U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	208135
Drug Name:	Tetracaine Hydrochloride Ophthalmic Solution 0.5% (STERI-UNIT®)
Indication(s):	For procedures requiring a rapid and short acting ophthalmic anesthetic
Applicant:	Alcon research ltd
Date(s):	Stamp date: April 30, 2015
	PDUFA date: February 29, 2016
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Abel Tilahun Eshete
Concurring Reviewers:	Yan Wang
Medical Division:	Ophthalmology
Clinical Team:	Medical Reviewer: Jennifer Harris
Project Manager:	Michael Puglisi

Keywords: Topical anesthesia, Pain scores, Tetracaine .

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This NDA seeks approval of tetracaine hydrochloride ophthalmic solution 0.5% for procedures requiring a rapid and short acting topical ophthalmic anesthetic. The proposed dose and administration is one drop topically in the eye(s) as needed. The applicant states that they have been producing tetracaine hydrochloride ophthalmic solution 0.5% (tetracaine 0.5%) since 1959 and the drug has been in use as an unapproved product for over 50 years. This NDA is a 505(b)(2) application that depends solely on publication data to support the rapid and short acting topical ophthalmic anesthetic indication for tetracaine 0.5%. The efficacy summary for this review is based on nine publications. Eight of the nine publications were selected by the applicant and one publication was identified by this reviewer. All nine publications were randomized and controlled studies. In seven of these publications, only an active control was included and in the remaining two publications both an active control and a placebo (saline) were included. The lidocaine gel 2% was the active control in four of the nine publications while proparacaine 0.5% (NDA 40277) was used in two publications. Proxymetacaine, bupivacaine and ketorolac were the active controls used in the reaming three studies (Table 1).

The average pain score or the proportion of subjects who experienced little or no intraoperative and/or no postoperative pain, or the rate of successful tonometry were reported as efficacy endpoints in the nine published studies. Because the published studies used slightly different scales for pain measurement and evaluated different dosing regimen of tetracaine 0.5% in patients undergoing different procedures, the reviewer did not perform a formal meta-analysis. Three publications (Moshirfar 2014, Chalam 2009 and Rifkin 2009), in which a total of 209 subjects received at least one dose of tetracaine 0.5%, reported a statistically significant efficacy results for tetracaine 0.5% (Table 2). However, the results in two of these publications (Rifkin 2009 and Moshirfar 2014) should be interpreted with caution because the results in Moshirfar 2014 were not adjusted for multiple comparisons, and the reviewer's analysis of the data from Rifkin 2009 did not show statistically significant results for the pairwise comparison of tetracaine 0.5% to the other treatment groups.

One publication (Shafi 2008) reported a statistically non-significant but numerically favorable tonometry success rate compared with proxymetacaine (Table 2). The remaining five publications reported treatment differences that were not statistically significant; either between tetracaine 0.5% and saline (Carden 1998 and Kim 2003; Table 2) or between tetracaine 0.5% and lidocaine gel 2% ((b) (4) Barequet 2000, (b) (4) Table 2). Likely based on the numerical similarity of the observed average postoperative pain scores or the proportion of subjects with little or no pain, the authors in three of the above five publications ((b) (4) , Barequet 2000, (b) (4) Therefore, the evaluation of the clinical relevance of these findings is deferred to the clinical reviewer.

Similar to the efficacy evaluation, the applicant did not conduct prospective randomized clinical trials to assess the safety of tetracaine 0.5%. The applicant provided a safety summary from

three publications (Havener 1983, McGee 2007, Weaver 2003) and a list of adverse event cases collected through pharmacovigilance through 31 December 2014. In the three publications, burning and numbing sensations and potential punctate corneal erosion were reported. A total of 143 adverse events, 47 of which were serious, were collected through the applicant's pharmacovigilance. The most frequently reported adverse events in the applicant's pharmacovigilance summary were eye irritation, eye pain, ocular discomfort, endophthalmitis and toxic anterior segment syndrome (Table 3). The authors in one study identified by this reviewer (Sha et al. 2010) stated that multiple administration of tetracaine is known to be associated with corneal epithelial toxicity and delayed epithelial healing.

In conclusion, statistically significant lower average pain scores in the tetracaine 0.5% arm were reported in three studies. Although, the superiority results from two of these three studies were questionable from a statistical perspective, the observed efficacy results for tetracaine 0.5% were numerically better than the active control (proparacaine 0.5%). Similarly, in the active controlled studies where the treatment differences were not statistically significant, the efficacy results of tetracaine 0.5% were numerically comparable with the active controls. Because there was no pre-specified and justified equivalence margin, the reviewer was not able to evaluate the equivalence claim. From a safety perspective, adverse events such as endophthalmitis, eye pain, and eye irritation after multiple administrations have been reported.

It is however important to note that, in the aforementioned nine publications, the drug products containing tetracaine 0.5% have been referred to by different names. For example, Chalam 2009 compared Tetracaine hydrochlorid 0.5%; OCuSOFT which goes by the name "*TetraVisc* solution" to lidocaine gel 2%. In Rifkin 2009, two drug products both containing tetracaine 0.5% "TetraVisc (tetracaine HCI 0.5% gel; Cynacon/OCuSOFT)" and "tetracaine HCI ophthalmic solution (Alcon Surgical)" were compared against each other and against proparacaine. This reviewer cannot determine whether all the drugs containing tetracaine in the nine publications can be considered clinically equivalent with the applicant's product. Therefore this determination and the assessment of the overall risk-benefit for this product and the subsequent decision to recommend for approval are deferred to the clinical review team.

2 Introduction

2.1 Overview

Tetracaine hydrochloride ophthalmic solution 0.5% has been on the market as an unapproved drug and has been produced by Alcon Inc. since 1959. This NDA is a 505(b) (2) application that depends solely on publication data to support the rapid and short acting topical ophthalmic anesthetic indication for tetracaine 0.5%.

2.2 Submission History

This NDA was originally submitted on 04/30/2015. In the original submission, based on relevance of study objectives and results, the applicant selected nine publications to support the rapid and short acting topical ophthalmic anesthetic indication. Of these nine publications, five provided results for the to-be-marketed dose of tetracaine (0.5%) and the remaining four included summary results evaluating either a higher dose of tetracaine (1%) or a combination of tetracaine with other products. Upon an initial review, it was deemed that the statistical evidence provided in the originally submitted publications was not sufficient for granting ophthalmic anesthetic indication. Consequently, an information request was sent to the applicant on 06/29/2015. The agency requested the applicant to submit the search criteria used to identify the submitted publications. The agency also recommended the applicant to perform a comprehensive search of all possible publications that might provide adequate evidence of efficacy for this product. The agency advised the applicant to also include publications written in non-English languages and those evaluating higher doses or different dosing regimens of tetracaine.

The applicant provided responses on 07/27/2015. In this response to the agency's information request, the applicant submitted the search criteria used and provided a refined efficacy summary of the original nine publications. Additionally, the applicant provided four new publications, three of which summarized efficacy results for the tetracaine 0.5%. This reviewer has also identified one publication (Chalam 2009) which summarized a study evaluating the anesthetic efficacy of tetracaine 0.5%. Therefore this review is mainly based on the nine publications (8 identified by the applicant and 1 identified by this reviewer) that summarized studies that evaluated the to-be-marketed dose of tetracaine.

2.3 Data Sources and Quality

The full NDA can be accessed in the FDA electronic document room at the following link: \\CDSESUB1\evsprod\NDA208135\208135.enx. The information provided in the NDA was very limited. Using PubMed, the applicant identified several publications. Based on relevance of study objectives and results, completeness of information and quality (i.e. well-controlled, blinded, randomized and balanced designs), the applicant selected 13 publications (nine in the original submission and four more publications in response to an information request) to support their 505(b) (2) application for the rapid and short acting topical ophthalmic anesthetic

indication for tetracaine 0.5%. This reviewer has also identified one publication. Therefore a total of fourteen publications; thirteen publications selected by the applicant and one identified by this reviewer were considered. However because only nine of these fourteen publications evaluated the to-be-marketed dose of tetracaine, the statistical review of efficacy for this submission will rely on summary statistics from the nine publications only.

The lidocaine gel 2% was the active control in four of the nine publications while proparacaine 0.5% was used in two publications. Proxymetacaine, bupivacaine and ketorolac were the active controls used in the reaming three. A search on CDER Drugs@FDA did not provide approval information for Proxymetacaine. Using the same source it is noted that, although lidocaine gel 2% was not approved at this concentration, higher dose of lidocaine (lidocaine 3.5% gel; NDA 22221) was approved for the indication of a topical local anesthetic for ophthalmic use. Proparacaine 0.5% was also approved for ophthalmic anesthetic use under NDA 12583. Bupivacaine (NDA 18053) is approved and is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedure. Ketorolac (NDA 19700) is indicated for the treatment of inflammation following cataract surgery and the temporary relief of ocular itching due to seasonal allergic conjunctivitis.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

A brief summary of the design of the studies summarized in the nine publications which served as basis for this statistical review is presented in Table 1. A summary of key findings from each publication is presented in Table 2. A detailed efficacy summary for each publication separately is presented in the appendix Section 5.1.

Three of the nine publications (Chalam 2009, Moshirfar 2014 and Rifkin 2009; Table 2) reported statistically favorable results in support of the anesthetic efficacy of tetracaine 0.5%. Studies in Rifkin 2009 and Moshirfar 2014 used proparacaine 0.5% as comparator and the study in Chalam 2009 used lidocaine gel 2% as comparator. In the three publications combined, a total of 209 subjects received at least one dose of tetracaine 0.5%.

Chalam 2009 reported that tetracaine 0.5% has a statistically significant lower average intraoperative pain score compared to lidocaine gel 2% (0.7 ± 0.31 vs 1.8 ± 0.4). The observed treatment difference was -1.1 (95% CI: -1.21, -0.98; $P<0.001$). Rifkin 2009 also reported that tetracaine 0.5% has a statistically significant pain control ($P<0.01$) compared to the other two treatment arms (Proparacaine 0.5% and TetraVisc). This publication reported that subjects in the tertracaine 0.5% arm had the lowest mean pain score (lower pain) (3.05 ± 2.18) compared to TetraVisc 0.5% (3.17 ± 2.18) and proparacaine (3.39 ± 2.28). This reviewer's post-hoc pairwise comparison between tetracaine 0.5% and proparacaine 0.5, Tetra Visc and proparacaine 0.5 and between tetracaine 0.5% and TetraVisc however did not show statistically significance differences. The observed differences (95% CI) were: (-0.34; (-0.94, 0.26); tetracaine vs. proparacaine), (-0.12; (-0.70, 0.46); tetracaine vs. TetraVisc) and (-0.22; (-0.84, 0.40);

TetraVisc vs. proparacaine). Additionally, the ANOVA approach does not appear to account for possible dependence between measurements taken from the same subject. Therefore the results from this publication should be interpreted with caution.

