = common treatment reaction; DAE = delayed adverse event; DTH = delayed-type hypersensitivity; HA = hyaluronic acid; h/o = history of; ISR = injection site reaction; NR = not reported; SD = standard deviation; TEAE = treatment emergent adverse events; TRAE = treatment-related adverse events

Table 21: Dermal Fillers - Health Effects (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Nie et al. 2019[74]

Study Design: Comparative animal study

Device or Material: HA (Restylane) vs PMMA (Artecoll)

Route: Ear (intra-arterial injection)

Dose: 0.1 mL or 0.2 mL

Frequency/Duration: Single administration

Response: Embolism, Necrosis

Species (strain): Rabbit (white)

Gender: Male

Number per group: 30 rabbits total (n = 20 ears for 0.1 ml PMMA and 0.1 ml HA groups; and n = 10 ears for 0.2 ml PMMA and 0.2 ml HA groups).

Observations on adverse effects (brief): With 0.1 ml injected volume, PMMA was dispersed within a few minutes and only 5% of the injected ears had mild necrosis on day 7, while HA tended to form obvious transparent emboli, an indication of blood vessel clotting, and 60% of injected ears showed necrosis on day 7. With 0.2 ml injected volume, PMMA had a risk of complete blood vessel clotting in between 0.1 ml PMMA group and 0.1 ml HA group, and 30% of injected ears had necrosis; in contrast, 100% of 0.2 ml HA-injected ears showed transparent emboli and necrosis. The necrosis areas were significantly increased in the HA groups compared with PMMA groups at the same injection volumes. HA injection also caused dilation of small blood vessels.

Timing of adverse effects: Within 7 days of injection

Factors that predict response: NR

HA: hyaluronic acid; PMMA: poly (methyl methacrylate)

Table 22: Intraocular/Ophthalmic Viscoelastic Solution/Fluid - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Malvankar-Mehta et al. 2020[75]

Study Design: Systematic review

Device or Material: Ophthalmic viscoelastic devices (Healon, Healon5, Healon GV, 2% HPMC, Viscoat, OcuCoat, Provisc, Soft Shell)

Contact Duration: 1 day to 3 months

Dose: NR

Frequency/Duration: 1 injection/eye

Response: Corneal edema, Intraocular pressure (IOP), Macular edema

Patient characteristics (gender, mean age): Gender NR; mean age ranged from 63 to 77 years across studies.

Number per group: 3893 subjects in 36 RCTs identified were included for analysis.

Observed adverse effects: Significant increase in postoperative IOP in 1-day follow-up with Healon (SMD = 0.37, CI: [0.07, 0.67]), Viscoat (SMD = 0.29, CI: [0.13, 0.45]), Provisc (SMD = 0.46, CI: [0.17, 0.76]), and Soft Shell (SMD = 0.58, CI: [0.30, 0.86]) was computed. Conversely, results implied a non-significant increase in postoperative IOP with Healon GV (SMD = 0.07, CI: [−0.28, 0.41]), Healon5 (SMD = 0.15, CI: [−0.33, 0.64]), 2% HPMC (SMD = 0.32, CI: [−0.0, 0.64]), and OcuCoat (SMD = 0.26, CI: [−0.37, 0.9]). Additionally, a non-significant reduction in postoperative IOP was inferred with Viscoat + Provisc (SMD = −0.28, CI: [−2.23, 1.68]). Meta-analysis showed statistically non-significant reduction in post-operative IOP in 1-week follow-up with Healon (SMD = −0.35, CI: [−0.71, 0.0]), Viscoat (SMD = −0.13, CI: [−0.4, 0.14]), 2% HPMC (SMD = 0.06, CI: [−0.3, 0.42]), and OcuCoat (SMD = −0.41, CI: [−0.98, 0.17]) compared to a statistically significant reduction in postoperative IOP in 1-week follow-up with Healon GV (SMD = −0.5, CI: [−0.89, −0.11]) and Healon5 (SMD = −0.42, CI: [−0.68, −0.17]). Statistically significant reductions in IOP across devices were seen at 1 month, 3 months and 6 months follow-up. Across 4 studies, corneal edema rates ranged from 0.6% to 2.5%. Across 2 studies, macular edema rates ranged from 0.6% to 0.9%.

Timing of adverse effects: Most events occurred between 1 hour and 1 week post-surgery.

Factors that predict response: NR

Source Citation: Dugan et al. 2020[78]

Study Design: Retrospective comparative study

Device or Material: Ophthalmic viscoelastic device (Provisc)

Contact Duration: 3 months

Dose: NR

Frequency/Duration: Single injection

Response: IOP, Microhyphema, Layered hyphema, Choroidal effusions, Tube leak, Other complications

Patient characteristics (gender, mean age): 55% female, mean age 76.4 years

Number per group: Ahmed Glaucoma valve implantation with OVD fill (n = 105) or without OVD fill (n = 54).

Observed adverse effects: IOP did not differ between the 2 groups at any visit, except at 6 months when the OVD-fill group had lower IOP than the control group (13.8 ± 3.7 vs. 16.6 ± 5.3 mm Hg, P=0.002). At most recent

follow-up, the IOP was 15.4 ± 6.4 mm Hg in the OVD-fill group and 15.6 ± 6.9 mm Hg in the non–OVD-fill group (P=0.47). Compared with baseline, the mean change in IOP was greater in the OVD-fill group at 1-month follow-up (−17.5 ± 10.2 vs. −13.9± 9.39 mm Hg, P=0.04), but there were no statistically significant differences at any other postoperative visits (P ≥ 0.06). There were 5 (5.9%) patients in the OVD-fill group and 3 (8.1%) in the non–OVD-fill group with IOP spikes to ≥30 mm Hg within the first postoperative month (P=0.70). In the first postoperative month, there were 19 (21.8%) patients with hypotony in the OVD-fill group and 5 (13.2%) patients in the non–OVD-fill group (P=0.26). There was no difference in complication rates between the 2 groups, except at week 1 in which 20 of 95 (21.1%) of patients with OVD fill had a layered hyphema compared with 2 of 45 (4.4%) in the control group (P=0.01). There was 1 patient (1.0%) in the OVD group and 1 patient (2.2%) in the non-OVD group that required drainage of choroidal effusions within the first postoperative month. Other complications included a retinal detachment in a patient without OVD fill and a clogged tube shunt that occurred in a patient who received OVD fill.

Timing of adverse effects: 1 day to 3 months post-surgery.

Factors that predict response: NR

Source Citation: Fezza 2018[81]

Study Design: Prospective single-arm study

Device or Material: Cross-linked hyaluronic acid (xlHA) gel occlusive device (Restylane-L™, Q Med, Uppsala, Sweden)

Contact Duration: 6 months

Dose: 0.2 mL

Frequency/Duration: Single injection

Response: No events related to the device

Patient characteristics (gender, mean age): 48 female, 15 male; mean age 67 years

Number per group: 74 patients with dry eye (63 completed the study).

Observed adverse effects: Adverse events were rare and included two cases of periocular itching, which was attributed to seasonal allergies and one case of conjunctivitis that occurred at month 2 and resolved and was likely to be an incidental viral infection not related to the gel, as a family member had previously contracted a "pink eye." Importantly, there were no cases of dacryocystitis, canaliculitis, swelling, pain, bruising, or Tyndall effect.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Auffarth et al. 2017[76]

Study Design: RCT

Device or Material: Ophthalmic viscoelastic device (Twinvisc and Duovisc)

Contact Duration: 3 months

Dose: Twinvisc (0.7 mL dispersive, 0.7 mL cohesive); Duovisc (0.35 or 0.5 mL dispersive, 0.4 or 0.55 mL cohesive)

Frequency/Duration: Administration of dispersive and cohesive OVD into a single eye

Response: IOP spikes, Inflammation, Ocular hypertension, Corneal edema, Capsule break, Viscoat bubbles

Patient characteristics (gender, mean age): 62% female, mean age 72 years. All patients received cataract surgery.

Number per group: 109 (Twinvisc, group 1) and 111 (Duovisc, group 2)

Observed adverse effects: Six hours after the surgery, 7 patients in Group 1 and 8 patients in Group 2 had an IOP of 30 mm Hg or higher. No statistically significant difference between groups at any follow-up was found in terms of incidence of IOP peaks of 30 mm Hg or higher or 24 mm Hg or higher. All the cases of IOP peaks of 30 mm Hg or higher resolved either with appropriate medication or paracentesis reopening (6 and 5 eyes in Group 1 and Group 2, respectively) or spontaneously (1 eye and 3 eyes in Group 1 and Group 2, respectively). There was evidence of mild inflammation in both groups at 6 hours, 24 hours, and 7 days postoperatively for all criteria (corneal opacity, inflammatory cells, fibrin, flare, and iritis symptoms). However, at 30 days and 90 days postoperatively, the inflammation level was very close to baseline values. There was no statistically significant difference between the 2 groups at any follow-up for any of the criteria, with the exception of the number of inflammatory cells at 90 days in favor of the OVD 1 group (P = 0.029). No serious adverse events related to the studied OVDs were reported. Other adverse events potentially related to the OVDs: In Group 1, there were 14 cases (12.6%) of ocular hypertension, 1 case (0.9%) of corneal edema, and 1 case (0.9%) of cystoid macular edema. Adverse events in group 2 included 20 cases (17.6%) of ocular hypertension, 1 case (0.9%) of corneal edema, 1 case (0.9%) of inflammation, 1 case (0.9%) of capsule break, and 1 report (0.9%) of bubbles in the Viscoat OVD. None of the between-group differences were statistically significant.

Timing of adverse effects: 6 hours to 3 months post-surgery.

Factors that predict response: NR

Source Citation: Altintas et al. 2017[82]

Study Design: Retrospective single-arm study

Device or Material: Ophthalmic viscoelastic device (either 2.0% or 1.4% HA)

Contact Duration: 2 weeks

Dose: NR

Frequency/Duration: Single injection

Response: Toxic anterior segment syndrome (TASS)

Patient characteristics (gender, mean age): 47% female, mean age 67 years

Number per group: 34 patients who developed TASS after routine cataract surgery.

Observed adverse effects: Nine patients developed a moderate degree of corneal edema, mild inflammation of AC in 24–48 h following surgery. No patient had purulent secretion, chemosis, lid involvement, and pain. Other ten patients underwent phacosurgery at the following day, all of them had corneal edema and AC inflammation. Four cases out of ten had severe corneal stromal edema extending from limbus to limbus combining with fibrin formation in the AC, and two cases had hypopyon, but conjunctival inflammation was minimal without discharge and chemosis. None of them had periocular pain. The authors identified the source of TASS as OVD derived from rooster comb; when they substituted with OVD derived from bacterial fermentation no further cases of TASS were observed.

Timing of adverse effects: Initial symptoms occurred within 1 day following surgery.

Factors that predict response: OVD derived from rooster comb that had been stored improperly was responsible for the outbreak.

Source Citation: Jaramillo et al. 2014[83]

Study Design: Retrospective single-arm study

Device or Material: Ophthalmic viscoelastic device (Healon GV, 1.4% HA)

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Healon GV was injected every 2 to 3 clock hours to a total of 8 times in all cases.

Response: Descemet membrane detachment (DMD) with or without intracorneal hemorrhage

Patient characteristics (gender, mean age): The average age of the DMD group was 68. 6 years, and there were 7 male and 5 female patients. Mean age for all patients was 68.5 years.

Number per group: 162 eyes of 115 patients who received canaloplasty for glaucoma.

Observed adverse effects: Twelve patients developed DMD after canaloplasty (7.4%) (12 eyes of 162). Intracorneal hemorrhage within DMD occurred in 58% (7/12), whereas 42% (5/12) developed DMD with intracorneal viscoelastic (Healon GV) alone. Two patients had large detachments measuring 5 to 6 mm extending into the visual axis. DMD resolved completely with or without drainage except for 1 patient who developed corneal decompensation, needing penetrating keratoplasty.

Timing of adverse effects: DMD was noticed at the time of surgery in all cases. All cases resolved in 4 to 10 weeks (3 patients required additional surgery to resolve the DMD).

Factors that predict response: No between-group differences in baseline variables were identified between DMD and non-DMD eyes. The authors noted "DMD could be related to excessive amounts of Healon GV injection into the Schlemm canal during the viscodilation portion of the surgery."

Source Citation: Uemoto et al. 2013[79]

Study Design: Retrospective comparative study

Device or Material: Ophthalmic viscoelastic device with brilliant blue G (Visco-BBG) versus balanced salt solution with BBG (BSS-BBG)

Contact Duration: Visco-BBG was removed 30 seconds after injection

Dose: 0.3 mL

Frequency/Duration: Single injection

Response: No complications with Visco-BBG

Patient characteristics (gender, mean age): All patients had undergone par plana vitrectomy (PPV) combined with internal limiting membrane (ILM) peeling. Patient characteristics NR.

Number per group: Visco-BBG (40 eyes), BSS-BBG (34 eyes)

Observed adverse effects: No ocular hypertension or undue inflammation (endophthalmitis) attributable to residual visco-BBG was evident postoperatively. There were no alterations of the retinal pigment epithelium due to dye toxicity in all cases. An accidental retinal perforation occurred in an epimacular membrane case of the BSS-BBG group.

Timing of adverse effects: The only adverse event occurred during surgery.

Factors that predict response: NR

Source Citation: Leszczyski et al. 2012[80]

Study Design: Prospective comparative study

Device or Material: Ophthalmic viscoelastic device (SKGEL, reticulated HA)

Contact Duration: Follow-up was 24 months

Dose: NR

Frequency/Duration: Single injection

Response: See intraoperative, early post-operative and late post-operative complications under observed adverse events

Patient characteristics (gender, mean age): 28 men and 40 women, mean age 64.8±11.6 years. The study compared non-penetrating very deep sclerectomy (NPVDS) with the use of hyaluronic acid implant (SKGEL) to trabeculectomy (TB) in patients with medically uncontrolled glaucoma.

Number per group: NPVDS (39 eyes); TB (39 eyes)

Observed adverse effects:

Intraoperative:	NPVDS	TB	p-value
Anterior chamber flattening	1 (2.6 %)	4 (10.3 %)	0.029
Anterior chamber hemorrhage	1 (2.6 %)	4 (10.3 %)	0.029
Perforation of trabeculo-Descemet membrane	2 (5.1 %)	0 (0.0 %)	0.0676
Early post-operative:			
Choroidal detachment	2 (5.1 %)	4 (10.3 %)	0.124
Hyphema	2 (5.1 %)	5 (12.8 %)	0.054
Inflammation	0 (0.0 %)	1 (2.6 %)	0.079
Late post-operative:			
Cataract progression	4 (10.3 %)	12 (30.8 %)	0.002
Bleb fibrosis	2 (5.1 %)	1 (2.6 %)	0.207
All complications:	14 (35.9 %)	31 (79.5 %)	0.00011

Overall complication rate higher in TB group.

Timing of adverse effects: Intraoperative to late post-operative, but timing of late events not reported.

Factors that predict response: NR

Source Citation: Modi et al. 2011[77]

Study Design: RCT

Device or Material: Ophthalmic viscoelastic device (DisCoVisc or Healon)

Contact Duration: 3 months

Dose: 0.85 mL (Healon), 1 mL (DisCoVisc)

Frequency/Duration: Single injection (Healon), double injection (DisCoVisc)

Response: IOP ≥30mmHg, Aqueous cells, Severe corneal edema, Ocular discomfort, Conjunctival hyperemia, Conjunctival injection, Conjunctival erythema

Patient characteristics (gender, mean age): 63% female, mean age 69 to 70 years between groups.

Number per group: DisCoVisc (128 eyes), Healon (121 eyes)

Observed adverse effects: At 6 hours after surgery, both OVD groups had 15 patients with IOP ≥ 30 mmHg, yielding a similar percentage of patients with IOP ≥ 30 mmHg (13.0% of DisCoVisc OVD patients, 13.3% of Healon OVD patients). At 24 hours after surgery, both OVD groups had seven patients with IOP ≥ 30 mmHg (similar between groups, at 6.1% of DisCoVisc OVD patients and 6.2% of Healon OVD patients). By postoperative day 7, only one Healon OVD patient (0.9% of cases) and no DisCoVisc OVD patients had IOP ≥ 30 mmHg. No IOPs ≥ 30 mmHg were observed in any patient following postoperative day 13. For the aqueous cells parameter, 3 eyes exhibited clinically significant scores: two eyes in the Healon OVD group (one eye at 1 day postoperative and one eye at 7 days postoperative) and one eye in the DisCoVisc OVD group at an unscheduled visit (41 days postoperative). The latter case was not related to the OVD, but was attributed to residual lens fragments after surgery in an eye with a very small pupil, and was resolved after treatment with prednisolone acetate and atropine. Severe corneal edema was observed in one eye in the DisCoVisc OVD group and in one eye in the Healon OVD group; both cases occurred 1 day postoperative. The most frequently reported clinical observations of events related to the safety and tolerability of the OVDs occurred in both study groups and included ocular discomfort, conjunctival hyperemia, conjunctival injection, or conjunctival erythema.

Timing of adverse effects: See above

Factors that predict response: NR

Source Citation: Shafi et al. 2011[84]

Study Design: Retrospective single-arm study

Device or Material: Ophthalmic viscoelastic device (Healon GV, 1.4% HA)

Contact Duration: Follow-up 12 months

Dose: 0.4 mL of Healon GV plus subconjunctival injection of 5-FU (10 mg in 0.4 mL)

Frequency/Duration: Single injection of Healon GV, single injection of 5-FU

Response: Reported complications likely related to the needling procedure, not Healon GV

Patient characteristics (gender, mean age): 41.5% female, mean age 67.13 ± 15.76 years

Number per group: 46 patients (53 eyes) who had undergone primary bleb needling revision (BNR) with adjunctive 5-FU and routine subconjunctival Healon GV.

Observed adverse effects: Of 53 needling procedures, 16 eyes (30%) had a complication. Reported complications (early hypotony, needle-track leak, subconjunctival hemorrhage, anterior uveitis flareup) more likely related to the needling procedure than Healon GV, a controlled study would be needed to determine complications related to Healon GV.

Timing of adverse effects: Most complications occurred and were resolved within 2 weeks post-needling.

Factors that predict response: NR

FU = fluorouracil; HA = hyaluronic acid; IOP = intraocular pressure; NA = not applicable; NR = not reported; OVD = ophthalmic viscoelastic device; RCT = randomized controlled trial

Table 23: Eye Drops - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Groß et al. 2018[85]

Study Design: RCT

Device or Material: Hyaluronic acid (HA) drops versus 0.5% carboxymethylcellulose (CMC) drops for keratitis or keratoconjunctivitis related to dry eye disease

Contact Duration: NR

Dose: 1 drop

Frequency/Duration: 3 times/day for 35 days

Response: Chronic arthrosis, Episodic crackling feeling under the lid, Episodic chalazion, Chronic eye stinging

Patient characteristics (gender, mean age): Female = 56 (70%), Male = 24 (30%); mean age = 55.81 years

Number per group: HA = 41, CMC = 39

Observed adverse effects: 4 adverse events (9.7%) in HA group (chronic arthrosis, episodic crackling feeling under the lid, episodic chalazion, chronic eye stinging) 3 adverse events (5.1%) in the CMC group (episodic lid edema, episodic eye in one patient stinging, chronic lid eczema in one patient) Stinging was improved more with HA compared to CMC on day 84 (p=0.0106) Itching was improved more with HA compared to CMC on day 84 (p=0.0179) No difference in pain was observed between the two groups

Timing of adverse effects: Within 85 days

Factors that predict response: NR

Source Citation: Labetoulle et al. 2017[93]

Study Design: RCT

Device or Material: Osmoprotectants, carboxymethylcellulose and hyaluronic acid (O/CMC/HA) versus HA drops for moderate to severe symptomatic dry eye

Contact Duration: NR

Dose: 1-2 drops

Frequency/Duration: 2-6 times/day for 3 months

Response: Eye pruritus, dry eye, eye irritation, eyelid irritation

Patient characteristics (gender, mean age): Female = 100%; mean age = 62.9 (O/CMC/HA) & 61.4 (HA)

Number per group: 40

Observed adverse effects: Eye pruritus (n=2, 5%) was reported in the O/CMC/HA group, Dry eye (n=2, 5%) was reported in the HA group, Eye irritation (n=2, 5%), was reported in the HA group, Eyelid irritation (n=1, 2.5%) was reported in the HA group. In the O/CMC/HA group, 9 (22.5%) adverse events were mild, 4 (10%) adverse events were moderate and 3 (7.5%) adverse events were severe. In the HA group, 11 (27.5%) adverse events were mild, 4 (10%) adverse events were moderate and 1 (2.5%) adverse event was severe.

Timing of adverse effects: Within 3 months

Factors that predict response: NR

Source Citation: Cagini et al. 2017[86]

Study Design: RCT

Device or Material: Cross linked HA (0.2%) versus HA (0.2%) for Sjögren syndrome-related dry eye

Contact Duration: 60 minutes

Dose: 1 drop

Frequency/Duration: Once

Response: None

Patient characteristics (gender, mean age): 100% Female (20); mean age = 57.8 years

Number per group: Treatment group = 20, control group = 20

Observed adverse effects: No stinging or other adverse events in either group

Timing of adverse effects: 60 minutes

Factors that predict response: NR

Source Citation: Groß et al. 2017[87]

Study Design: RCT

Device or Material: 0.2% HA (Hylo Confort Plus/HydoGel) versus 0.18% HA (Vismed® Multi) for moderate to severe dry eye and noninfectious, nonviral keratitis, or keratoconjunctivitis

Contact Duration: 35 days

Dose: NR

Frequency/Duration: NR

Response: Grittiness exacerbation, Important ocular fatigue + ocular irritation, Ocular irritation

Patient characteristics (gender, mean age): 59 Female (69.4%), 26 male (30.6%); Mean age = 59.7 years

Number per group: 0.2% HA = 38; 0.18% HA = 32

Observed adverse effects: The rate of adverse events (AE) was 2.3% for 0.2% HA (1 episodic allergy) and 7.1% for 0.18% HA (1 grittiness exacerbation, 1 ocular irritation, 1 important ocular fatigue + ocular irritation) with no serious AE.

Timing of adverse effects: 84 days

Factors that predict response: NR

Source Citation: Lambiase et al. 2017[88]

Study Design: RCT

Device or Material: Lubricin versus HA for grade 2-3 moderate dry eye disease

Contact Duration: 14 days

Dose: 2-6 drops

Frequency/Duration: Once/day for 7 days

Response: Transient adverse events

Patient characteristics (gender, mean age): Lubricin: 94.7% female, 5.3% male; mean age = 51.9 years. HA: 90% female, 2% male; mean age 61.8 years.

Number per group: Lubricin: N=19. HA: N=20.

Observed adverse effects: Transient adverse events: lubricin=2, HA=2, Treatment related adverse events: none

Timing of adverse effects: 14 days

Factors that predict response: NR

Source Citation: Chiambaretta et al. 2017[94]

Study Design: RCT

Device or Material: HA-trehalose (Thealoz Duo®/Thealose®) versus HA (Vismed®) for moderate to severe dry eye disease

Contact Duration: 84 days

Dose: 1 drop

Frequency/Duration: 3-6 times/day for 84 days

Response: Eye disorders, eye pruritus, chalazion, conjunctival irritation, conjunctivitis allergic, eye irritation, eye pain, keratitis, ulcerative keratitis, infections, conjunctivitis viral

Patient characteristics (gender, mean age): HA-trehalose: 11 (21.2%) male, 41 (78.8%) female, mean age = 60 years. HA: 8 (15.1%) male, 45 (84.9%) female, mean age = 58.5 years. Overall mean age = 59.2 years

Number per group: HA-trehalose = 52; HA=53

Observed adverse effects: At least one ocular treatment-emergent AE: HA-trehalose = 1 (1.9%), HA = 7 (13.2%) Eye disorders: HA trehalose = 0, HA = 6, Eye pruritus: HA trehalose = 0, HA = 2, Chalazion: HA trehalose = 0, HA = 1, Conjunctival irritation: HA trehalose = 0, HA = 1, Conjunctivitis allergic: HA trehalose = 0, HA = 1, Eye irritation: HA trehalose = 0, HA = 1, Eye pain: HA trehalose = 0, HA = 1, Keratitis: HA trehalose = 0, HA = 1, Ulcerative keratitis: HA trehalose = 0, HA = 1, Infections and infestations: HA trehalose = 1, HA = 1, Conjunctivitis viral: HA trehalose = 1, HA = 1, Significantly fewer adverse events in the HA-trehalose group, compared to the HA group.

Timing of adverse effects: 84 days

Factors that predict response: NR

Source Citation: Robert et al. 2016[95]

Study Design: RCT

Device or Material: Cationic emulsion (CE) versus 0.18% hyaluronate sodium (HS) for moderate to severe dry eye disease.

Contact Duration: 3 months

Dose: 1 drop

Frequency/Duration: 4 times/day

Response: Installation site erythema, instillation site pain, instillation site pruritus, blepharitis, conjunctival hyperemia, conjunctivitis, eye irritation, eye pain

Patient characteristics (gender, mean age): 9 (20.5%) male, 35 (79.5% female in the CE group. 7 (17.1%) male, 34 (82.9%) female in the HS group. 16 (18.8%) male, 69 (81.2%) female overall. Mean age = 60 years in the CE group. Mean age = 65.3 years in the HA group. Mean age = 62.6 years overall.

Number per group: CE = 44. HS = 41.

Observed adverse effects: Patients with at least one adverse event: CE = 8, HS = 11. Patients with at least one ocular adverse event: CE = 7, HS = 8. Patients with treatment-related adverse event: CE = 3, HS = 4. Installation site erythema: CE = 1, HS = 0. Instillation site pain: CE = 2. HS = 1. Instillation site pruritus: CE = 0, HS = 1. Blepharitis: CE = 1, HS = 0. Conjunctival hyperemia: CE = 0, HS = 1. Conjunctivitis: CE = 1, HS = 0. Eye irritation: CE = 0, HS = 1. Eye pain: CE = 0, HS = 1. No major differences between treatments were found with respect to local ocular tolerance.