Moshirfar 2014 reported a statistically significant pain control in favor of tetracaine 0.5% at 30 minutes postoperative time (2.2± 0.1 vs. 1.3±0.1; diff (95% CI) -0.9 (-1.2, -0.62); P<0.001). It is noted that the authors in this publication preformed several treatment comparisons at different time points and for two different subgroups (LASIK and PRK). The reported p-values however were not adjusted for multiplicity. This should be taken into consideration when interpreting the positive findings in this publication.

One publication (Shafi 2008) provided mixed efficacy evidence. Compared to proxymetacaine, tetracaine 0.5% had a statistically significant higher mean stinging duration (3.2 vs 22.1; p<0.001) and mean discomfort score (14.2 vs. 2.6; p=0.01) but also had favorable outcome in terms of a slightly higher tonometry success rate (98% vs 93%; diff (95% CI): 5% (-2.3%, 13.6%); p=0.08; Table 2).

In the remaining 5 publications, the reported treatment differences were not statistically significant; either between tetracaine 0.5% and saline (Carden 1998 and Kim 2003; Table 2) or between tetracaine 0.5% and lidocaine gel 2% (b) (4) Barequet 2000, (b) (4)). In these five publications combined, a total of 152 subjects received at least one drop of tetracaine 0.5%. The authors in the three publications (b) (4), Barequet 2000, (b) (4) Table 2) concluded that tetracaine 0.5% is as effective as lidocaine gel 2%. Their conclusion seems to be informed by the numerically similar reported pain scores. (b) (4)

(Proportion of no or minimal pain: 61.5% vs. 58.3%: Barequet 2000; Table 2). (b) (4)

Although the lidocaine gel 2% was not approved for ophthalmic use in the US, this formulation is widely used and is proven to have a clinically relevant anesthetic efficacy as evidenced in several publications. A study by Sinah (2013) reported that compared with proparacaine 0.5% eye drops, a single application of lidocaine gel 2% improves perioperative analgesia and reduces the incidence of postoperative nausea and vomiting in elective pediatric squint surgery. Similarly, based on a literature review of several publications, Page (2009) concluded that lidocaine gel 2% is safe and effective. Therefore, the anesthetic efficacy of lidocaine gel 2% appears to be clinically relevant. However, derivation of an equivalence margin to assess the statistical equivalence was not possible due to differences in endpoints, study population and lack of placebo-controlled studies.

In addition to the aforementioned nine publications, the applicant submitted three publications that summarized studies that evaluated the tetracaine ophthalmic solution 1% (tetracaine 1%).

Statistically significant results in favor of tetracaine 1% were reported in two of the three publications (Watson 2009 and Anninger 2007). In the two publications combined, a total of 79 children under the age of 15 years (20 in Watson 2009 and 59 in Anninger 2007) received at least one drop of tetracaine 1%. Watson 2009 reported that compared to saline, there was a statistically significant lower mean pain score in the tetracaine 1% group (11.4 vs. 19.5; P<0.001). Anninger 2007 showed that a statistically significantly (P=0.02) higher proportion of subjects randomized to the tetracaine 1% drops alone (79%) or together with a normal saline (74%) reported a pain score less than 5 (less pain) at 5 minutes after surgery compared with subjects who received saline only group (43%).

The third publication (Yu 2009), reported that, compared to lidocaine gel 2%, tetracaine 1% has a statistically significant higher patient reported mean pain score (5.3 vs. 2.6; P=0.01) and higher number of subjects in this arm required additional drops (5 (35.7%) vs. 11 (78.6); P=0.02). In this publication, 14 subjects received tetracaine 1% in one eye and lidocaine gel 2% in the other.

3.2 Evaluation of Safety

Similar to the efficacy evaluation, the applicant did not conduct prospective randomized clinical trials to assess the safety of tetracaine 0.5% (STERI-UNIT®). A safety summary from three publications (Havener 1983, McGee 2007, Weaver 2003) and what the applicant referred to as post-marketing adverse event cases collected through pharmacovigilance through 31 December 2014 were provided. In the three studies, burning and numbing sensations and potential punctate corneal erosion were reported. A total of 143 adverse events, 47 of which were serious, were collected through the applicant's pharmacovigilance. The most frequently reported adverse events in the applicant's pharmacovigilance summary were eye irritation, eye pain, ocular discomfort, endophthalmitis and toxic anterior segment syndrome (Table 3). This reviewer has also identified one publication (Sha et al. 2010). The authors in this publication stated that multiple administration of tetracaine is known to be associated with corneal epithelial toxicity and delayed epithelial healing (Table 3).

4 Summary and Conclusions

4.1 Statistical issues

Because the published studies used slightly different scales for pain measurement and evaluated different dosing regimen of tetracaine 0.5% in patients undergoing different procedures, the reviewer did not perform a formal meta-analysis. Additionally, in general, there are several limitations in relying on evidence from the published literature. These include the possibility of publication bias, lack of pre-specified protocols, non-standardized reporting of results, lack of study site inspections to ensure data quality, and lack of patient-level data with which to conduct independent analysis. Specific to the publications submitted in this NDA, only few of the publications had complete information that enabled the reviewer to perform further analysis and/or verify the reported results.

4.2 Conclusions and recommendation

In conclusion, statistically significant lower average pain scores in the tetracaine 0.5% arm were reported in three studies. Although, the superiority results from two of these three studies were questionable from a statistical perspective, the observed efficacy results for tetracaine 0.5% were numerically better than the active control (proparacaine 0.5%). Similarly, in the active controlled studies where the treatment differences were not statistically significant, the efficacy results of tetracaine 0.5% were numerically comparable with the active controls. Because there was no pre-specified and justified equivalence margin, the reviewer was not able to evaluate the equivalence claim. From a safety perspective, adverse events such as endophthalmitis, eye pain, and eye irritation after multiple administrations have been reported.

It is however important to note that, in the aforementioned nine publications, the drug products containing tetracaine 0.5% have been referred to by different names. For example, Chalam 2009 compared Tetracaine hydrochlorid 0.5%; OCuSOFT which goes by the name "*TetraVisc* solution" to lidocaine gel 2%. In Rifkin 2009, two drug products both containing tetracaine 0.5% "TetraVisc (tetracaine HCI 0.5% gel; Cynacon/OCuSOFT)" and "tetracaine HCI ophthalmic solution (Alcon Surgical)" were compared against each other and against proparacaine. This reviewer cannot determine whether all the drugs containing tetracaine in the nine publications can be considered clinically equivalent with the applicant's product. Therefore this determination and the assessment of the overall risk-benefit for this product and the subsequent decision to recommend for approval are deferred to the clinical review team.

Table 1: Publications evaluating analgesic efficacy of tetracaine ophthalmic solution 0.5%

Reference	Study Objectives	Total # of Patients	Dosing Regimen	Study Design
Chalam 2009*	To assess the comparative efficacy of topical Tetra Visc versus lidocaine gel 2% in cataract surgery	122	5 drops of Tetra Visc (tertracaine 0.5%) or 5 doses of lidocaine gel 2% every five minutes	Randomized
Moshirfar 2014*	To compare the efficacy of tetracaine and proparacaine for pain control in laser in situ keratomileusis and photorefractive keratectomy	128	Single application of proparacaine or 1 drop of tetracaine 0.5%	Randomized, controlled, Single-masked
Rifkin 2009*	To determine factors that are associated with greatest patient comfort in intravitreal injection	60	Five monthly injection of 3× 1 drop of tetracaine 0.5% versus 1 drop of Tetra Visc versus 1 drop of proparacaine	Randomized
Shafi 1998*	To compare patient comfort following installation of topical proxymetacaine and amethocaine	53	1 drops of amethocaine in one eye and one drop of proxymetacaine in the other eye	Randomize, double-masked
				(b) (4)
Barequet 1999	To compare the efficacy of lidocaine with tetracaine for topical anesthesia in clear corneal cataract surgery	25	Single application of lidocaine gel 2% or 1 drop of tetracaine 0.5%	Randomized
				(b) (4)
Carden 1998*	To test the effect of tetracaine on reducing postoperative pain, vomiting, and length of stay in children having strabismus repair	62	2 drops of tetracaine 0.5%, subconjunctival bupivacaine 0.5%, or placebo (saline)	Randomized, controlled, observer masked
Kim 2003*	To compare the effect of placebo to intraoperative topical tetracaine 0.5% (amethocaine) or topical ketorolac 0.5% on pain control after strabismus surgery in children	51	2 drops of tetracaine 0.5%, ketorolac 0.5%, or placebo (saline) at the start and end of strabismus repair surgery	Randomized, double-masked, placebo-controlled

Source: Applicant's summary and the *reviewer's summary based on submitted publications

Table 2: Summary of key findings from publication evaluating tetracaine 0.5%

Reference	Pain Measurement Scale	Summary of Key Results
Chalam 2009	Visual analog pain scale (0-10): 0 = no pain 10 =agonizing pain	A statistically significant difference in mean visual analog pain score (0.7+0.32 vs. 1.8+0.31; diff (95% CI) -1.1 (-1.21, -0.99); p<0.001)
Moshirfar 2014	Pain severity scale: 0 = no pain 5 = moderate pain 10=severe pain	There was no statistically significant difference in mean pain score during surgery (1.6±0.2 vs. 1.2±0.2; p=0.067) and immediately after surgery (0.9±0.1 vs. 0.9±0.1; p=0.600) but there was a statistically significant difference in mean pain score 30 minutes post-surgery (1.3±0.1 vs.