Timing of adverse effects: 3 months

Factors that predict response: NR

Source Citation: Gong et al. 2015[89]

Study Design: RCT

Device or Material: Diquafosol ophthalmic solution (diquafosol) versus sodium hyaluronate solution (HA) for dry eye

Contact Duration: 6 weeks

Dose: NR

Frequency/Duration: 6 times/day

Response: Mild and moderate treatment related adverse events and eye disorders

Patient characteristics (gender, mean age): Diquafosol: 53 (22%) male, 188 (78%) female HA: 55 (22.2%) male, 193 (77.8%) female. Mean age not reported.

Number per group: Diquafosol = 241, HA = 248

Observed adverse effects: Mild adverse events: diquafosol = 17, HA = 11, Moderate adverse events: diquafosol = 13, HA = 4, No severe adverse events. There are statistically significantly less adverse events in the HA group compared to the diquafosol group (p=0.0186). Mild eye disorders: diquafosol = 17, HA = 11. Moderate eye disorders: diquafosol = 12, HA = 4. No severe eye disorders.

There are statistically significantly less eye disorders in the HA group compared to the diquafosol group (p=0.0267).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Prabhasawat et al. 2015[90]

Study Design: RCT

Device or Material: 0.3% Hydroxypropyl methylcellulose/dextran (TearsNaturale®) versus 0.18% sodium hyaluronate (Vislub®) for moderate to severe dry eye disease

Contact Duration: 28 days

Dose: 1 drop

Frequency/Duration: 4 times/day

Response: none

Patient characteristics (gender, mean age): HPMC/dextran: 10 (28.6%) male, 25 (71.4%) female. SH: 13 (37.1%) male, 22 (62.9%) female

Number per group: HPMC/dextran = 35 SH = 35

Observed adverse effects: No serious adverse events were reported for either group

Timing of adverse effects: 28 days

Factors that predict response: N/A

Source Citation: Jee et al. 2014[91]

Study Design: RCT

Device or Material: Preservative free 0.1% fluorometholone (Humeron) and 0.1% sodium hyaluronate (Tearin) (1 month) then 0.1% sodium hyaluronate and 0.05% cyclosporine (Restasis) (2 months) versus preserved 0.1% fluorometholone (Ocumetholone) and 0.1% sodium hyaluronate (Lacure) (1 month) then 0.1% sodium hyaluronate and 0.05% cyclosporine (Restasis) (2 months) for moderate to severe dry eye syndrome.

Contact Duration: 3 months

Dose: NR

Frequency/Duration: 2-4 times/day

Response: Stinging eyes

Patient characteristics (gender, mean age): Preservative free: 15 male, 35 female; mean age NR. Preserved: 12 male, 38 female; mean age NR

Number per group: 50

Observed adverse effects: Preservative free: 3 (6%), Preserved: 5 (10%)

Timing of adverse effects: 3 months

Factors that predict response: NR

Source Citation: Kinoshita et al. 2013[96]

Study Design: RCT

Device or Material: 2% rebamipide versus 0.1% sodium hyaluronate for dry eye

Contact Duration: 4 weeks

Dose: 1 drop

Frequency/Duration: 4-6 times/day

Response: Conjunctival hemorrhage, eye irritation, eye pain, visual impairment, eye pruritus

Patient characteristics (gender, mean age): Rebamipide: 10 (10.8%) male, 83 (89.2%) female; mean age NR. Sodium Hyaluronate: 15 (15.8%) male, 80 (84.2%) female; mean age NR

Number per group: Rebamipide = 93 Sodium, Hyaluronate = 95

Observed adverse effects: Conjunctival hemorrhage: Rebamipide = 1 (1.1%), Sodium hyaluronate = 2 (2.1%), Eye irritation: Rebamipide =0, Sodium hyaluronate = 2 (2.1%), Eye pain: Rebamipide = 0, Sodium hyaluronate

= 3 (3.2%), Visual impairment: Rebamipide = 2 (2.2%), Sodium hyaluronate = 0, Eye pruritus: Rebamipide = 4 (4.3%), Sodium hyaluronate = 2 (2.1%)

Timing of adverse effects: 4 weeks

Factors that predict response: NR

Source Citation: Liu et al. 2012[92]

Study Design: RCT

Device or Material: 0.1% topical pranoprofen + 0.1% topical sodium hyaluronate versus 0.1% sodium hyaluronate for dry eye

Contact Duration: 30 days

Dose: NR

Frequency/Duration: 4 times/day

Response: None

Patient characteristics (gender, mean age): Prenoprofen/sodium hyaluronate: 18 female, 12 male; mean age = 41.51 years. Sodium hyaluronate: 20 female, 10 make; mean age = 42.12 years

Number per group: 30

Observed adverse effects: None observed

Timing of adverse effects: 30 days

Factors that predict response: NR

Source Citation: Takamura et al. 2012[97]

Study Design: RCT

Device or Material: 3% diquafosol versus 0.1% sodium hyaluronate for dry eyes

Contact Duration: 2 weeks

Dose: 1 drop

Frequency/Duration: 6 times/day

Response: Blepharitis, eye discharge, eye irritation, eye pain, foreign body sensation, conjunctival hyperaemia, eye pruritus, ocular discomfort

Patient characteristics (gender, mean age): Diquafosol: 120 (83.3%) female; mean age = 55.3 years. Sodium hyaluronate: 125 (88%) female; mean age = 56.9 years

Number per group: Diquafosol = 144. Sodium hyaluronate = 139

Observed adverse effects: No statistically significant difference in adverse events between groups. Adverse drug reaction incidence rates were significantly lower in the sodium hyaluronate group (4.9%) compared to the diquafosol group (15.3%), p=0.005. Blepharitis: Diquafosol = 0, Sodium hyaluronate = 2 (1.4%). Eye discharge: Diquafosol = 4 (2.8%), Sodium hyaluronate = 0. Eye irritation: Diquafosol = 9 (6.3%), Sodium hyaluronate = 1 (0.7%). Eye pain: Diquafosol = 2 (1.4%), Sodium hyaluronate = 1 (0.7%). Foreign body sensation: Diquafosol = 4 (2.8%), Sodium hyaluronate = 1 (0.7%). Conjunctival hyperaemia: Diquafosol = 2 (1.4%), Sodium hyaluronate = 1 (0.7%). Eye pruritus: Diquafosol = 2 (1.4%), Sodium hyaluronate = 2

(1.4%). Occular discomfort: Diquafosol = 2 (1.4%), Sodium hyaluronate = 0. No serious adverse events in either group.

Timing of adverse effects: 4 weeks

Factors that predict response: NR

Source Citation: Baudouin et al. 2012[98]

Study Design: RCT

Device or Material: OsPR-CMC (OPTIVE®) versus Na-HY (Vismed®) for dry eye

Contact Duration: 3 months

Dose: 1 drop

Frequency/Duration: 3-6 times/day

Response: Conjunctival hemorrhage, Conjunctival hyperemia, Cystitis, Erythema of eyelid, Infection, Installation site pain, Keratitis, Meibomian gland dysfunction, Nasopharyngitis, Pain, Viral conjunctivitis

Patient characteristics (gender, mean age): OPTIVE®: 35 (87.5%) female; mean age = 58.1 years. Vismed®: 34 (91.9%) female; mean age = 55.4 years

Number per group: OPTIVE® = 40. Vismed® = 37

Observed adverse effects: EYE DISORDERS - Keratitis: OPTIVE® = 1 (2.4%), Vismed® = 1 (2.6%), Conjunctival hemorrhage: OPTIVE® = 1 (2.4%), Vismed® = 0, Conjunctival hyperemia: OPTIVE® = 0, Vismed® = 1 (2.6%), Erythema of eyelid: OPTIVE® = 0, Vismed® = 1 (2.6%), Meibomian gland dysfunction: OPTIVE® = 0, Vismed® = 1 (2.6%)

INFECTIONS - Viral conjunctivitis: OPTIVE® = 0, Vismed® = 1 (2.6%), Cystitis: OPTIVE® = 0, Vismed® = 1 (2.6%), Nasopharyngitis: OPTIVE® = 0, Vismed® = 1 (2.6%)

GENERAL - Installation site pain: OPTIVE® = 0, Vismed® = 1 (2.6%)

Timing of adverse effects: 3 months

Factors that predict response: NR

AE = adverse events; CE = cationic emulsion; CMC = carboxymethylcellulose; HA = hyaluronic acid; HPMC = hydroxypropyl methylcellulose; HS = hyaluronate sodium; NR = not reported; O = osmoprotectants; RCT = randomized controlled trial

Appendix D3. Evidence Tables – Adhesion Barrier and Bulking Agent Applications

Table 24: Hyaluronic acid as a Material – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Redorta et al. 2021[101]

Study Design: Multicenter, unblinded RCT of men undergoing radiotherapy for prostate cancer

Device or Material: HA and CS instilled into the bladder (intravesical) prior to radiation therapy plus oral intake. Control group received no treatment.

Contact Duration:

Dose: Sterile solution containing sodium HA 1.6%, 800 mg/50 ml and CS 2%, 1 g/50 ml (HA-SC; iAluRil Prefill; IBSA, Lodi, Italy) for bladder. Oral: 200 mg of CS, 20 mg of HA, 200 mg of quercetin, and 100 mg of curcumin.

Frequency/Duration: Weekly intravesical instillation for 6 weeks plus oral formulation twice a day for 12 weeks

Response: Haematuria

Patient characteristics (gender, mean age): HA/CS: 67 years, all male. Control: 71 years, all male

Number per group: HA/CS: 25. Control: 24

Observed adverse effects: "Intravesical treatment was very well tolerated, as substantiated by full compliance for all patients, who retained the intravesical solution in the bladder for at least 30 min without any distress. Overall, there were seven mild to-moderate (grade 1–2) drug-related adverse events, including *haematuria, and nausea*, and urticaria reported by three patients. There were no serious (grade 3–4) drug-related adverse events or treatment-related withdrawals." No reports of adverse events in the control group.

Timing of adverse effects: ---

Factors that predict response: Lacks a placebo control group.

Systemic Response/Toxicity

Source Citation: Redorta et al. 2021[101]

Study Design: Multicenter, unblinded RCT of men undergoing radiotherapy for prostate cancer

Device or Material: HA and CS instilled into the bladder (intravesical) prior to radiation therapy plus oral intake. Control group received no treatment.

Contact Duration:

Dose: Sterile solution containing sodium HA 1.6%, 800 mg/50 ml and CS 2%, 1 g/50 ml (HA-SC; iAluRil Prefill; IBSA, Lodi, Italy) for bladder. Oral: 200 mg of CS, 20 mg of HA, 200 mg of quercetin, and 100 mg of curcumin.

Frequency/Duration: Weekly intravesical instillation for 6 weeks plus oral formulation twice a day for 12 weeks

Response: Nausea, Uticaria

Patient characteristics (gender, mean age): HA/CS: 67 years, all male. Control: 71 years, all male

Number per group: HA/CS: 25. Control: 24

Observed adverse effects: "Intravesical treatment was very well tolerated, as substantiated by full compliance for all patients, who retained the intravesical solution in the bladder for at least 30 min without any distress. Overall, there were seven mild to-moderate (grade 1–2) drug-related adverse events, including haematuria, nausea, and *urticaria* reported by three patients. There were no serious (grade 3–4) drug-related adverse events or treatment-related withdrawals."

Timing of adverse effects: ---

Factors that predict response: Lacks a placebo control group.

NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day; HA = hyaluronic acid; CS = chondroitin sulfate

Table 25: Adhesion Barrier - Health Effects (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Borghese et al. 2021[120]

Study Design: SR of absorbable adhesion barriers to prevent adhesion formation after laparoscopic myomectomy (surgical procedure to remove uterine fibroids)

Device or Material: Auto-cross-linked HA gel and HA+CMC versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Review with 8 RCTs involving 748 patients. Intervention group: mean age range 28.8 to 37 years, Control group: mean age range 30.1 to 44.3 years.

Number per group: Intervention group: n=392, Control group: n=356.

Observed adverse effects: "None of the selected studies reported any serious adverse event nor complication related to anti-adhesion materials application."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Guo et al. 2021[103]

Study Design: SR of Seprafilm on postoperative small bowel obstruction

Device or Material: Seprafilm

Contact Duration: Absorbed

Dose: 1 or more sheets, surface area varied

Frequency/Duration: Single administration

Response: Small bowel obstruction, Anastomotic leaks, Fistulae

Patient characteristics (gender, mean age): 9 clinical control trials involving 4,351 patients were included. 4 RCTs

Number per group: 2,123 in the Seprafilm group and 2,228 in the control group

Observed adverse effects: "The overall analysis showed that the pooled risk ratio was 0.45 (95% confidence interval = 0.34 to 0.60; P < .00001), indicating that the risk of postoperative small bowel obstruction can be significantly decreased by the application of Seprafilm."

Timing of adverse effects: NR

Factors that predict response: "Although Seprafilm is used to decrease adhesions and obstructions, it is also associated with an increase in anastomotic leaks and fistulae, especially when wrapped around the bowel."

Source Citation: Hajibandeh et al. 2021[102]

Study Design: SR of Seprafilm use on outcomes of abdominal surgery

Device or Material: HA+CMC barrier (Seprafilm) versus no treatment (control)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Anastomotic leak, Ileus, Intra-abdominal abscess, small bowel obstruction, SSIs

Patient characteristics (gender, mean age): Review of 13 RCTs involving 3,665 patients. Patient characteristics NR

Number per group: Seprafilm group: n= 1800, Control group: n=1865

Observed adverse effects: Use of Seprafilm was associated with significantly higher risk of anastomotic leak (3.1%) compared to control (1.6%) (RR 1.85, 95% CI 1.15–3.00, p=0.01). The rate of ileus in the Seprafilm group (4.7%) was not significantly different than the control group (4.8%) (RR 0.97 95% CI 0.68–1.38, p=0.87). The rate of intra-abdominal abscess in the Seprafilm group (3.6%) was not significantly different than the control group (2.5%) (RR 1.46, 95 CI 0.92–2.32, p=0.11). Use of Seprafilm was associated with significantly lower incidence of small bowel obstruction (3.0%) compared to control (5.9%) (RR 0.53, 95% CI 0.38–0.73, p=0.0001). The SSI rates were not significantly different between the Seprafilm (5.2%) and control (4.3%) groups (RR 1.21, 95 CI 0.86–1.70, p=0.28).

Timing of adverse effects: NR

Factors that predict response: Use of Seprafilm in lower gastrointestinal surgeries, open surgeries, elective surgeries, and to treat benign disease demonstrated significantly lower rates of small bowel obstruction and higher rates of anastomotic leaks.

Source Citation: Tafti et al. 2021[128]

Study Design: Single-center, double-blind RCT of females undergoing uterine septum resection

Device or Material: Intrauterine injection of HA

Contact Duration: Absorbed after 7 days

Dose: 1 mL HA gel (100% HA)

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 65 females. HA group 34 years, Control group 33.5 years

Number per group: HA group: n=34, Control group: n=31

Observed adverse effects: "Evidenced by the results, intrauterine injection of hyaluronic acid reduced the incidence of Asherman's syndrome [IUA] in the case [HA] group than the controls with no reported complications."

Timing of adverse effects: 2 months

Factors that predict response: NR

Source Citation: Zhao et al. 2021[104]

Study Design: SR of Seprafilm use to prevent intestinal obstruction after gastrointestinal neoplasms surgery

Device or Material: Seprafilm versus control

Contact Duration: NR

Dose: 1 or more sheets

Frequency/Duration: Single administration

Response: Intestinal obstruction, Complications, Anastomotic leakage, Intra-abdominal infection, Wound infection

Patient characteristics (gender, mean age): Review of 5 RCTs and 5 clinical studies involving 2,937 patients. Patient characteristics were not reported equally across the 10 studies.

Number per group: Seprafilm group n=1334, Control group n=1603

Observed adverse effects: The incidence of postoperative intestinal obstruction was significantly lower in the Seprafilm group than the control (RR, 0.52; 95% CI, 0.38–0.70; p<0.0001). Post-operative complications were significantly lower in the Seprafilm group compared to control (RR, 0.77; 95% CI, 0.61–0.97; p = .03) with low heterogeneity (I^2=24%). Both groups had a similar incidence of: anastomotic leakage (RR, 1.25; 95% CI, 0.68–2.31; p=.48) with low heterogeneity (I^2=0%), intra-abdominal infection (RR, 0.86; 95% CI, 0.46–1.62; p=.65) with low heterogeneity (I^2=0%), and postoperative wound infection (RR, 0.85; 95% CI, 0.39–1.85; p=.68).

Timing of adverse effects: NR

Factors that predict response: "The results of the subgroup analyses based on numbers of Seprafilm used showed that there were significant differences in the incidence of postoperative intestinal obstruction [1 sheet (RR, 0.48; 95% CI, 0.28–0.80); p=.005); 2 sheets (RR, 0.57; 95% CI, 0.34–0.96; p=.04)]". "We concluded that there was no difference in the incidence of anastomotic leakage between the Seprafilm group and the control group. This may be related to the fact that surgeons avoid using Seprafilm around the anastomosis during surgery".

Source Citation: Ekin et al. 2020[131]

Study Design: Single-center RCT of females who underwent laparoscopic surgery due to Deep Infiltrating Endometriosis

Device or Material: NCH gel

Contact Duration: Absorbed

Dose: 40 mL of NCH gel

Frequency/Duration: Single administration

Response: Pain, Dysmenorrhoea, Dyschezia (constipation associated with a defective reflex for defecation), Dyspareunia (genital pain associated with sexual intercourse)

Patient characteristics (gender, mean age): 124 females. NCH gel: 34.4 years, Sterile saline control: 36.4 years

Number per group: NCH gel: n=62, Sterile saline control: n=62

Observed adverse effects: "There was a statistically significant reduction in dysmenorrhoea, dyschezia, dyspareunia at 3rd and 6th month, and in VAS scores at 6th month in NCH gel group compared to the control group."

Timing of adverse effects: NR

Factors that predict response: "One of the reasons why NCH gel may have a positive effect on the quality of life scores can be explained by its anti-proliferative effects on endometriotic implants."

Source Citation: Fei et al. 2020[124]

Study Design: SR of HA gel to prevent IAU formation after miscarriage

Device or Material: HA gel versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Review of 4 RCTs involving 625 females. Patient age NR

Number per group: HA group: n=290, Control group: n=335

Observed adverse effects: No complications were reported for the HA and control groups.

Timing of adverse effects: 6 weeks to 8 months

Factors that predict response: "The matrix composed of hyaluronic acid and fibrin is gradually degraded, and low-molecular-weight hyaluronic acid produced by degradation promotes angiogenesis, which plays an important role in wound healing and helps to prevent the occurrence of adhesions."

Source Citation: Mao et al. 2020[114]

Study Design: Single-center RCT of females with moderate to severe IUAs

Device or Material: NCH gel (MateRegen)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 306 females. MateRegen group mean age 35.9 years. Control group mean age 36.7 years.

Number per group: MateRegen group: n=202, Control group: n=104

Observed adverse effects: "No adverse reaction was observed in both groups of participants."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Wang et al. 2020[133]

Study Design: Single-center RCT of females after operative hysteroscopy for intrauterine adhesions

Device or Material: Auto-cross-linked HA

Contact Duration: Absorbed

Dose: 3 m

Frequency/Duration: Single administration

Response: Bleeding, Infection

Patient characteristics (gender, mean age): HA only: 31.7 years, all female. HA plus IUD: 31.7 years, all female. IUD only: 33.9 years, all female.

Number per group: HA only: n=30, HA plus IUD: n=24, IUD only: n=35

Observed adverse effects: "None of the 89 patients showed excessive bleeding, infection, or other complications."

Timing of adverse effects: NR

Factors that predict response: "The endometrium after therapy and the clinical pregnancy rate had a superior trend toward in the HA group than the IUD group. In our opinion, IUDs may induce an excessive inflammatory reaction that would cause IUA recurrence and thin the endometrium. Physical barriers such as HA gel are interposed between adjacent injured surfaces to avoid direct contact after surgery."

Source Citation: Zheng et al. 2020[125]

Study Design: SR of HA gel to prevent IUA after intrauterine operation

Device or Material: HA gel versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Review of 7 RCTs involving 952 females

Number per group: HA group: n=455, Control group: n=497

Observed adverse effects: "None of the seven studies reported gel-related or surgical-related complications, including hemorrhage, perforation or cervical laceration."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Zhou et al. 2020[115]

Study Design: Single-center, double-blind RCT of females with moderate to severe IUAs

Device or Material: Auto-cross linked HA gel (MateRegen gel) versus control

Contact Duration: NR

Dose: 3 m

Frequency/Duration: Single administration

Response: Change in menstrual pattern

Patient characteristics (gender, mean age): 145 females. HA group: mean age 31.9 years, Control group: mean age 31.9 years.

Number per group: HA group: n=122, Control group: n=123

Observed adverse effects: No surgical complications were reported for the HA and control groups. The change in the menstrual pattern after surgery in the treatment group (87.7%, 107/122) was not significantly different (p = .064) from that of the control group (76.4%, 97/123).

Timing of adverse effects: 1, 2 and 3 months

Factors that predict response: NR

Source Citation: Fei et al. 2019[126]

Study Design: SR of HA gel to prevent IAU formation after hysteroscopic adhesiolysis

Device or Material: HA gel versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Review of 2 RCTs and 4 clinical studies involving 394 females

Number per group: HA group: n=176, Control group: n=218

Observed adverse effects: No complications were reported for the HA and control groups.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kim et al. 2019[112]

Study Design: Single-center RCT of patients undergoing laparoscopic radical cystectomy

Device or Material: HA+CMC gel (Guardix-sol, Hanmi Medicare, Seoul, South Korea)

Contact Duration: NR

Dose: 5 g evenly applied on whole the lower abdominal cavity including the anastomotic site using the spray instrument

Frequency/Duration: Single administration

Response: Adhesive bowel obstruction, Rectal injury from surgery, Other complications not described

Patient characteristics (gender, mean age): Guardix-sol group: 64.6 years, 32 male, 6 female, Control group: 68.6 years, 32 male, 6 female

Number per group: Guardix-sol group: n=38, Control group: n=38

Observed adverse effects: One patient in the experimental group suffered a rectal injury during surgery. 8 patients in the Guardix-sol group and 20 patients in the control group "had postoperative complications other than blood transfusion. Complication rates did not differ significantly in the experimental and control groups, except for adhesive bowel obstruction, which occurred in zero and six patients, respectively ($p = 0.025$)."

Timing of adverse effects: NA

Factors that predict response: "High molecular weight HA is hydrophilic, non-immunogenic, and viscoelastic, enabling it to coat the mucosal surface and have lubricating activity. HA reduces or prevents trauma in surgical patients due to its physical properties."

Source Citation: Lee et al. 2019[109]

Study Design: Single-center RCT of patients undergoing colorectal surgery

Device or Material: HA+CMC barrier (Seprafilm) or HA+CMC gel (Guardix) versus control

Contact Duration: Absorbed

Dose: 5 g of Guardix

Frequency/Duration: Single administration

Response: Small bowel obstruction rate, Pneumonia, SSI, Anastomosis leakage, Intra-abdominal abscess

Patient characteristics (gender, mean age): Seprafilm group: 63.2 years, 103 male, 64 female, Guardix group:60.3 years, 87 male, 68 female, Control group: 62.5 years, 87 male, 78 female

Number per group: Seprafilm group: n=167, Guardix group: n=155, Control group: n=166

Observed adverse effects: "The overall complication rates did not differ significantly between the Guardix and Seprafilm groups (12.9% vs. 15.5% vs. 18.7%; P = 0.533." Complications included pneumonia, SSI, anastomosis leakage, intra-abdominal abscess; all related to surgery."Small bowel obstruction developed in 9 patients (5.8%) in the Guardix group and 9 patients (7.1%) in the Seprafilm group and 19 patients (11.4%) in the control group."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Li et al. 2019[116]

Study Design: Multi-center, double-blind RCT of females undergoing dilation and curettage

Device or Material: NCH gel (MateRegen) versus control

Contact Duration: NR

Dose: 3 m

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 274 females. MateRegen group: mean age 26.94 years, age range 17-44 years. Control group: mean age 26.84 years, age range 19-45 years.

Number per group: MateRegen group: n=137, Control group n=137

Observed adverse effects: "No serious adverse events were observed during the study period, and there were no prolonged hospitalizations or reoperations owing to adverse events. Furthermore, no adverse events were attributed to the NCH gel treatment." "No signs of postoperative infection were reported in either group."

Timing of adverse effects: 3 months

Factors that predict response: NR

Source Citation: Saito et al. 2019[107]

Study Design: Single-center RCT of patients who underwent elective colectomy for colon cancer

Device or Material: HLA+CMC barrier (Seprafilm) versus control

Contact Duration: Absorbed in 7 days

Dose: 2 sheets (12.7 cm × 14.7 cm)

Frequency/Duration: Single administration

Response: SSI, Suture failure, Respiratory complications, Cardiovascular complications

Patient characteristics (gender, mean age): Seprafilm group: median age 69 years, 90 male, 76 female, Control group: median age 70 years, 98 male, 81 female

Number per group: Seprafilm group: n=166, Control group: n=179

Observed adverse effects: "As for perioperative complications, surgical-site infection (1.2% in the seprafilm group and 3.4% in the control group), suture failure (3.6% and 6.7%), and respiratory complications (1.2% and 0%) and cardiovascular complications (1.2% and 0.6%) did not differ significantly between the groups."