		2.2±0.1; diff (95% CI) -0.8 (-1.2, -0.50); p<0.001)
Rifkin 2009	Visual analog pain scale (0-10): 0 = no pain 10 =agonizing pain	There was a statistically significant difference in mean pain scores between tetracaine and the other two (Tetracaine: 3.05±2.01vs. Tetra Visc: 3.39±2.26 vs. Proparacaine: 3.17±2.18; p<0.01). Pairwise comparisons however did not show statistical significance differences. Diff (95% CI): Tetracaine vs. Proparacaine: -0.34 (-0.94, 0.26); Tetra Visc vs. Proparacaine: -0.22 (-0.84, 0.40)
Shafi 1998	Descriptive discomfort score: 0 = no pain 1 = mild pain 2 = moderate pain 3=severe pain 4=very severe pain	There was a statistically significant difference in mean descriptive discomfort score (14.2 vs. 2.6; p=0.01) and there was a numerically favorable but statistically non-significant difference in tonometry success rate (98% vs 93%; diff (95% CI): 5% (-2.3%, 13.6%); p=0.08)
[redacted]		(b) (4)
Barequet 1999	Cochet–Bonnet aesthesiometer (0-6): 0 = no sensation 6 =maximum sensation Pain scale: 0 = no pain 1 = minimal pain 2 = moderate pain 3=significant pain	There was no statistically significant difference in the proportion of patients with a grade of zero five minutes after application of the topical anesthesia (100% vs. 92%; diff (95% CI): 8.0% (-7.3%, 24.0%)). There was also no significant difference in proportion of subjects with pain score of 0 or 1 (satisfactory comfort) (61.5% vs. 58.3%; diff (95% CI): 3.2% (-30.5%, 41.6%))
[redacted]		(b) (4)
Carden 1998	Modified Wong-Baker scale: 0 = Nil 1 = mild 2 = moderate 3=severe	There was no statistically significant difference at all measurement time points (30, 60, 120 and 180 minutes). Only plots and p-values were provided (0.240, 0.680, 0.07, and 0.390 respectively)
Kim 2003	Modified children hospital of eastern Ontario pain scores (CHEOPS)	There was no statistically significant difference in mean (range) pain score (5 (4-9) vs. 5 (4-9) and mean anesthesia time (60±12 vs. 57±13; diff (95% CI): 3 (-5.4, 11.4)) versus placebo

Source: Reviewer's summary based on submitted publications

Table 3: Safety summary from post-marketing data

Body System	Preferred Term	Event Seriousness	Event Count
Cardiac disorders	Bradycardia	Serious	1
Cardiac disorders - Total			**1**
Eye disorders	Corneal oedema	Not serious	1
	Corneal opacity	Not serious	2
	Corneal thinning	Serious	1
	Eye irritation	Not serious	12
	Eye oedema	Not serious	3
	Eye pain	Not serious	9
	Eyelid ptosis	Not serious	1
	Foreign body sensation in eyes	Not serious	1
	Lacrimation increased	Not serious	1
	Mydriasis	Not serious	1
	Ocular discomfort	Not serious	19
	Ocular hyperaemia	Not serious	2
	Ulcerative keratitis	Not serious	1
	Vision blurred	Not serious	3
	Visual acuity reduced	Not serious	1
Eye disorders - Total			**58**
General disorders and administration site conditions	Drug effect decreased	Not serious	4
	Drug ineffective	Not serious	18
	No adverse event	Not serious	2
General disorders and administration site conditions - Total			**24**
Immune system disorders	Hypersensitivity	Not serious	1
Immune system disorders - Total			**1**
Infections and infestations	Endophthalmitis	Serious	9
Infections and infestations - Total			**9**
Injury, poisoning and procedural complications	Circumstance or information capable of leading to medication error	Not serious	2
	Corneal abrasion	Not serious	1
	Graft complication	Serious	1
	Medication error	Not serious	3
	Surgical procedure repeated	Serious	1
	Toxic anterior segment syndrome	Serious	30
Injury, poisoning and procedural complications - Total			**38**
Investigations	Oxygen saturation decreased	Serious	1
Investigations - Total			**1**
Nervous system disorders	Dizziness	Not serious	1
	Paraesthesia	Not serious	1
	VIIth nerve paralysis	Not serious	1
Nervous system disorders - Total			**3**

Respiratory, thoracic and mediastinal disorders	Throat tightness	Not serious	1
	Wheezing	Not serious	1
Respiratory, thoracic and mediastinal disorders - Total			**2**
Surgical and medical procedures	Off label use	Not serious	3
		Serious	3
Surgical and medical procedures - Total			**6**
Overall - Total			**143**

EVENT SERIOUS OVERALL COUNT	
Event seriousness	**Seriousness Event Count**
Serious	47
Not serious	96
Overall - Total	**143**