Timing of adverse effects: Perioperative

Factors that predict response: NR

Source Citation: Can et al. 2018[117]

Study Design: Single-center RCT of females who underwent curettage for retained placental tissue

Device or Material: NCH gel (MateRegen) versus control

Contact Duration: Absorbed

Dose: 5 mL NCH gel

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): NCH gel group: 30.1 years, all women, Control group: 28.9 years, all women

Number per group: NCH gel group: n=20, Control group: n=28

Observed adverse effects: "No complications or adverse events associated with intrauterine application of gel were reported in the intervention group, and no complications related to curettage or follow-up hysteroscopy were observed in either group."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Farag et al. 2018[1]

Study Design: SR of HA gel to prevent IAU formation after laparoscopic gynecologic surgery

Device or Material: HA gel (Hyalobarrier Gel) versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Adhesions

Patient characteristics (gender, mean age): One RCT involving 43 females. Patient age NR

Number per group: HA group: n=25, Control group: n=18

Observed adverse effects: "Hyalobarrier Gel placement and "full conditioning" resulted in a significantly decreased incidence of adhesions compared with standard laparoscopy (25% and 100%, respectively; p = .0005)."

Timing of adverse effects: NR

Factors that predict response: "Pain was associated with adhesions, as shown by conscious laparoscopic pain mapping. Filmy mobile adhesions resulted in the highest verbal pain scores followed by dense mobile adhesions, filmy fixed adhesions, and dense fixed adhesions. Pain scores were highest when adhesions were between a segment of bowel and an ovary."

Source Citation: Hooker et al. 2018[129]

Study Design: Multi-center, double-blind RCT of females undergoing dilation and curettage

Device or Material: Auto-cross-linked HA gel versus control

Contact Duration: NR

Dose: 10 mL HA gel

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 143 females. HA group: mean age 34.1 years, age range 20-44 years. Control group: mean age 33.6 years, age range 19-44 years.

Number per group: HA group: n=73, Control group: n=70

Observed adverse effects: No complications were reported for the HA and control groups.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Liu et al. 2018[127]

Study Design: SR of HA gel to prevent IAU formation after gynecologic surgery

Device or Material: HA gel versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Discomfort, Uterine perforation

Patient characteristics (gender, mean age): Review of 6 RCTS involving 564 females. HA group: mean age 32.8 years. Control group: mean age 32.8 years.

Number per group: HA group: n=286, Control group: n=278

Observed adverse effects: "Only one trial, conducted by Hooker et al. [9], reported complications associated with use of hyaluronic acid gel. The major complications were patient discomfort and uterine perforation, with no statistically significant differences between the 2 groups."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Yan and Xu 2018[121]

Study Design: SR of adjuvants to prevent IAU formation after gynecologic surgery

Device or Material: Auto–cross-linked HA gel and HA+CMC barrier versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Review of 7 RCTs involving 748 females. Patient age NR for all RCTs.

Number per group: NR

Observed adverse effects: Patient complications were not reported for the included RCTs.

Timing of adverse effects: 1 month to 8 months

Factors that predict response: NR

Source Citation: Hooker et al. 2017[130]

Study Design: Multi-center, double-blind RCT of females undergoing dilation and curettage

Device or Material: Auto-cross-linked HA gel

Contact Duration: NR

Dose: 10 mL HA gel

Frequency/Duration: Single administration

Response: Cervix laceration, Excessive bleeding, Infection, Pain, Uterus perforation

Patient characteristics (gender, mean age): 149 females. HA group: mean age 35.0 years, age range 20-44 years. Control group: mean age 33.9 years, age range 19-44 years.

Number per group: HA group: n=77, Control group: n=72

Observed adverse effects: Cervix laceration was experienced by one patient in the HA group (1.3%) and no patients in the control group (p=1.00). Three patients in the HA group had excessive bleeding (3.9%) compared to one patient in the control group (1.4%) (p=0.62). Two patients in the HA group had postoperative infections (2.6%) compared to one patient in the control group (1.4%) (p=1.00). Four patients in the HA group had postoperative pain (5.2%) compared to three patients in the control group (4.2%) (p=1.00). Uterus perforation was experienced by one patient in the HA group (1.3%) and no patients in the control group (p=1.00).

Timing of adverse effects: 10 weeks

Factors that predict response: NR

Source Citation: Healy et al. 2016[122]

Study Design: SR of postoperative prevention measures on IAU formation after operative hysteroscopy

Device or Material: HA gel versus control, HA+CMC gel versus control

Contact Duration: NR

Dose: 10 ml HA gel, 10 ml HA+CMC gel

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Review of 3 clinical studies involving 262 females. Patient age for HA groups NR. HA+CMC and HA+CMC control groups: age range 18-65 years.

Number per group: HA group: n=112, HA control group: n=110, HA+CMC group: n=18, HA+CMC control group: n=22

Observed adverse effects: No complications were reported for the HA, HA control, HA+CMC, or HA+CMC control groups.

Timing of adverse effects: 9 weeks to 3 months

Factors that predict response: NR

Source Citation: Kiefer et al. 2016[108]

Study Design: Multicenter, single (patient)-blinded, RCT of women undergoing caesarean delivery

Device or Material: HA+CMC barrier (Seprafilm) versus control

Contact Duration: Absorbed in 7 days

Dose: 1 sheet

Frequency/Duration: Single administration

Response: Postoperative complications (ileus, abscess formation, wound complication Bowel or bladder injury, hysterectomy, blood transfusion, and uterine rupture or dehiscence

Patient characteristics (gender, mean age): 753 females. HA+CMC group: 30.4 years, Control group: 30.9 years

Number per group: HA+CMC group: n=380, Control group: n=373

Observed adverse effects: HA+CMC vs. Control Any wound complication: 2.1% vs. 0.8%, p = 0.22, RR = 2.8(0.7 – 11.0)

Timing of adverse effects: 6 to 8 weeks

Factors that predict response: "Routine use of a HA-CMC adhesion barrier did not reduce the incidence of adhesions at the time of subsequent cesarean delivery. Similarly, no differences in operative times or the incidence of complications were identified." "With regard to the safety of HA-CMC, we did not identify any short-term safety concerns. While not specifically powered for safety data, the large number of enrolled patients, the lack of adverse events, and similar postoperative course for both groups are reassuring."

Source Citation: Hindocha et al. 2015[123]

Study Design: SR of solid agents, gel agents, liquid agents and pharmacological agents, used as adjuvants to prevent formation of adhesions after gynecologic surgery

Device or Material: HA+CMC barrier versus control

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Adverse outcomes, Pelvic pain (new pain, change in severity of pain)

Patient characteristics (gender, mean age): Review of two SRs with 47 RCTs. "Patient characteristics were reported inconsistently across the studies in the reviews."

Number per group: Between 59 and 127 females in HA+CMC and control groups

Observed adverse effects: "Ahmad 2014(a) identified only one trial that investigated the adverse effects of sodium hyaluronate and carboxymethylcellulose, with a total of 59 participants treated with the agent. No adverse effects secondary to the agent were reported." "No review found any trials that investigated the effect of sodium hyaluronate and carboxymethylcellulose on postoperative pelvic pain."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Liu et al. 2015[118]

Study Design: Multi-center, reviewer blinded, RCT of patients undergoing laparoscopic surgery for the primary removal of adhesion, myoma, ovarian cyst, or endometriotic cyst

Device or Material: NCH gel (HyaRegen NCH gel) versus saline placebo

Contact Duration: NR

Dose: 160 ml NCH gel or saline

Frequency/Duration: Single administration

Response: Adverse events were noted but not described

Patient characteristics (gender, mean age): 196 females, age range 18-45 years

Number per group: NCH group: n=102, Saline group: n=94

Observed adverse effects: "During the study period, no adverse events were attributed to the NCH gel treatment. No serious adverse events were observed. The adverse events were mostly mild, spontaneously resolved, and comparable in the 2 groups."

Timing of adverse effects: 3 days, 30 days, 9 weeks

Factors that predict response: "In a preclinical animal study, the maximum volume of NCH gel administered without any adverse effects was at least 15-fold higher than that applied in this study (unpublished data)." "Owing to the high safety threshold, 160 mL of NCH gel was applied to the abdominopelvic cavity to provide broad coverage on the organ and tissue surfaces that sustained surgical trauma as well as their adjacent and suspected adhesiogenic surfaces, and thus a global effect on reduced adhesion formation throughout the cavity. In the contrast, the doses for most site-specific gels are within 40 mL because of safety and/or cost concerns".

Source Citation: Hu et al. 2015[132]

Study Design: Single-center, double blind, RCT of patients undergoing colorectal surgery with a defunctioning ileostomy or colostomy

Device or Material: HA gel or chitosan versus control

Contact Duration: HA is absorbed

Dose: NR

Frequency/Duration: Single administration

Response: Post-operative short-term complications: peristomal curaneous infection, intra-abdominal hemorrhage, abscess Long-term postoperative complications: intestinal obstruction, anastomotic leakage

Patient characteristics (gender, mean age): HA gel group: 50.3 years, 52% male, Chitosan group: 53 years, 31% male, Control group: 51 Years, 72% male

Number per group: HA gel group: n=29, Chitosan group: n=29, Control group: n=29

Observed adverse effects: No postoperative complications, 30 days. Long-term complications were similar for each group: Sodium hyaluronate gel 10.5%, chitosan 16.2%, control 17.9%.

Timing of adverse effects: See above. Longest follow-up was 42 months.

Factors that predict response: NR

Source Citation: Berdah et al. 2014[110]

Study Design: Multicenter, single (patient)-blinded, RCT of patients undergoing laparoscopic colorectal and/or small bowel surgery

Device or Material: HA+CMC powder (Sepraspray Adhesion Barrier) versus no adhesion barrier

Contact Duration: HA+CMC powder is completely absorbed in less than 28 days

Dose: 1 to 10 grams, mean ± SD amount of powder applied was 2.7 ± 1.4 g

Frequency/Duration: Single administration

Response: Serious adverse events: pelvic abscess, abdominal abscess, SSI, Anastomotic fistula, Peritonitis

Patient characteristics (gender, mean age): HA+CMC group: 57.6 years, 50.5% male. Control group: 56.1 years, 49% male

Number per group: HA+CMC group: n=105, Control group: n=104

Observed adverse effects: Any adverse event: HA+CMC 62.9%, control 39.4%, p <0.001. At least 1 serious adverse event: HA+CMC 27.6%, control 10.6%, p <0.001. Pelvic abscess: HA+CMC 4.8%, control 1.9%. Abdominal abscess: HA+CMC 3.8%, control 0%. Ileus: HA+CMC 2.9%, control 0%. "At least one SSI was experienced by 22/105 (21%) of patients in the HA/CMC powder group versus 15/104 (14%) in the no adhesion barrier group (P = 0.216), and at least one serious SSI by 13/105 (12%) versus 9/104 (9%), respectively (P = 0.38)." HA/CMC versus control: serious SSIs of pelvic abscess (4.8% and 1.9%, respectively), anastomotic fistula (2.9% and 3.8%), and peritonitis (1.9% and 2.9%) were not statistically different.

Timing of adverse effects: Study assessment was 28 to 35 days post-surgery. HA+CMC powder is completely absorbed in less than 28 days.

Factors that predict response: There was no relationship between the amount of HA+CMC powder used and incidence of adverse events or serious adverse events. "The probability of a serious adverse event was greater in the HA/CMC powder versus the no adhesion barrier group (OR = 4.08; 95% CI, 1.67–9.95; P = 0.002), in younger patients (for age in years, OR = 0.94; 95% CI, 0.91–0.98; P = 0.002), and in patients who smoked frequently (OR = 1.06; 95% CI, 1.02–1.10; P = 0.006)." "The powder formulation of HA/CMC used in this study is likely to be an important contributing factor for the increased frequency of adverse events and serious adverse events." "Due to the potential for greater diffusion of the powder formulation, the authors speculate that migration away from the application site to anastomoses could have occurred in some cases. Furthermore, over-hydration of the HA/CMC powder might have resulted in pooling of the resulting gel away from the application site, raising the possibility of migration onto an anastomosis or provision of a nidus for abscess; such migration to anastomoses might increase the rate of SSIs."

Source Citation: Chung et al. 2013[113]

Study Design: Single-center RCT of patients undergoing surgery for chronic epididymitis

Device or Material: HA+CMC barrier (Guardix-sol) versus control

Contact Duration: Evaluated at 24 weeks

Dose: 3 g

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): HA+CMC group: 56.6 years, all male. Control group: 58.5 years, all male

Number per group: HA+CMC group: n=22, Control group: n=21

Observed adverse effects: There were no postoperative complications such as wound infection or hematoma in either group. HA+CMC was not responsible for any adverse events. HA+CMC was effective at reducing pain associated with epididymitis.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Dupré et al. 2013[106]

Study Design: Multi-center RCT of metastatic colorectal cancer patients requiring 2-stage hepatectomy

Device or Material: HA+CMC barrier (Seprafilm) versus control

Contact Duration: Up to 90 days after surgeries

Dose: 4 sheets (12.7 × 15.2 cm^2)

Frequency/Duration: Single administration

Response: Complications, Mortality, Parietal abscess, Right portal vein embolization, Small bowel obstruction

Patient characteristics (gender, mean age): First-stage Seprafilm group: 19 male, 22 female, mean age 61 years, age range 40-79 years. First-stage Control group: 11 male, 2 female, mean age 55 years, age range 48-76 years. Second-stage Seprafilm and Control group patient characteristics NR.

Number per group: First-stage Seprafilm group: n=41, First-stage Control group: n=13, Second-stage Seprafilm group: n=30, Second-stage Control group: n=11

Observed adverse effects: "No patient died within 90 days of the first-stage hepatectomy. The overall complication rate was 48.8% in the HA membrane group [First-stage Seprafilm group] and 30.8% among controls [First-stage Control group]." "Eighteen patients had a grade I or II complication (36.6% in the HA membrane group [First-stage Seprafilm group] and 23.1% in controls [First-stage Control group]). Most of these minor complications were related to urinary tract infections, minor pleural effusion, blood transfusion, or positioning of a gastric tube. The rate of parietal abscess was low (2.4% in the HA membrane group [First-stage Seprafilm group] and 15.4% in controls [First-stage Control group]). Seven patients (5 in the HA membrane group [First-stage Seprafilm group] and 2 controls [First-stage Control group]) had postoperative right portal vein embolization." Seven patients had at least one complication in the Second-stage Seprafilm group (23.3% and six patients had at least one complication in the Second-stage Control group (p=0.07). "One patient in each [Second-stage] group required a percutaneous drainage for a biloma (grade IIIa), and 2 patients in the [Second-stage] control group had a reoperation (grade IIIb), one for a small bowel obstruction and the other for a major parietal abscess."

Timing of adverse effects: 30 days and 90 days after surgeries

Factors that predict response: "Although the immediate postoperative complication rate was somewhat higher in the HA membrane group, this was due to nonspecific events unrelated to its use or to liver surgery."

Source Citation: Ouaïssi et al. 2012[105]

Study Design: SR of surgical literature published between 1995 and 2009 on post-operative adhesions after gastrointestinal surgery

Device or Material: Seprafilm

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Post-operative adhesions, Intestinal fistula

Patient characteristics (gender, mean age): 5 RCTs: Fazio et al. . Reduction in adhesive small-bowel obstruction by Seprafilm(registered trademark) adhesion barrier after intestinal resection. Dis Colon

Number per group: Rectum 2006;49(1):1—11. RCT, n = 1,791. Kunosoki et al. Bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm) in surgery for rectal carcinoma: A prospective randomized clinical trial. Surgery Today 2005;35(11):940—5. RCT, n = 62. Becker et al... Prevention of postoperative abdominal adhesions by a sodium hyaluronate based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. J Am Coll Surg 1996;183(4):297—306. RCT, n = 183. Tang et al. . Bioresorbable adhesion barrier facilitates early closure of the defunctioning ileostomy after rectal excision: a prospective, randomized trial. Dis Colon Rectum 2003;46(9):1200—7. RCT, n = 70. Vrijland et al. Fewer intraperitoneal adhesions with use of hyaluronic acid carboxymethylcellulose membrane: A randomized clinical trial. Ann Surg 2002;235(2):193—9. RCT, n = 71.

Observed adverse effects: "As regards adverse effects, the use of Seprafilm has not been shown to result in a significant increase in morbidity, but it must be noted that when Seprafilm was placed in direct contact with intestinal anastomoses, a significant increase in the rate of intestinal fistulas and their secondary morbidity was observed."

Timing of adverse effects: NR

Factors that predict response: "In sum, there are sufficient studies with an adequate level of evidence to prove that the use of Seprafilm allows a significant reduction in the number, extent, and severity of post-operative adhesions, both at the incisional interface and at the operative site.

Source Citation: Mais et al. 2012[119]

Study Design: SR of HA gel use to prevent intraperitoneal adhesion and IUA after endoscopic gynecological surgery

Device or Material: Auto-cross-linked HA gel (Hyalobarrier) versus control

Contact Duration: Up to 3 months

Dose: NR

Frequency/Duration: Single administration

Response: Abdominal complaints (nausea, vomiting), Nausea, Vomiting

Patient characteristics (gender, mean age): Review of 5 RCTs involving 335 females. Patient characteristics NR for all RCTs.

Number per group: Hyalobarrier group: n=167, Control group: n=168

Observed adverse effects: "A total of six adverse events (three in gel [Hyalobarrier] groups and three in control groups) were reported in the two RCTs performed in laparoscopy. In one trial two patients had nausea and one patient had vomiting in gel [Hyalobarrier] group and one patient had nausea in control group [8]. No adverse events were reported in the three RCTs performed in hysteroscopy [16,17,19]."

Timing of adverse effects: Two or three months

Factors that predict response: NR

Source Citation: Fossum et al. 2011[111]

Study Design: Multicenter, double-blinded, RCT of patients undergoing laparoscopic myomectomy

Device or Material: HA+CMC barrier (Sepraspray Adhesion Barrier)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Adverse events, Deep vein thrombosis, Intra-abdominal abscess, SSI rate

Patient characteristics (gender, mean age): 41 females. Sepraspray group: mean age 36 years. Control group: mean age 37 years.

Number per group: Sepraspray group: n=21, Control group: n=20

Observed adverse effects: "No overall difference was noted in the number of patients with adverse events in either the control (n=12; 60% of patients) or Sepraspray Adhesion Barrier treated (n=14; 67% of patients) groups. No adverse event directly related to Sepraspray Adhesion Barrier was identified by the surgeons, nor was there any report of surgical site infection, intra-abdominal abscess formation, or deep vein thrombosis."

Timing of adverse effects: 1 week, 1 month

Factors that predict response: NA

Source Citation: van der Wal et al. 2011[150]

Study Design: RCT of patients requiring Hartmann's procedure for sigmoid diverticulitis or obstructed rectosigmoid, long-term follow-up

Device or Material: Seprafilm under the midline and in the pelvis during laparotomy or no barrier

Contact Duration:

Dose: NR

Frequency/Duration: Single administration

Response: Abdominal complaints (pain, nausea, obstipation)

Patient characteristics (gender, mean age): Seprafilm: 66.9 years, 65% male, Control: 67.8 years, 44% male

Number per group: Seprafilm: 16, Control: 19

Observed adverse effects: "Analysis of the questionnaire revealed that abdominal complaints (pain, nausea, obstipation [severe form of constipation]) occurred significantly less often in the Seprafilm group than in the control group: 6 patients (35%) in the Seprafilm group experienced at least 1 episode of abdominal complaints of 3 months or longer, whereas 14 patients (78%) in the control group went through at least 1 episode of abdominal complaints of 3 months or longer (P = 0.018)."

Timing of adverse effects: Follow-up: Seprafilm 96 months (11 – 118), control 98 months (19 – 119)

Factors that predict response: NR

Source Citation: Zhao et al. 2021[104]

Study Design: SR of Seprafilm use to prevent intestinal obstruction after gastrointestinal neoplasms surgery

Device or Material: Seprafilm versus control

Contact Duration: NR

Dose: 1 sheet

Frequency/Duration: Single administration

Response: Aspartate aminotransferase concentration, Alanine aminotransferase concentration, Blood urea nitrogen concentration, Creatinine concentration, WBC count

Patient characteristics (gender, mean age): Review of 2 RCTs and 1 clinical study involving 750 patients. Seprafilm group: 214 male, 137 female. Control group: 231 male, 168 female.

Number per group: Seprafilm group n=351, Control group n=399

Observed adverse effects: WBC counts and concentrations of aspartate aminotransferase, alanine aminotransferase, and blood urea nitrogen were not significantly different between groups on POD5 and 7. On POD 5, serum creatinine was significantly higher in the Seprafilm group than the control group (WMD, 0.15; 95% CI, 0.05–0.25; I^2=78%; p=.003), but there was not a significant difference between groups on POD 7.

Timing of adverse effects: POD 5 and 7

Factors that predict response: The authors noted "that Seprafilm did not cause acute postoperative inflammation in short term and had almost no effect on the liver and renal function of the patients."

Source Citation: Kiefer et al. 2016[108]

Study Design: Multicenter, single (patient)-blinded, RCT of women undergoing caesarean delivery

Device or Material: HA+CMC barrier (Seprafilm) compared with no treatment

Contact Duration: Absorbed in 7 days

Dose: 1 sheet

Frequency/Duration: Single administration

Response: Fever

Patient characteristics (gender, mean age): HA+CMC: 30.4 years, all women, No treatment: 30.9 years, all women

Number per group: HA+CMC: 380 No treatment: 373

Observed adverse effects: HA+CMC vs. no treatment, Fever: 4.5% vs. 3.0%, p = 0.34, RR = 1.5 (0.7 – 3.3)

Timing of adverse effects: 6 to 8 weeks

Factors that predict response: "With regard to the safety of HA-CMC, we did not identify any short-term safety concerns. While not specifically powered for safety data, the large number of enrolled patients, the lack of adverse events, and similar postoperative course for both groups are reassuring."

Source Citation: Liu et al. 2015[118]

Study Design: Multi-center, reviewer-blinded, RCT of patients undergoing laparoscopic surgery for the primary removal of adhesion, myoma, ovarian cyst, or endometriotic cyst

Device or Material: NCH gel (HyaRegen NCH gel) versus saline placebo

Contact Duration: NR

Dose: 160 ml NCH gel or saline

Frequency/Duration: Single administration

Response: C-reactive protein concentration, Platelet count, RBC count, WBC count, Neutrophil count, Hemoglobin concentration, Aspartate aminotransferase concentration, Alanine aminotransferase concentration, Albumin concentration, Globin concentration, Total protein concentration, Blood urea nitrogen concentration,

Creatinine concentration, Total bilirubin concentration, Glucose concentration, Potassium concentration, Sodium concentration, Chloride concentration

Patient characteristics (gender, mean age): 196 females, age range 18-45 years

Number per group: NCH group: n=102, Saline group: n=94

Observed adverse effects: "Two adverse events from laboratory tests, defined as clinically significant changes from baseline (WBC count and blood glucose level), were reported at 9 weeks after surgery in the control group, whereas there were no clinical significantly changes from baseline in the NCH gel group. There were no prolonged hospitalizations or surgeries related to the adverse events."

Timing of adverse effects: 3 days, 30 days, 9 weeks

Factors that predict response: NR

Source Citation: Hu et al. 2015[132]

Study Design: Single-center, double blind, RCT of patients undergoing colorectal surgery with a defunctioning ileostomy or colostomy

Device or Material: HA gel or chitosan versus control

Contact Duration: HA is absorbed

Dose: NR

Frequency/Duration: Single administration

Response: WBC count, Liver function, Renal function, Liver toxicity, Renal toxicity

Patient characteristics (gender, mean age): HA gel group: 50.3 years, 52% male, Chitosan group: 53 years, 31% male, Control group: 51 Years, 72% male

Number per group: HA gel group: n=29, Chitosan group: n=29, Control group: n=29

Observed adverse effects: "There was no significant toxicity to liver or kidney related to the use of sodium hyaluronate gel or chitosan. Liver function, renal function, and white blood cell (WBC) levels within 2 weeks after the initial surgery were comparable among the 3 groups."

Timing of adverse effects: Up to 42 months

Factors that predict response: NR

Source Citation: Mais et al. 2012[119]

Study Design: SR of HA gel use to prevent intraperitoneal adhesion and IUA after endoscopic gynecological surgery

Device or Material: Auto-cross-linked HA gel (Hyalobarrier) versus control

Contact Duration: Up to 3 months

Dose: NR

Frequency/Duration: Single administration

Response: Fever

Patient characteristics (gender, mean age): w of 5 RCTs involving 335 females. Patient characteristics NR for all RCTs.

Number per group: Hyalobarrier group: n=167, Control group: n=168

Observed adverse effects: In one RCT performed in laparoscopy, two patients in the Control group "had postoperative fever (≤38.5°C)."

Timing of adverse effects: Two or three months

Factors that predict response: NR

ACH = alginate hyaluronate-carboxymethylcellulose; CMC = carboxymethylcellulose; HA = sodium hyaluronic acid; IUA = intrauterine adhesion; IUD = intrauterine device; NA = not applicable; NCH = new crosslinked hyaluronan; NR = not reported; Obs = observational; POD = post-operative day; Retro = retrospective; R = reliable; RBC = red blood cell; RR = risk ratio; SR = systematic review; SSI = surgical site infection; Dose = mg/kg/day; WBC = white blood cell

Table 26: Anti-adhesion: Nasal packing - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Deng et al. 2018[136]

Study Design: Single-center RCT of patients undergoing tympanoplasty for adhesive otitis media

Device or Material: HA (MeroGel)

Contact Duration: Absorbed in 2 weeks

Dose: Two identical pieces about 0.5 0.5 0.2 cm3 in size.

Frequency/Duration: Single administration

Response: Hearing loss, Re-otorrhea (ear discharge), Prosthesis extrusion

Patient characteristics (gender, mean age): HA: 40.8 years, 44 male, 28 female, Cartilage: 38.6 years, 25 male, 39 female, HA plus cartilage: 39.2 years, 35 male, 34 female

Number per group: HA: 72, Cartilage: 64, HA plus cartilage: 69

Observed adverse effects: "No patient needed reoperations or suffered from sensorineural hearing loss after surgery. There were no significant differences between any two of the three groups in the rates of re-otorrhea, or extrusion of the prosthesis."