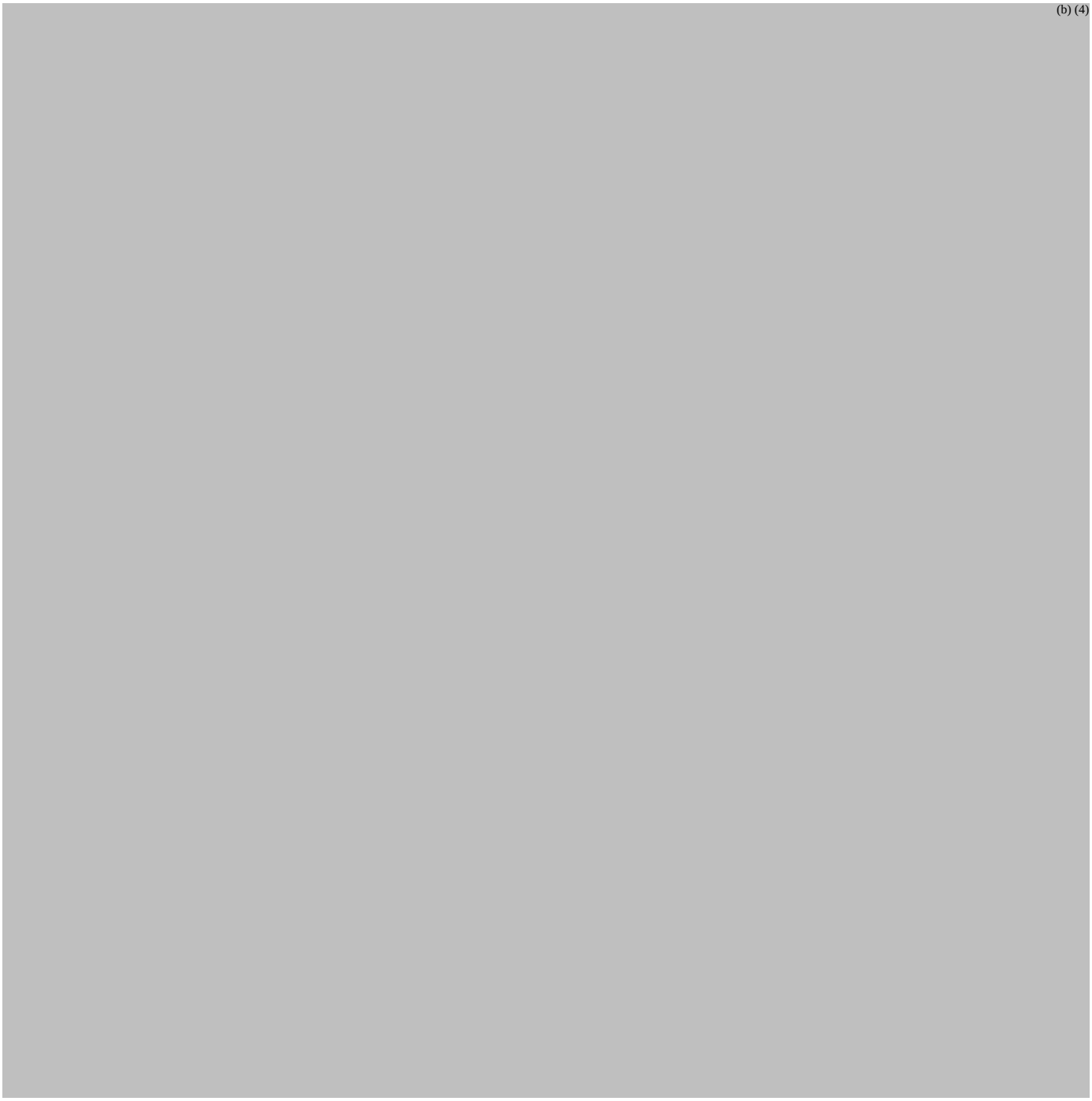
Source: Applicant's summary

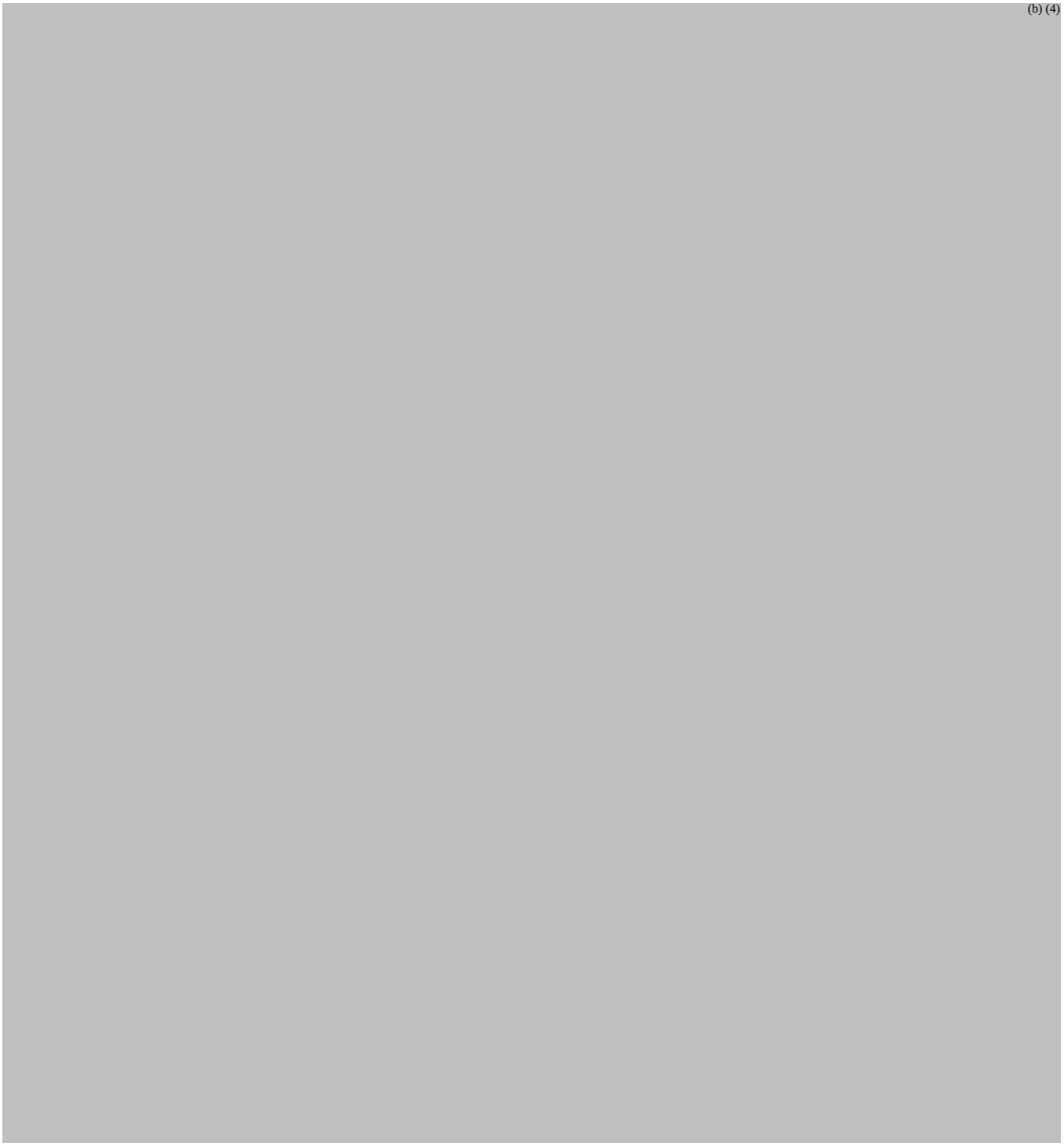
5 Appendix

5.1 Publications evaluating tetracaine ophthalmic solution 0.5%

This section provides brief summaries of each of the nine publications that evaluated the analgesic efficacy of tertracaine ophthalmic solution 0.5%. Unless stated otherwise, all tables, figures and other summaries are taken from the results presented in the publications.

(b) (4)




(b) (4)

5.1.3 Barequet et al (1999): Provision of anesthesia with single application of lidocaine gel 2%

This study included a preliminary toxicity study and a randomized study designed to compare the efficacy of a single application of lidocaine gel 2% with tetracaine 0.5% drops for topical anesthesia in clear corneal cataract surgery. In the randomized part of the study, 25 patients between the ages of 50-94 years were randomized in a 1:1 ratio to receive either lidocaine gel 2% (12 subjects; 4 males and 8 females) or tetracaine drops (13 subjects; 1 male and 12 females). Twenty minutes after the conclusion of surgery the patients were asked to describe the comfort using a predefined scale (0=no pain, 1=minimal pain, 2=moderate pain, 3=significant pain). The surgeon's subjective impression of patient comfort and ease of surgery was also assessed using the same scale. Additionally, corneal sensation was measured with the Cochet-Bonnet aesthesiometer before any medicine was applied, 5 minutes after application of the topical anesthesia, and at the conclusion of surgery. In this study, patient level data for comfort score and corneal sensitivity was provided.

The proportion of subjects who reported a satisfactory comfort level (grade 0 or 1) was 61.5% in the tetracaine group and 58.3 % in the lidocaine gel group (Diff: 3.2% (95% CI: -35.2%, 41.6%)). The corresponding values as reported by the surgeon were also 61.5% in the tetracaine group and 58.3 % in the lidocaine gel group. Two eyes in the lidocaine gel group (17%) and 4 (31%) in the tetracaine drops group received additional local anesthesia (P=0.64).

The median preoperative corneal sensitivity was 5 in the lidocaine gel group and 6 in the tetracaine drops group. Five minutes after application of the topical anesthesia and at the conclusion of surgery, the median values were 0 in both groups.

The authors concluded that a single preoperative application of lidocaine 2% gel provided satisfactory patient comfort to conduct safe clear corneal cataract surgery with IOL implantation and was comparable to the comfort achieved with multiple doses of tetracaine drops for topical anesthesia.

5.1.4 Carden (1998): Adjunctive intra-operative local anesthesia in pediatric strabismus surgery: A randomized controlled trial

This study was a prospective, randomized, three-armed clinical trial. The study involved treatment comparison between tropical amethocaine, sub-conjunctival bupivacaine and a normal saline (placebo). The purpose of this study was to test the hypothesis that adjunctive local anesthesia decreases post-operative pain, vomiting or length of stay in children having strabismus repair.

This study enrolled a total of 71 children between the ages of 54-71 Months who were booked for planned day surgery squint repair and whose patients consented to the study. The children

were randomized in a 1:1:1 ratio to receive either 2 drops of 0.5% guttae amethocaine, or sub-conjunctival bupivacaine or a saline. All treatments were provided at the end of surgery before emergence from anesthetic. The study indicated that patients booked for planned inpatient stay for strabismus were excluded for the study; therefore, children with chronic disease severe enough to mandate overnight stay due to previously known comorbidities as well as strabismus were excluded.

Pain was assessed by masked nurses using a modified Wong-Baker faces pain rating scale (0=Nil, 1=mild, 2=moderate and 3=severe) at 30, 60, 120 and 180 minutes and hourly thereafter until discharge. The pain outcome is listed as the principal objective outcome measure. The number of vomiting, the need for additional medication, time of discharge and a score on whether or not the children opened their eyes comfortably (yes or No) was also recorded.

After nine children with missing data were excluded, data from 20 children in the amethocaine group and 21chidren each in the sub-conjunctival bupivacaine and saline groups was used for analysis. The summary results (Table 5–Table 7) show that there were no major differences among the three treatment groups in the distribution of children by gender, age, operative and anesthesia data.

The study reported that based on a chi-square test at each time point, there was no statistically significant differences among the three treatment groups in pain score at all measurement times (P=0.24, 0.68, 0.07 and 0.39 at 30, 60, 120 and 180 minutes respectively; Figure 2). Although it is not clearly specified in the study, it seems that the test compared the proportion of subjects with a zero pain score (no pain) among the three treatment groups. As can be seen in Figure 2, the proportion of subjects with no pain was consistently higher in the amethocaine group compared to the placebo group. The study also showed that, although not statistically significant, there was a trend in the amethocaine arm in which there were less severe pain (pain score of 2 or 3) at 120 minutes (Figure 3).

According to the authors, by chance, subjects randomized to the placebo group were on average a year older. They stated that it is possible that the treatment effect was missed because subjects in the placebo arm had a better pain tolerance than those in the treatment arm. They reported that due to the small sample size, they were not able to perform subgroup analysis by age group. Because only graphical summary and P-values were presented in this study, the reviewer was not able to conduct further analysis or verify the reported results for the primary objective outcome of pain score.

No significance differences were observed among the three treatment groups with respect to number of vomiting, eye opening and sedation scores (Figure 3). Based on an ANOVA test, the study reported that there was also no significant difference in the mean discharge time among the three treatment groups (P=0.16). The mean (SD) discharge times for the amethocaine, bupivacaine and saline group were 186 (37), 208 (45), and 186 (43) respectively.

The publication states that this study was terminated after evaluating the 62 subjects because of the unexpected small difference between any of the groups. They also noted that the sample size calculation has shown that a sample size of 62 could yield a clinically significant difference (if one was truly present) with reasonable statistical power. They stated that the measured effect differences at the interim analysis were too small to warrant continued recruitment to the trial. They also state that the power of the present study turned out to be lower than planned and a small positive treatment effect may have been the conclusion of a larger study. They stated that they did not believe that any difference in outcome found by larger study would be high enough to warrant routine use of either technique.

Table 5: Patient demographics (Carden 1998)

COPYRIGHT MATERIAL WITHHELD

Table 6: Operative data (Carden 1998)

COPYRIGHT MATERIAL WITHHELD

Table 7: Anastasia data (Carden 1998)

COPYRIGHT MATERIAL WITHHELD

Figure 2 : Summary of pain scores (Carden 1998)

COPYRIGHT MATERIAL WITHHELD

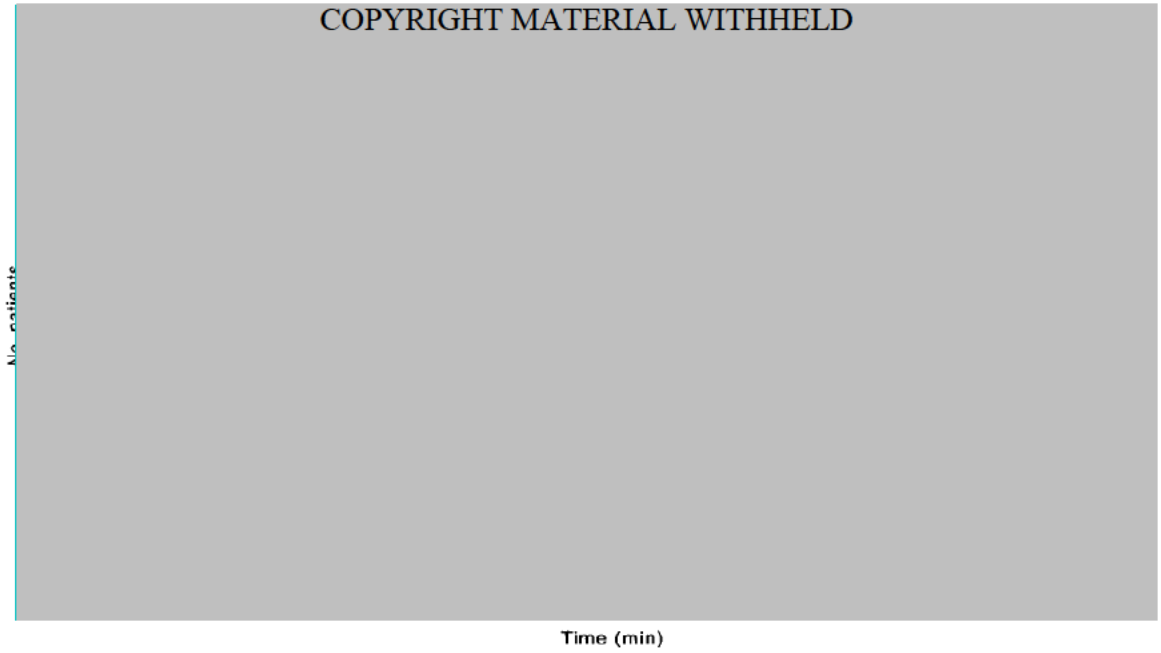


Figure 2. Pain scores (▥, 0; ▨, 1; ▩, 2; ▩, 3) at each measured time following either topical amethocaine (A), sub-conjunctival bupivacaine (B) or topical normal saline (S) (Using Chi-squared analysis at each time assessment and excluding patients who were 'not recorded' (■) or 'discharged' (□). Comparing pain scores among the three treatments: 30 min P = 0.24; 60 min P = 0.68; at 120 min P = 0.07; 180 min P = 0.39.)