Timing of adverse effects: NR

Factors that predict response: "HA can be safely and easily used in clinical applications. It is inert and stays at biologic sites over extended periods of time. Hyaluronic acid is suitable for otologic surgery because it has some physical properties, such as not causing or even regulating inflammatory reactions, and binding water as a viscoelastic cushion in the healing process."

Source Citation: Chen et al. 2017[134]

Study Design: SR of RCTs to investigate the influence of hyaluronan nasal dressing on the clinical outcome of ESS.

Device or Material: HA: Sepragel and MeroGel

Contact Duration: MeroGel absorbed in 2 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Synechia, Infection

Patient characteristics (gender, mean age): Mean ages were 44.8, 41.5, and 39.1 years with one study not reporting. Percent female was 22%, 6%, and 17% with one study not reporting.

Number per group: 4 RCTs n = 352

Observed adverse effects: HA nasal dressing failed to reduce synechia (adhesion in the nose) (OR 0.45 [95% CI, 0.19 –1.03]; p = 0.06), crust (OR 1.00 [95% CI, 0.20 –5.09]; p = 1.00), and infection (OR 0.84 [95% CI, 0.46 –1.53]; p = 0.56) compared with the control group in patients who underwent ESS. No adverse events or complications were reported in 2 of the included RCTs

Timing of adverse effects: Follow-up times of 8 and 12 weeks.

Factors that predict response: "Hyaluronan is known as an ideal material for nasal dressings with excellent biocompatibility and multifunctional role for scar-free wound healing. Results of previous studies revealed that

hyaluronan could improve the reepithelialization, modulate inflammatory response and stimulate angiogenesis, and markedly reduce fibrous scarring."

Source Citation: Fong et al. 2017[135]

Study Design: SR to evaluate endoscopic outcomes compared to standard regimens and controls for preventing post sinus surgery complications. RCTs used in meta-analysis.

Device or Material: HA versus a control for post-endoscopic sinus surgery care. Absorbable dressing packs of hyaluronic acid, non-absorbable dressing packs impregnated with hyaluronic acid, and topical preparations such as nebulised ampules, sprays and creams

Contact Duration: Reabsorbed and non-resorbable

Dose: NR

Frequency/Duration: Single administration of packs. Daily application of topical sprays

Response: Adhesions

Patient characteristics (gender, mean age): Used 3 categories of HA: Absorbable dressing packs of hyaluronic acid, non-absorbable dressing packs impregnated with hyaluronic acid, and topical preparations such as nebulised ampules, sprays and creams.

Number per group: 13 studies n = 501 (5 double-blind RCTs, 5 single-blind RCTs, and 3 prospective comparisons)

Observed adverse effects: "Absorbable hyaluronic acid dressing preparation appears to be well tolerated, according to patient satisfaction scores across two of the studies when compared with non-absorbable packs."

Timing of adverse effects: ---

Factors that predict response: "It is clear that hyaluronic acid in all preparations is safe and well-tolerated by patients, as evidenced by only one adverse event not related directly to hyaluronic acid, and the overall satisfaction with its use in absorbable nasal packs."

Source Citation: Shi et al. 2013[137]

Study Design: RCT of patients undergoing bilateral ESS

Device or Material: PureRegen Gel Sinus (absorbable crosslinked HA hydrogel)

Contact Duration: 7 day

Dose: 2 mL

Frequency/Duration: 2 applications, second application 2 days after surgery

Response: Synechia (adhesions), Scar tissue

Patient characteristics (gender, mean age): Treated: PureRegen Gel plus gelatin sponge and Merocel (compressed, dehydrated sponge composed of hydroxylated polyvinyl acetate). Control: Gelatin sponge and Merocel. Treatment was randomized to sinus side in each patient. 44.8 years, 43 males and 12 females

Number per group: 55 patients

Observed adverse effects: No adverse event related to treatment was observed.

Timing of adverse effects: ---

Factors that predict response: "In this prospective, multicenter, randomized, controlled trial, data analyses suggest PureRegen Gel Sinus as nasal dressing/packing after ESS is safe and promotes the postoperative

reepithelization process and reduces the postoperative presence of synechia (obstructing and non-obstructing), edema, crusting, and mild mucopurulent drainage."

Source Citation: Wu et al. 2011[138]

Study Design: RCT of patients with unilateral primary chronic dacryocystitis (an infection of the lacrimal sac, secondary to obstruction of the nasolacrimal duct) undergoing endonasal endoscopic dacryocystorhinostomy

Device or Material: MeroGel (esterified derivative of hyaluronan)

Contact Duration: Reabsorbed within 2 weeks

Dose: Gel covered wound

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Merogel: 41.8 years, 27 males, 85 females, Control: 40.4 years, 32 males, 83 females

Number per group: Merogel: 112, Control: 115

Observed adverse effects: None reported

Timing of adverse effects: ---

Factors that predict response: "We observed that the rate of scar formation was lower in the Merogel group, with a lower incidence of ostial failure than in the control group. These results suggest that Merogel coverage can significantly improve the success rate of ostial patency for EES-DCR by stimulating wound healing and mucosa epithelialization and by preventing the formation of fibrotic tissue around the ostia."

ESS = endoscopic sinus surgery; NA = not applicable; NR = not reported; Obs = observational; OR = odds ratio; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 27: Barrier gel for oral lesions - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Al-Shammari et al. 2018[139]

Study Design: RCT using split-mouth design of patients with moderate to severe chronic periodontitis

Device or Material: Gengigel HA gel

Contact Duration: Study lasted 12 weeks, unclear how long the HA remained in place

Dose: 1 mL of 0.8% HA gel

Frequency/Duration: Single subgingival application

Response: None reported

Patient characteristics (gender, mean age): 10 males, 14 females 24 to 57 years

Number per group: 24

Observed adverse effects: None reported

Timing of adverse effects:

Factors that predict response: "Hyaluronic acid showed positive effects in influencing local inflammation."

Source Citation: Casale et al. 2016[99]

Study Design: SR to examine potential effects of HA as an adjuvant treatment for chronic inflammatory disease, in addition to its use to improve healing after common dental procedures.

Device or Material: HA

Contact Duration: Varied across studies

Dose: Topical application of 0.2% and 0.8% HA gel

Frequency/Duration: Gel application twice daily for 4 weeks was a common application.

Response: Inflammation

Patient characteristics (gender, mean age): "25 relevant publications were included, three of them regarding gingivitis, 13 of them relating to chronic periodontitis, seven of them relating to dental surgery, including implant and sinus lift procedures, and the remaining three articles describing oral ulcers."

Number per group: All controlled studies.

Observed adverse effects: No adverse events observed

Timing of adverse effects:

Factors that predict response: "High-molecular-weight HA suppresses the immune response preventing excessive exacerbations of inflammation." "As a consequence of the many functions attributed to HA, advances have been made in the development and application of HA-based biomaterials in the treatment of various inflammatory conditions." "HA promotes a remission of symptoms, not only in the marginal gingiva, but also in the deeper-seated periodontal tissues, via the known mechanisms established for hyaluronan in wound healing."

Source Citation: Sapna and Vandana 2011[140]

Study Design: RCT using split-mouth + cross-over (mixed-design) study of patients with plaque-induced gingivitis

Device or Material: Gengigel HA gel

Contact Duration: 21 days

Dose: 0.2% HA

Frequency/Duration: Twice daily topical application for 21 days. Intrasulcular applied on alternate days.

Response: Inflammation

Patient characteristics (gender, mean age): Quadrants: Control; Scaling and topical HA gel; Only topical HA gel; Topical and intrasulcular HA gel. 18-35 years; gender not reported

Number per group: 28

Observed adverse effects: "There was a reduction in inflammatory infiltrates from baseline to day 21 in all the groups. The reduction was higher in the scaling + topical HA group (50%), followed by the scaling group (44%), topical + intrasulcular HA group (33.34%), and the topical group (16.67%)." "No adverse effects to the gel were observed on clinical examination and as reported by the patients."

Timing of adverse effects: ---

Factors that predict response: ---

NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 28: Bulking Agents - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Salih et al. 2021[141]

Study Design: RCT of pediatric patients with grades III and IV primary VUR

Device or Material: Dx/HA

Contact Duration:

Dose: 1 mL

Frequency/Duration: Single administration, endoscopic injection

Response: Obstruction, Urine leak, UTI, Renal scarring

Patient characteristics (gender, mean age): Dx/HA: median 59 months, 33% male, Surgery: median 52 months, 30% male

Number per group: Dx/HA: 30, Surgery: 30

Observed adverse effects: Dx/HA "early postoperative complications (within the first 2 weeks postoperatively) such as fever was recorded in 3 cases (10%) and obstruction in 1 case (3.3%) was managed by double J stent insertion, whereas in [surgery] fever was recorded in 6 cases (20%) and urine leak in 2 cases (6.6%); there was a statistically significant difference between the two groups (P = .003)." "As regards late complication, in [Dx/HA], UTI was recorded in 6 cases (20%) (febrile UTI in 2 cases [6.7%] and nonfebrile UTI in 4 cases [13.3%]). The need for CAP was recorded in 2 patients (6.7%) and new renal scarring in 2 patients (6.7%). In [surgery], UTI was recorded in 5 cases (16.7%) (febrile in 3 cases [10.2%] and nonfebrile UTI in 2 cases [6.5%]). The need for CAP was recorded in 2 patients (6.7%) and new renal scarring in 2 patients (6.7%)."

Timing of adverse effects: Patients were followed for 1 year.

Factors that predict response: NR

Source Citation: Kirchin et al. 2017[143]

Study Design: SR to assess the effects of periurethral or transurethral injection therapy on the cure or improvement of urinary incontinence in women. Include 1 study using HA

Device or Material: HA with dextranomer (Zuidex™) was used in 1 study published in 2009

Contact Duration: 12-month follow-up

Dose: NR

Frequency/Duration: NR

Response: Injection site complications: pain, abscesses

Patient characteristics (gender, mean age): A single trial compared mid-urethral HA with bladder neck collagen (Lightner 2009). All women

Number per group: A total of 344 women were included in this 2:1 RCT of Zuidex via the Implacer device versus transurethral bladder neck collagen (Lightner 2009).

Observed adverse effects: "Dextranomer hyaluronic acid compound treated patients appeared to have significantly higher rates of injection site complications (16% with the hyaluronic acid compound versus none with collagen; RR 37.78, 95% CI 2.34 to 610.12) and this product has now been withdrawn from the market." Concerns about high levels of pseudo-abscess formation have led to Zuidex's withdrawal from the market. "Adverse events were more frequent in the Zuidex™ group: 68% versus 50% in the collagen-treated patients (RR 1.35, 95% CI 1.10 to 1.64). Retention, dysuria and urinary tract infection rates were similar for the two groups but micturition urgency (11% Zuidex™, 4.3% collagen) and injection site pain (8.4% Zuidex™, 2.6% collagen) were more frequently reported in the Zuidex™ group. Injection site sterile abscess (8.4%), injection site mass (4.4%) and pseudo-cyst formation (2.2%) were only seen in the Zuidex™ group (RR for injection site complications 37.78, 95% CI 2.34 to 610.12); 28 of the 36 patients with periurethral collections required secondary outpatient drainage procedures.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Graf et al. 2011[142]

Study Design: International, multicenter, double-blind, sham controlled RCT in patients with fecal incontinence

Device or Material: NASHA Dx (Q-Med AB, Uppsala, Sweden)

Contact Duration: Up to 12 months

Dose: 1 mL of NASHA Dx was injected through an anoscope into each quadrant of the submucosa, roughly 5 mm above the dentate line. Injected volume of NASHA Dx for patients in the active treatment group was 4–8 mL.

Frequency/Duration: Patients with continuing symptoms were given follow-up injections at 1 month.

Response: Prostatic abscess, Rectal abscess, Proctalgia, Rectal hemorrhage, Diarrhea

Patient characteristics (gender, mean age): Active: 61.8 years, 90% female, Control: 60.1 years, 87% female

Number per group: Active 136, Control 70

Observed adverse effects: Two of the treatment-related adverse events were serious, both of which were in the active treatment group. One was a prostatic abscess that resolved after antibiotic treatment and the other was a rectal abscess that needed surgical drainage. Both these events resolved completely. Other adverse events seen in 5% or more of the treatment group not common in the control group: Proctalgia (14%) (pain due to a spasm of the pelvic floor muscles, the muscles of the anal sphincter, or the muscles of the rectum), fever (8%), rectal hemorrhage (7%), diarrhea (5%). No migration, protrusion, or leakage of the injected agent with bowel movements.