Figure 3: Summary of pain scores (Mild versus Severe) (Carden 1998)

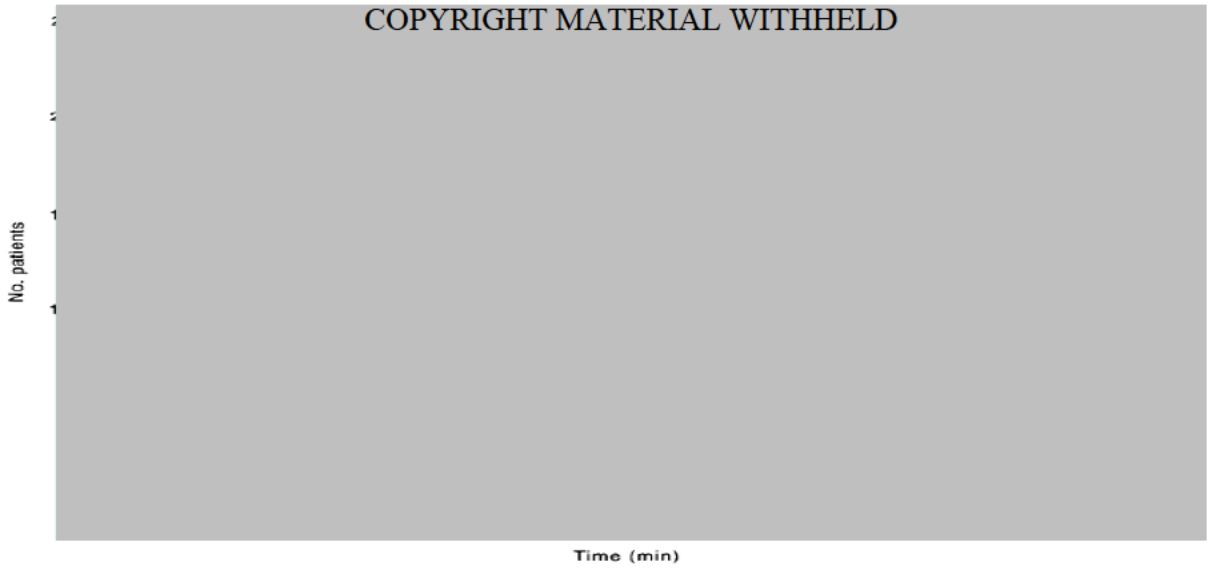


Figure 3. Mild pain (▨, pain score of 0 or 1) compared with severe pain (▩, pain score of 2 or 3) following either topical amethocaine (A), sub-conjunctival bupivacaine (B) or topical normal saline (S). (Using Chi-squared analysis and excluding patients who were 'not recorded' (■) or 'discharged' (□). Comparing pain scores between the three treatments: at 30 min $P = 0.34$; at 60 min $P = 0.16$; at 120 min $P = 0.06$; at 180 min $P = 0.43$.)

5.1.5 Kim el al (2003): Amethocaine or ketorolac eyedrops provide inadequate analgesia in pediatric strabismus surgery

This study was a prospective randomized, double-blind placebo controlled clinical trial. The study compared the effect of placebo to intraoperative 0.5% topical amethocaine or 0.5% topical ketorolac on pain control after strabismus surgery in children. In this study, a total of 51 healthy children between the ages of two and seven years who were undergoing elective bilateral recession surgery were randomized to receive either amethocaine (19 subjects) or ketorolac (14 subjects) or placebo (18 subjects). Two drops of the study medication were placed in each eye at the start and end of the surgery. Pain was assessed with a modified children's hospital of eastern Ontario pain scores (CHEOPS). According to the authors, CHEOPS is a behavioral scale intended for children ages 1 through 7 which contains six indicators (cry, facial, verbal, torso, touch, legs). Each behavioral indicator is scored with 1 or 2 except "cry", "facial" and "verbal". Cry is scored using a 1, 2 or 3. Facial and verbal are scored using a 0, 1 or 2 (Table 8). The minimum score for a given patient is 4 and the maximum score is 13.

As can be seen in Table 9, there was no statistically significant difference in selected baseline demographic characteristics (age sex and weight) among the three treatment groups. The study also reported that there was no statistically significance difference in pain scores between the three groups. The reported median (range) pain scores were 5(4-7), 5(5-9), and 5 (4-8) in the placebo, ketorolac and amethocaine groups respectively (Table 10). Because no variability

measure was provided, the reviewer was unable to provide interval estimates for the treatment differences. It is stated in the study that, patients with a pain score greater than 6 were given oral acetaminophen. If the oral acetaminophen does not alleviate the pain, codeine was chosen as a second line analgesic at a dose of 1.0 mg·kg–1. The study reported that overall 43% of children required acetaminophen postoperatively and this was distributed equally amongst the three groups. No summary data is provided for this. The publication concluded that the study did not demonstrate a beneficial effect of topical ketorolac or amethocaine versus placebo for pain control in children undergoing strabismus surgery.

Table 8: Modified children's hospital of eastern Ontario pain scores (Kim 2003)

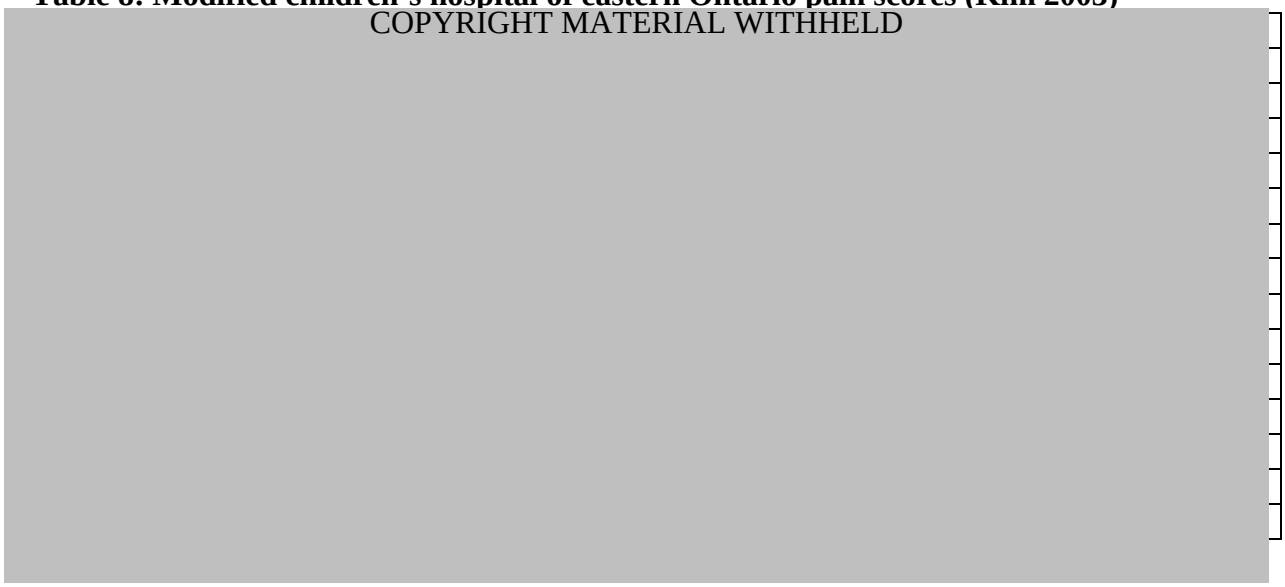


Table 9 : Patient demographics (Kim 2003)

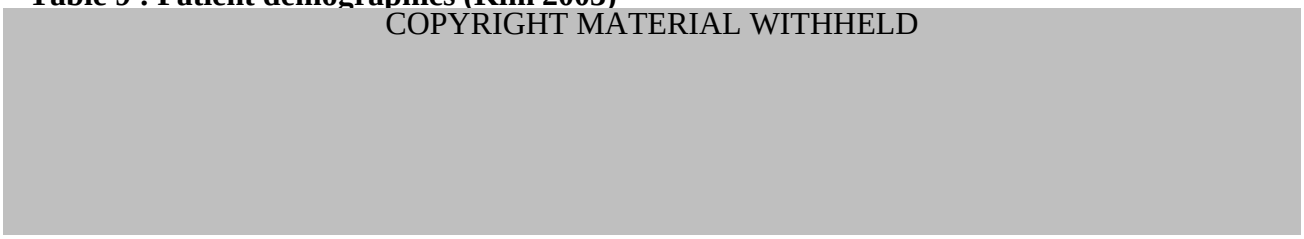
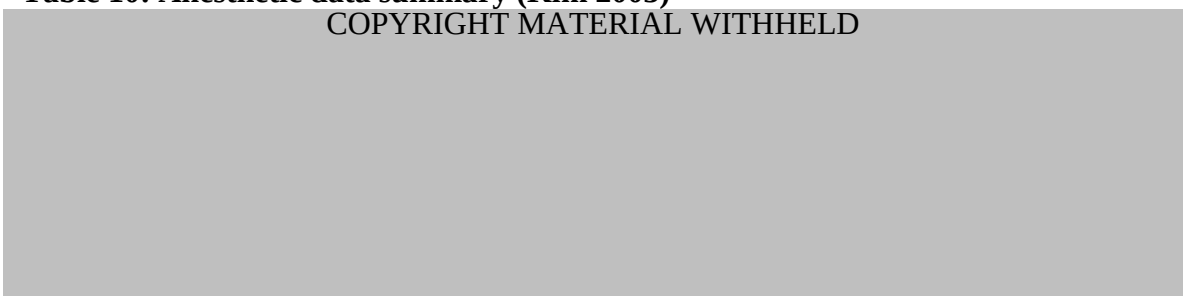


Table 10: Anesthetic data summary (Kim 2003)



COPYRIGHT MATERIAL WITHHELD

5.1.6 Rifkin et al (2012): Factors Affecting patient's pain intensity during in office iIntravitreal injection procedure.

This is a prospective, randomized study which included 60 patients in a single center receiving at least 5 consecutive intravitreal injections for various conditions (diabetic macular edema, age-related macular degeneration, and central retinal vein occlusion). The main objective of this study was to determine factors that are associated with greatest patient comfort in intravitreal injection.

In this study, patients were randomized to 1 of 3 accepted and commonly used forms of anesthesia: TetraVisc (tetracaine HCl 0.5% gel; Cynacon/Ocusoft, Rosenberg, TX), proparacaine HCl (CompuMed, Inc, Los Angeles, CA), or tetracaine HCl ophthalmic solution (Alcon Surgical, Fort Worth, TX). A single drop of anesthetic was given 3 times over a 5-minute period and each patient received at least 5 consecutive injections at monthly intervals. For those patients who received more than five injections within the study period, only the first five were studied for pain analysis. All patients were naive to injection before enrollment, and the patients were balanced in terms of treated pathology; patients with macular degeneration, diabetic macular edema, and vein occlusion were distributed evenly among the treatment groups.

Fifteen minutes after treatment, patients were asked to rate their pain from 0 to 10 using a Visual Analog Pain score survey, where 0 = no pain/no distress and 10 = agonizing pain/unbearable distress. The publication states that the visual analog pain scale used in this study has been shown to be a reliable and reproducible method of measuring patient pain. The outcomes of the self-reported pain scores were recorded and stratified by age, gender, diagnosis, injected eye, injection number, substance injected, needle gauge, and perception of visual acuity improvement from previous injection.

Analysis of variance was used as the statistical analysis of choice to compare the three groups of anesthetics, substance injected, diagnosis, injection number, and needle gauge. Student's t-test was used to compare effect of perception of visual acuity measurement from previous injection on pain score, and gender, age, and injected eye. In this summary the focus will be on the comparison of the average pain score among the three anesthetics.

The publication reported that there was a statistically significant difference (P <0.01) between patients receiving different topical anesthesia before their intravitreal injection. It states that patients receiving tetracaine (Group 3) reported the lowest pain score of 3.05 + 2.01. Patients in Group 2 (TetraVisc) reported an average pain score of 3.17 + 2.18 and patients in Group 1 (proparacaine) reported the highest pain score, of 3.39 + 2.26 (Figure 4). Because pain outcomes were recorded for each of the 20 subjects after each of the five intravitreal injections, the total number of pain measurements per subject is 5. The average pain score for each group was thus based on 100 pain measurements.

In addition to comparing average pain score among the three anesthetics, the study also performed comparison of the average pain score by gender, age, improvement of visual acuity, treatments used for the underlining condition (Avastin, Lucentis), and the type of disease (AMD, DME, CRVO). The summary results are presented in Figure 5.

The results in this study should be interpreted with caution. Firstly, despite the statistical significance, the authors reported that a clinical significance is unlikely as the magnitude of difference between the groups was quite small. Secondly, it is not clear if the statistical analysis (ANOVA) in this study appropriately accounted for within-subject dependence due to multiple measurements per eye. Thirdly, even if we trust the reported p-value from the ANOVA model, it only provides evidence that there is a difference among the three treatments. This reviewer's pairwise comparison using the reported summary data (Mean$\pm$ SD) did not show a statistical significant difference for any pair of treatments. The observed differences (95% CI) were: (-0.34; (-0.94, 0.26); tetracaine vs. proparacaine), (-0.12; (-0.70, 0.46); tetracaine vs. TetraVisc) and -0.22; (-0.84, 0.40); TetraVisc vs. proparacaine).

Figure 4 : Comparison of average pain score among three anesthetics (Rifkin 2012)

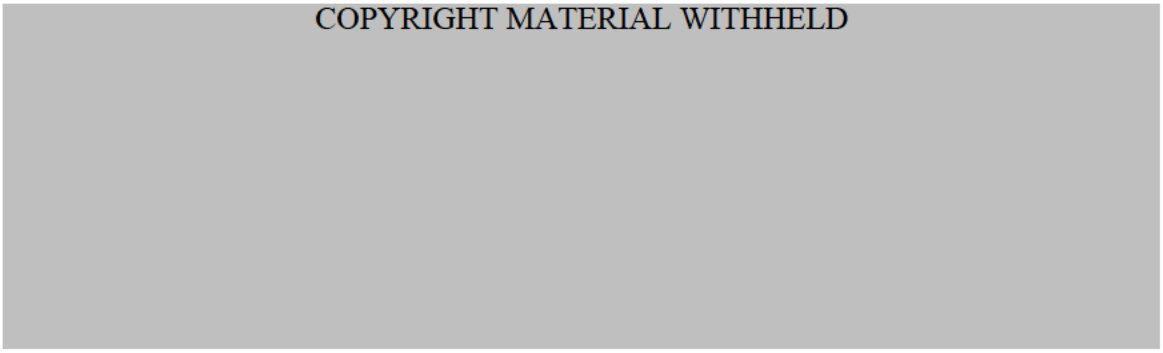


Fig. 1. Comparison of average pain scores of patients receiving proparacaine (Group 1), TetraVisc (Group 2), and tetracaine (Group 3) before injection. Analysis of variance detected a statistically significant difference between Group 3 and the other 2 groups.

Figure 5 : Comparison of average pain score among subgroups made based on demographic and disease characteristics (Rifkin 2012)

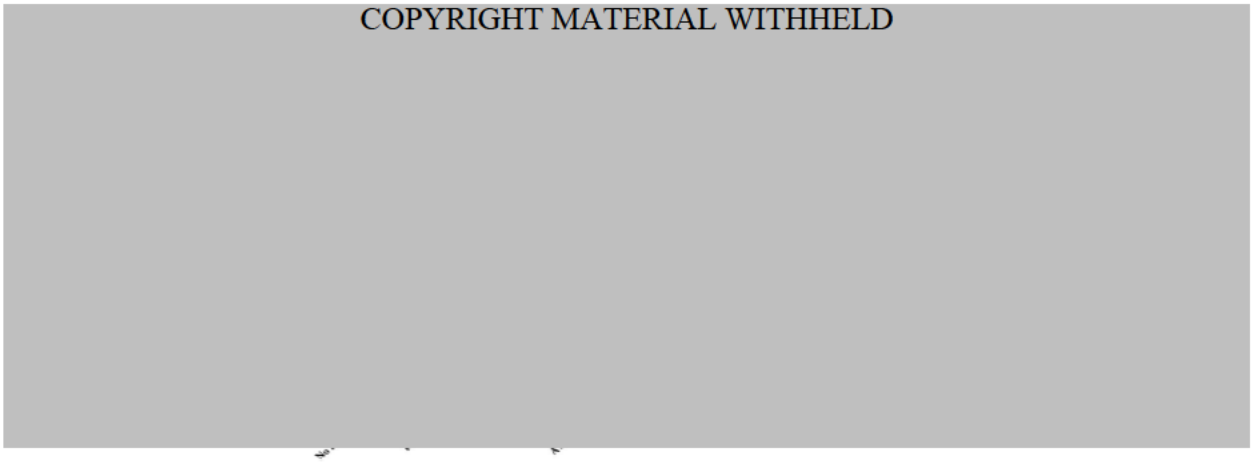


Fig. 2. Comparison of average pain scores of patients by demographics. Statistical significance was found with sex of the patient, age, perception of improvement of vision from previous injection and time of day of injection.

5.1.7 Moshirfar et al (2014) : Prospective, randomized, contralateral eye comparison of tetracaine and proparacaine for pain control in laser in situ keratomileusis and photorefractive keratectomy

This study is prospective, single-masked, randomized study. The study is comprised of 256 eyes from 128 consecutive patients over the age of 21 who are being treated with LASIK or photorefractive keratectomy (PRK). These subjects were randomized to receive tetracaine in one eye and proparacaine in the other. The patients were blinded as to which anesthetic agent was used in each eye. Patient demographic and treatment summary is presented in Table 11.

Pain was the primary outcome variable, measured upon instillation of proparacaine or tetracaine intraoperatively, immediately postoperatively, 30 minutes postoperatively, overnight, and on postoperative day 1. Patients were asked to grade the degree of pain in each eye on a numeric pain rating scale according to severity (0= no pain, 5= moderate pain, 10= severe pain). Additionally, patients were asked 30 minutes after surgery which anesthetic agent they would choose.

The publication states that the study outcomes were modeled using multivariable mixed effects regression models, which permitted a paired comparison between eyes in the same patient, while controlling for covariates. Mixed effects linear regression was used for continuous outcomes, and mixed effects logistic regression was used for binary or dichotomous outcomes.

The average pain scores experienced at the various time points in the study are shown in Table 12. Upon drop instillation, patients perceived 2.1 points more pain in eyes treated with tetracaine than in eyes treated with proparacaine (95% CI: 1.8–2.5, P<0.001), after controlling

for baseline pain. Intraoperatively, patients perceived a marginally significant 0.4 points more pain in the eye treated with tetracaine than in the eye treated with proparacaine (95% CI 0.0–0.8, P=0.067), after controlling for pain experienced during drop instillation. Immediately following surgery, patients discerned a non-significant (0.1 point) increase in pain perception in the eye treated with proparacaine relative to the eye treated with tetracaine (95% CI -0.2, 0.3, P=0.58), after controlling for pain experienced during surgery.

At 30 minutes postoperatively, there was a distinction between patients who underwent LASIK surgery rather than PRK surgery. The PRK patients did not perceive a difference in pain control between proparacaine and tetracaine (0.1 points difference, 95% CI -0.2, 0.5, P=0.53; Figure 6). The LASIK patients, however, perceived 1.5 points greater pain in the eye treated with proparacaine as opposed to the eye treated with tetracaine (95% CI 1.0–2.0, P<0.001; Figure 7). No differences in pain were seen overnight or one day after the procedure.

In summary, both anesthetic agents resulted in diminished amounts of subjective pain in patients undergoing LASIK and PRK. Tetracaine caused significantly more pain upon instillation than proparacaine for both LASIK and PRK patients. However, LASIK patients noted significantly less pain 30 minutes after surgery when treated with tetracaine. Significantly more LASIK patients preferred the eye treated with tetracaine. These differences were not present in the PRK group. Based on these findings, the authors concluded that both tetracaine and proparacaine are effective methods of topical anesthesia in LASIK and PRK. However, tetracaine resulted in greater analgesia 30 minutes after surgery in the LASIK group and patients in the LASIK group expressed a preference for tetracaine over proparacaine. There was no significant drop preference among PRK patients.