Timing of adverse effects: Within 12 months of the injections

Factors that predict response: NR

Source Citation: Salih et al. 2021[141]

Study Design: RCT of pediatric patients with grades III and

IV primary VUR

Device or Material: Dx/HA

Contact Duration:

Dose: 1 mL

Frequency/Duration: Single administration

Response: Fever

Patient characteristics (gender, mean age): Dx/HA: median 59 months, 33% male, Surgery: median 52 months, 30% male

Number per group: Dx/HA: 30, Surgery: 30

Observed adverse effects: Dx/HA "early postoperative complications (within the first 2 weeks postoperatively) such as fever was recorded in 3 cases (10%) and obstruction in 1 case (3.3%) was managed by double J stent insertion, whereas in [surgery] fever was recorded in 6 cases (20%) and urine leak in 2 cases (6.6%); there was a statistically significant difference between the two groups (P = .003)." "As regards late complication, in [Dx/HA], UTI was recorded in 6 cases (20%) (febrile UTI in 2 cases [6.7%] and nonfebrile UTI in 4 cases [13.3%]). The need for [continuous antibiotic prophylaxis] was recorded in 2 patients (6.7%) and new renal scarring in 2 patients (6.7%). In [surgery], UTI was recorded in 5 cases (16.7%) (febrile in 3 cases [10.2%] and nonfebrile UTI in 2 cases [6.5%]). The need for CAP was recorded in 2 patients (6.7%) and new renal scarring in 2 patients (6.7%)."

Timing of adverse effects: Patients were followed for 1 year.

Factors that predict response: NR

Source Citation: Graf et al. 2011[142]

Study Design: International, multicenter, double-blind, sham controlled RCT in patients with fecal incontinence

Device or Material: NASHA Dx (Q-Med AB, Uppsala, Sweden)

Contact Duration: Up to 12 months

Dose: 1 mL of NASHA Dx was injected through an anoscope into each quadrant of the submucosa, roughly 5 mm above the dentate line. Injected volume of NASHA Dx for patients in the active treatment group was 4–8 mL.

Frequency/Duration: Patients with continuing symptoms were given follow-up injections at 1 month.

Response: Fever

Patient characteristics (gender, mean age): Active: 61.8 years, 90% female, Control: 60.1 years, 87% female

Number per group: Active 136, Control 70

Observed adverse effects: Two of the treatment-related adverse events were serious, both of which were in the active treatment group. One was a prostatic abscess that resolved after antibiotic treatment and the other was a rectal abscess that needed surgical drainage. Both these events resolved completely. Other adverse events seen in 5% or more of the treatment group not common in the control group: fever (8%), no fever reported in the control group. No migration, protrusion, or leakage of the injected agent with bowel movements.

Timing of adverse effects: Within 12 months of the injections

Factors that predict response: NR

CAP = continuous antibiotic prophylaxis; Dx = dextranomer; HA = hyaluronic acid; NA = not applicable; NASHA = non-animal stabilized hyaluronic acid; NR = not reported; Obs = observational; RCT = randomized controlled trial; Retro = retrospective; R = reliable; Dose = mg/kg/day; VUR = vesicoureteral reflux

Table 29: : Intravesical agents for bladder pain syndrome/interstitial cystitis therapy - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Özkıdık 2019[145]

Study Design: Double-blind RCT of bladder pain syndrome

Device or Material: Intravesical HA, CS, or HA + CS

Contact Duration: 24 moths

Dose: HA = 120 mg, CS = 80 mg

Frequency/Duration: Once a week for 6 weeks, then twice a month for 6 months, then continued once a month until 24th month.

Response: Symptomatic cardiac arrythmia, seriously elevation liver enzymes, Peripheral neuropathy, Intolerable GI side effects, Hematuria, UTI with fever

Patient characteristics (gender, mean age): HA: 37.1 years, 16% male, CS: 37.4 years, 12% male, HA+CS: 37.2 years, 12% males

Number per group: HA: 24, CS: 24, HA+CS: 24

Observed adverse effects: "No serious adverse event requiring discontinuation of treatment was seen in any of the participants during the 24 months follow-up period. … None of the patients in the study quit due to the side effects of the drugs, so tolerability was good in all groups during the 24 months follow-up period."

Timing of adverse effects:

Factors that predict response: NR

Source Citation: De Vita et al. 2013[144]

Study Design: SR to assess the value of HA and HA-CS treatment in reducing the occurrence of recurrent bacterial cystitis (RBC).

Device or Material: Intravesical instillations of HA and HA + CS

Contact Duration:

Dose: 2 studies: 40 mg HA, 2 studies: 50 ml HA 1.6% plus CS 2.0%.

Frequency/Duration: 3 studies: once a week for 4 weeks plus once a month for 4 or 5 months, 1 study: once a week for 4 weeks plus once every 2 weeks for a month

Response: None reported

Patient characteristics (gender, mean age): Included 4 studies: 35, 27, 34, 69 years. All patients were adult women.

Number per group: 143

Observed adverse effects: The combination of HA and CS significantly improved pelvis pain. No adverse events or complications were noted.

Timing of adverse effects:

Factors that predict response: HA and CS "decrease chronic pelvic inflammation and pain due to visceral hypersensitivity not only by inhibiting peripheral C-fiber nociceptors and blocking smooth-muscle contraction, but also by preventing immune-cell migration and mast-cell degranulation and extravasion."

CS = chondroitin sulphate; HA = hyaluronic acid; NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 30: Organ spacer - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Prada et al. 2016[146]

Study Design: Case series of patients undergoing high-dose-rate interstitial brachytherapy for prostate cancer

Device or Material: Transperineal HA injection into the peri-rectal fat

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Urinary tract pain, Urinary tract obstruction, Urinary retention

Patient characteristics (gender, mean age): Median 71 years

Number per group: 60 with prostate adenocarcinoma

Observed adverse effects: No adverse effects were associated with HA injection. At three months urinary tract pain (dysuria) grade 1 occurred in 4 patients (7%). At three months later 16 patients (40%) had grade 1 urinary tract obstruction. "No other chronic toxicity, such as incontinence, late urinary retention or urethral narrowing has been observed after treatment."

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Chapet et al. 2015[147]

Study Design: Case series of patients with low-risk to intermediate-risk prostate cancer undergoing hypofractionated radiation therapy

Device or Material: HA (NASHA Spacer gel)

Contact Duration: NR

Dose: 10 mL

Frequency/Duration: Single administration injection

Response: Lower abdominal pain, Hematuria

Patient characteristics (gender, mean age): 71 years

Number per group: 36

Observed adverse effects: "At the time of injection, the mean pain score was 4.6 ± 2.3 (n = 28). Thirty minutes after the injection, 1 patient still reported pain scored as 2/10, and 1 patient reported pain scored as 3/10, which persisted." One patient each experiencing lower abdomen pain, hematuria. "A hematoma developed in 1 patient between the rectum and the bladder, which had to be surgically removed." Patients had a moderate platelet deficit.

Timing of adverse effects: During and after injection

Factors that predict response: "At the time of injection patients reported moderate pain, which disappeared within 30 minutes. This pain was most commonly felt in the pelvic floor muscles, which are sensitive and difficult to anesthetize with an injection of lidocaine. This pain could be reduced by optimizing the local anesthesia procedure and adding the administration of anxiolytic medication before the injection. After the injection, the HA was very well tolerated."

Systemic Response/Toxicity

Source Citation: Chapet et al. 2015[147]

Study Design: Case series of patients with low-risk to intermediate-risk prostate cancer undergoing hypofractionated radiation therapy

Device or Material: HA (NASHA Spacer gel)

Contact Duration: NR

Dose: 10 mL

Frequency/Duration: Single administration injection

Response: Asthenia

Patient characteristics (gender, mean age): 71 years

Number per group: 36

Observed adverse effects: One patient experienced asthenia (abnormal physical weakness or lack of energy).

Timing of adverse effects: During and after injection

Factors that predict response: "At the time of injection patients reported moderate pain, which disappeared within 30 minutes. This pain was most commonly felt in the pelvic floor muscles, which are sensitive and difficult to anesthetize with an injection of lidocaine. This pain could be reduced by optimizing the local anesthesia procedure and adding the administration of anxiolytic medication before the injection. After the injection, the HA was very well tolerated."

HA = hyaluronic acid; NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 31: Protective topical agent for esophageal and gastric lesions in GERD - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Savarino and Scarpignato 2017[148]

Study Design: Multicenter, double-blind, placebo-controlled RCT of patients with non-erosive reflux disease treated with proton pump inhibitors

Device or Material: HA-CS (Esoxx)

Contact Duration: 2 weeks

Dose: 10 mL

Frequency/Duration: 4 times a day (after each meal and at bedtime)

Response: GI disorders, Respiratory disorders

Patient characteristics (gender, mean age): Esoxx: 63% female, 45 years, Control: 59% female, 45 years

Number per group: Esoxx: 76, Control: 78

Observed adverse effects: No serious adverse events in either group. All patients were also treated with proton pump inhibitors. Esoxx group: 23 drug-related adverse events, 5 lead to discontinuation; 13 gastrointestinal disorders, 4 respiratory (cough, rhinitis, throat irritation) Control: 7 gastrointestinal, 1 respiratory.

Timing of adverse effects:

Factors that predict response: Gastrointestinal adverse events may be related to the proton pump inhibitors. The increase in respiratory adverse events is likely related to using Esoxx.

Systemic Response/Toxicity

Source Citation: Savarino and Scarpignato 2017[148]

Study Design: Multicenter, double-blind, placebo-controlled RCT of patients with non-erosive reflux disease treated with proton pump inhibitors

Device or Material: HA-CS (Esoxx)

Contact Duration: 2 weeks

Dose: 10 mL

Frequency/Duration: 4 times a day (after each meal and at bedtime)

Response: Nervous system, Cardica, Vertigo, Hypertension, Infection

Patient characteristics (gender, mean age): Esoxx: 63% female, 45 years, Control: 59% female, 45 years

Number per group: Esoxx: 76, Control: 78

Observed adverse effects: No serious adverse events in either group. All patients were also treated with proton pump inhibitors. Esoxx group: 23 drug-related adverse events, 5 lead to discontinuation; 3 nervous system, 1 cardiac, 1 vertigo, 1 hypertension, 1 infection. Control: 1 cardiac, 3 infections.

Timing of adverse effects:

Factors that predict response: Gastrointestinal adverse events may be related to the proton pump inhibitors. The increase in respiratory adverse events is likely related to using Esoxx.

CS = chondroitin sulphate; HA = hyaluronic acid; NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 32: Vocal cord/fold medialization - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Wang et al. 2020[149]

Study Design: SR to synthesize evidence on the use of IL with HA for the treatment of UVFP.

Device or Material: HA

commercially available for IL: Hylan B gel and Restylane

Contact Duration:

Dose: "For the volume of injected HA: less than 1cc or 1cc of HA was injected in seven (50%) studies, 2cc was used in one (7.1%) study, while no detailed information was reported in the other six studies."

Frequency/Duration: Single administration

Response: Hematoma, Edema, Local hypersensitivity, Local inflammation which may be responsible for dysphonia, dyspnea, and dysphagia

Patient characteristics (gender, mean age):

Number per group: 14 case series (6 studies were conducted prospectively, 4 retrospectively, and 4 without specific mention of their study design) published between 2010 and 2018 were included in the SR, n = 442

Observed adverse effects: "Generally speaking, HA is quite safe for IL and only one patient experienced hematoma and one patient experienced edema of the aryteno-epiglottic fold and false vocal fold in our review of 14 studies. However, Hamdan [Adverse Reaction to Restylane: A Review of 63 Cases of Injection Laryngoplasty. Ear Nose Throat J. 2019, 98, 212–216.] and Dominguez [Inflammatory reaction to hyaluronic acid: A newly described complication in vocal fold augmentation. Laryngoscope 2017, 127, 445–449.] described complication rates of 4.7% and 3.8% in their studies of IL for different indications including UVFP. The most common adverse reactions are local hypersensitivity and inflammation. The hypothesized mechanisms for adverse reaction include (1) local hypersensitivity to the proteins incidentally produced in the HA manufacturing process, (2) vascular compression or occlusion by the injected HA, and (3) contamination of the injector device. Although, to date, no deaths have been reported following treatment with IL, adverse reactions may induce local edema, erythema, induration, tenderness, abscess formation, and decreased vocal fold pliability, among others, leading to dysphonia [difficulty in speaking], dyspnea [difficult or labored breathing], or dysphagia [difficulty or discomfort in swallowing]. Although adverse reactions may be treated with steroids or antibiotics, the length of adverse reaction may still range from hours to days, weeks to months, or may even have long-term sequelae without resolution (26 months)."

Timing of adverse effects:

Factors that predict response: HA "has a simple molecular structure with no structural differences across species from human to bacteria, and the lack of amino acids renders it non-immunogenic. In addition, the vocal fold lamina propria compartment is a pauci-cellular layer that mostly contains the extracellular matrix and HA. The viscoelastic properties of vocal folds after the injection of HA-based material are similar to the healthy vocal fold in animal studies. Owing to the aforementioned safety advantages, HA has become a commonly used material for IL.

HA = hyaluronic acid; IL = injection laryngoplasty; NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; UVFP = Unilateral vocal fold paralysis; Dose = mg/kg/day

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Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as a separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

The associated alerts are provided with this report as a separate PDF.