Table 11 : Patient demographics and treatment summary (Moshirfar 2014)

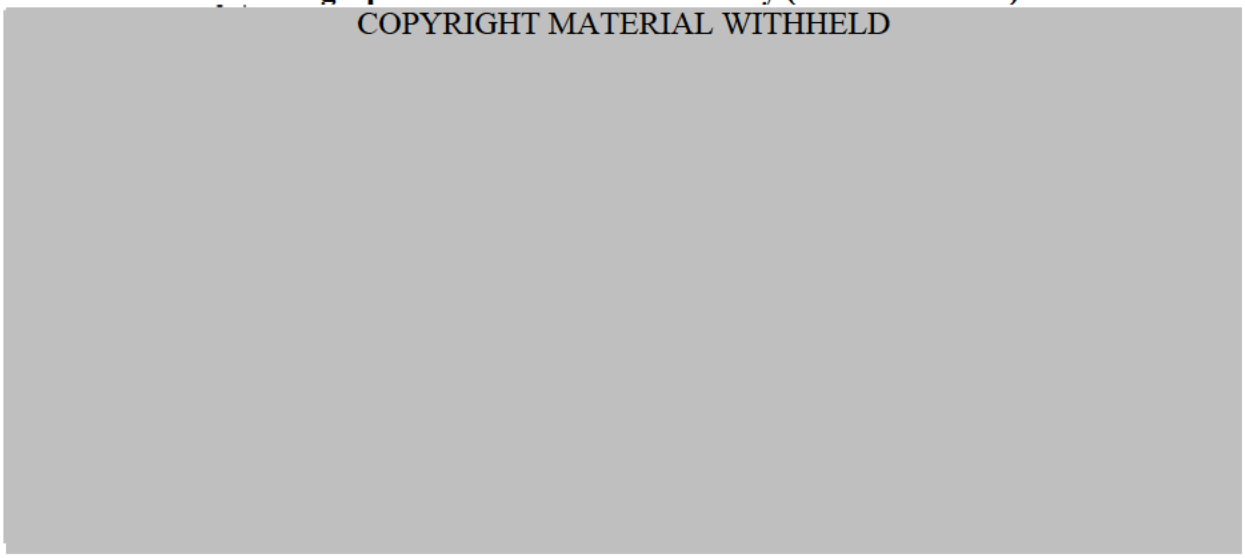


Table 12 : Pain outcome summary (Moshirfar 2014)

COPYRIGHT MATERIAL WITHHELD

Figure 6 : Pain outcomes for photorefractive keratectomy (PKR) (Moshirfar 2014)

COPYRIGHT MATERIAL WITHHELD

Figure 7 : Pain outcomes for LASIK (Moshirfar 2014)

COPYRIGHT MATERIAL WITHHELD

5.1.8 Chalam et al. (2009): Comparative efficacy of topical tetraVisc versus lidocaine gel in cataract surgery

This was a randomized, multi-surgeon, controlled clinical trial. In this study, 122 eyes of 122 patients were operated for cataract in the study: 61 patients were randomly assigned to receive five doses of lidocaine 2% gel or tetracaine solution 0.5% (TetraVisc, 0.5 ml) every 5 minutes 20 minutes before clear corneal phacoemulsification. Both the patient and the independent observer were masked to the anesthesia used. In tetracaine group there were 25 males and 36 females and in lidocaine group there were 28 males and 33 females. There was no statistically significant difference in the mean age of subjects between the tetracaine group (70.4 ± 4.1; (mean ± SD) years and in the lidocaine group was (70.6 ± 10.5; mean ± SD) years (p=0.89).

The main outcome measure was visual analog scale (0 to 10) recorded by the patients within 10 minutes of completion of surgery. This outcome was used to measure intra-operative pain. Secondary outcome measures included patients' discomfort due to tissue manipulation and surgeon graded patients' cooperation. Duration of surgery and intra-operative complications were also recorded.

The results of the study are summarized in Table 13. Intraoperative pain scores by VAS were 0.7 ± 0.31 (mean + SD) in the tetracaine group and 1.8 ± 0.4 (mean + SD) in the lidocaine group. This difference was statistically significant (P <0.001). Patient cooperation, as graded by the surgeon, was 8.3 ± 0.3 (mean ± SD) in tetracaine group and 8.4 ± 0.6 (mean ± SD) in the lidocaine group (p = 0.25). Intraoperative corneal clarity was good in 59 of 61 patients (97%) in the tetracaine group and in 55 of 61 patients (90%) in the lidocaine group (p = 0.16). The mean duration of surgery was 13.1 ± 2.7 minutes overall with mean of 13.4 ± 2.3, 12.4 ± 3.4 and 13.7 ± 2.1 minutes for the 3 surgeons who were involved in the study (p = 0.07). Mean VAS scores for the 3 surgeons were 8.20 ± 0.5, 8.1 ± 0.4 and 8.3 ± 0.4 respectively (p = 0.12). Based on the above findings, the authors concluded that topical TetraVisc solution was superior to lidocaine 2% gel for pain control in patients undergoing clear corneal phacoemulsification. Lidocaine 2% gel is similar to TetraVisc in patient comfort and surgeon satisfaction.

Table 13 : Patient characteristics and anesthetic efficacy summary (Chalam 2009)

5.1.9 Shafi et al. (1998): Randomised prospective masked study comparing patient comfort following the instillation of topical proxymetacaine and amethocaine

This was a randomized, masked, double blind, prospective study. The study involved a sample of 53 consecutive patients (17 Male and 36 females) with a mean age of 64.7 years attending the ophthalmic outpatient department requiring tonometry.

In this study, each patient received one drop of amethocaine 0.5% in one eye and one drop of and proxymetacaine 0.5% in the other eye. For each subject, the duration of the stinging sensation immediately after the instillation of the respective treatment was measured. The severity of discomfort following the eye drops was assessed using both a descriptive method and a linear analogue method. In the descriptive method, patients assigned the sensation of discomfort into categories—"no pain", "mild pain", "moderate pain", "severe pain", and "very severe pain". These five categories were arbitrarily scored from 0 to 4 respectively. This was followed by assessments using a 100 mm unmarked linear analogue discomfort scale. Subjects were asked to score the severity of their discomfort on the linear analogue scale ranging from "no pain" to "very severe pain".

Patients' preference of either drop or lack of preference was noted. To confirm the proper instillation of the anesthetic agents, scheduled tonometry using a Tonopen was performed 5 minutes after drop instillation, providing evidence of satisfactory anesthetic effect. Tonometry was regarded as a success if it was easily performed and without patient discomfort. Tonometry was regarded as unsuccessful if the patient felt uncomfortable.

The percentage of subjects experiencing "no pain", "mild pain", "moderate pain", "severe pain", and "very severe pain" on the descriptive discomfort scale for eyes receiving amethocaine and proxymetacaine is presented in Figure 8. The difference and the corresponding 95% CI for the difference in the proportion of subjects with no pain (amethocaine-proxymetacaine) was computed assuming independence of measurements coming from the same subject was -67% (-80.7%, -53.2%).

Using the wilcoxon rank sum test, the authors reported that there was a statistically significant difference in the mean descriptive discomfort score between proxymetacaine and for amethocaine (14.2 vs. 2.6; p= 0.01). There was also a statistically significance difference (p <0.001) in the mean duration of stinging between proxymetacaine (3.2 seconds (SD 6.3)) and amethocaine (22.1 seconds (SD 10.7)).

The distribution of discomfort along the unmarked linear analogue scale of length 100 mm for eyes receiving amethocaine and proxymetacaine is presented in Figure 9. Based on a t-test, the authors reported that there was a statistically significant difference in the mean linear analogue score between proxymetacaine and amethocaine (5.8 (0.9) vs, 35.6 (2.6); p<0.001).

Eighty nine per cent of patients (n=47) preferred proxymetacaine while only one patient preferred amethocaine. Nine per cent (n=5) felt that there was no difference in either using proxymetacaine or amethocaine. There was no statistically significant difference between proxymetacaine and amethocaine in the success of tonometry rate (93% vs 98%; diff (95% CI): 5.0% (-2.8%, 12.8%); p=0.08). Based on the above findings, the authors concluded that proxymetacaine is more comfortable on installation than amethocaine.

Figure 8 : Pain summary (Shafi 1998)

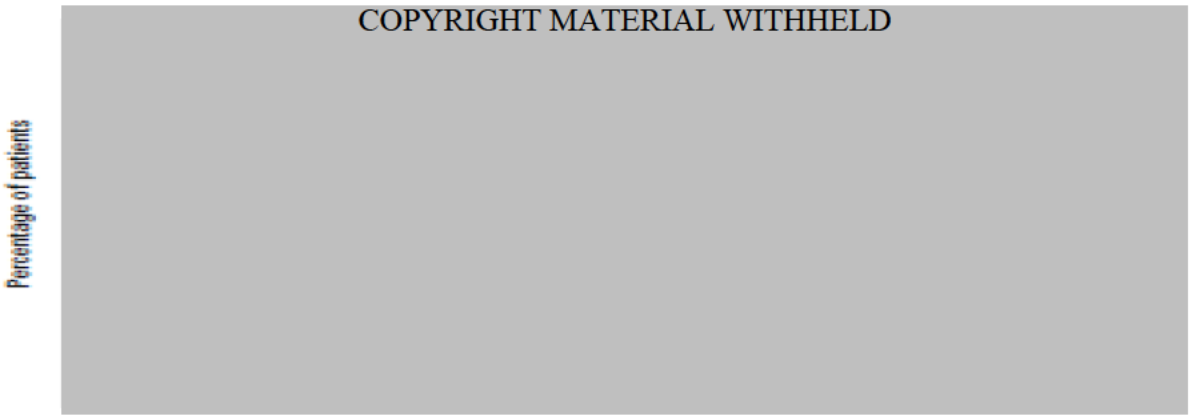
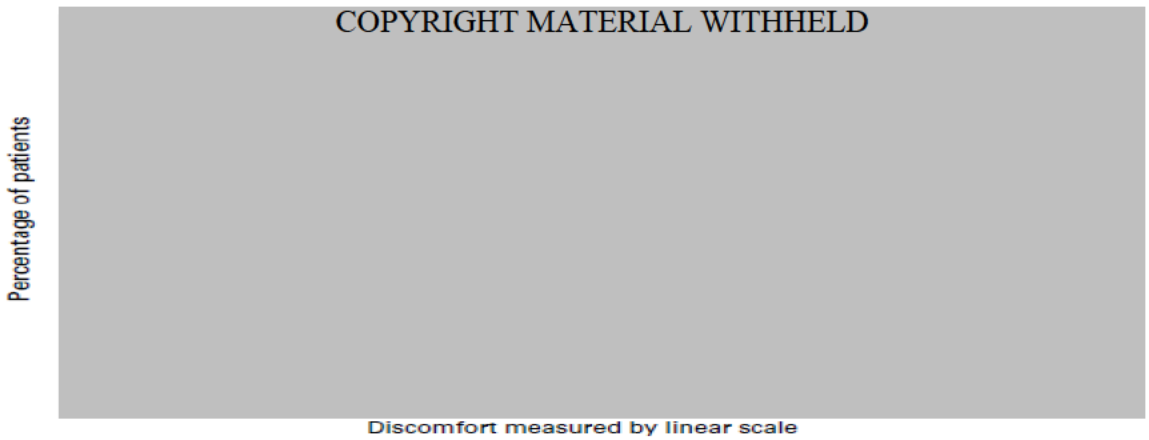


Figure 9 : Summary of discomfort measured by linear scale (Shafi 1998)



5.2 Publications evaluating tetracaine ophthalmic solution 1%

The sections below provide brief summaries of each of the three publications which evaluated the analgesic efficacy of the tetracaine 1%. Here also unless stated otherwise all summaries are gleaned from the publications. The design and summary of the key findings from these three publications are presented in Table 19 and Table 20 respectively.

5.2.1 Watson (1991): Topical amethocaine in strabismus surgery

This study was conducted to assess the effect of topical 1% amethocaine on post-operative analgesia requirements after strabismus surgery. In this study, a total of 40 children between the ages of 1-12 (mean of 4 years) who presented for elective surgery for correction strabismus were randomized in a 1:1 ratio to receive either 2 drops of 1% amethocaine or a saline.

The patient's pain was assessed by a blinded assessor on arrival and after 15, 30 minutes and at 1, 2, 4, 6 and 8 hours post-operation using a 4-point scale score (1=sleeping, 2=awake and quite, 3=agitated and 4=crying). For each subject the total score which is the sum of the scores across the 8 time points was calculated. Additionally, the need for additional analgesia, the pulse and respiratory rate were noted and the times of administration of any analgesics recorded. Statistical analysis was undertaken using the Chi-squared test for analgesic requirements and the Kruskal-Wallis one-way nonparametric test for assessment scores.

The study reported that there was a statistically significant difference in the mean total score in favor of the amethocaine group (11.4 (range 8-19) versus 19.5 (range 8-32); P<0.001; Kruskall Wallis). Using the total pain scores presented in Figure 10, the reviewer computed mean total scores were 11.8 and 19.5 in amethocaine group and saline group respectively (Diff: 7.3: 95% CI (3.4, 11.2)). The authors reported P-value is based on a non-parametric test.

The proportion of subjects who required no further analgesia was significantly higher in the amethocaine group compared to the control group (12(75%) vs 3 (1.5)). Only 3 (7.5%) of the 40 patients in the trial had any nausea or vomiting. One was in the control group and two were in the trial group. The authors concluded that topical 1% amethocaine provided significantly better postoperative analgesia as measured by the assessment of pain score and postoperative analgesia requirements.

Figure 10 : Summary of total postoperative assessment scores (Watson 1991)

Fig. 1. Total postoperative assessment scores; ■, trial group; ▨, control group.

5.2.2 Yu et al (2003): Comparison of lidocaine 2% Gel versus amethocaine as the sole anesthetic agent for strabismus Surgery

This study was designed to compare the effectiveness of lidocaine 2% with amethocain in terms of pain control in one-stage strabismus surgery. The study enrolled a total of 14 patients (10 females and 4 males) between the ages of 21-64 (mean age of 39.3). These patients were scheduled to undergo bilateral strabismus surgery at the Hong Kong eye hospital. The patients had selected topical anesthesia as their choice of anesthetic and had successfully completed a preoperative forced duction test. The right eye of the first 7 subjects was randomized to amethocaine 1% drops and the left eye to lidocaine 2% gel. For the reaming 7 subjects, the left eye was randomized to amethocaine 1% drops and the right eye received lidocaine 2% gel. The sample size calculation assumed a standard deviation of 1.7 and an expected effect difference of 1.2.

The principal outcome measures were pain and discomfort experienced during surgery, perceived by both the patient and surgeon independently. These parameters were measured by asking the subject to mark a plain 10-cm line labeled “no pain or discomfort” on one side and “severe pain and discomfort” on the other. A score was obtained by measuring from the left side of the line to the mark in centimeters. Hence, a lower score was equated with less pain and discomfort. In addition to the pain outcome, the proportion of subjects who required additional anesthetic drops during surgery and the mean number of additional drops was reported.

The mean pain score as reported by patients was 2.6 for the eyes randomized to lidocaine gel, compared with 5.3 for the amethocaine group (Student’s t-test P =0.01; Figure 1). The mean

discomfort score was 3.2 for the lidocaine group and 6.2 for the amethocaine group (P =0.01). From the surgeon's point of view, the subjective pain score was 2.2 for eyes receiving lidocaine and 4.6 for eyes receiving amethocaine (Student's t-test; P =0.01; Figure 2); comfort throughout surgery was 1.9 for the lidocaine group and 4.2 for the amethocaine group (P =0.01; Figure 3). Because no standard error estimates were provided and that there was no raw data, the reviewer was not able to construct confidence intervals for the mean differences or verify the reported results. Additionally, the authors reported P-vales from a Students t-test. It is not clear however if this refers to the paired t-test which should be the preferred method given the paired nature of the study design.

The proportion of subjects who required no additional anesthetic drops during surgery was 11 (78.6%) in the lidocaine group compared with 5 (35.7%) in the amethocaine group resulting in a treatment difference of 42.9% (95% CI: 6.3%, 66.7%). Note that, because of limited information, the confidence interval for the difference in proportion was constructed assuming the results from the two eyes are independent which might not be the case. The mean number of additional drops required was 0.3 (range, 0-2) for the lidocaine group and 1.6 (range, 0-6) for the amethocaine group (P=0.02; Fig 3). The authors concluded that lidocaine gel is superior to topical amethocaine (referred in this study as the standard of care) in terms of pain control.

Figure 11: Summary of patients subjective pain and discomfort and score (Yu 2003)

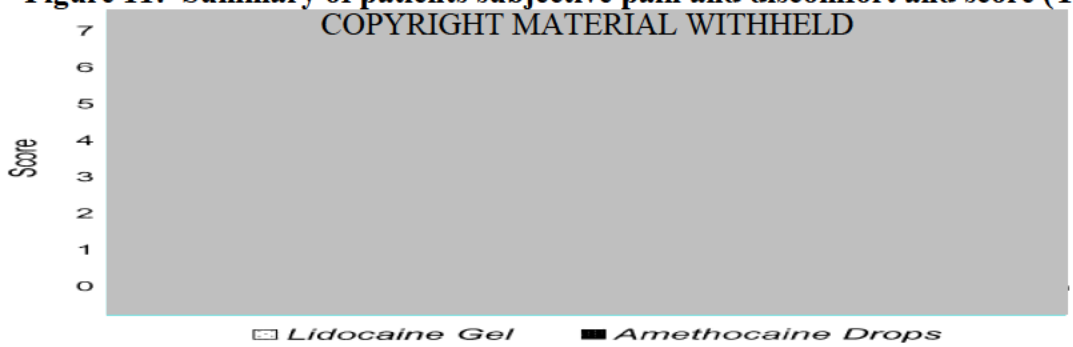


Figure 12: Summary of surgeon subjective pain and discomfort and score (Yu 2003)

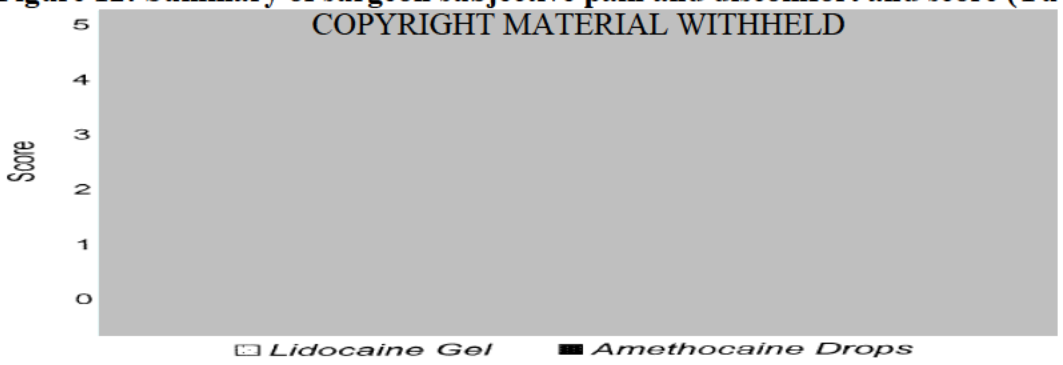
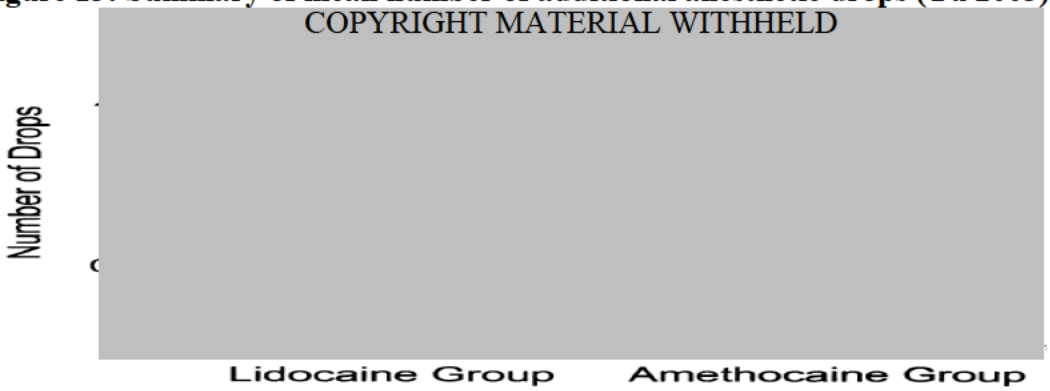


Figure 13: Summary of mean number of additional anesthetic drops (Yu 2003)



5.2.3 Anninger et al (2007): The effect of topical tetracaine eye drops on emergence behavior and pain relief after strabismus surgery

In this study, 88 subjects aged 1 to 12 years scheduled for strabismus surgery were enrolled in a double-masked randomized control trial. This study was designed to test the hypothesis that topical 1% tetracaine ophthalmic drops can decrease the intensity and incidence of postoperative pain and emergence agitation. The 88 patients were randomized to one of three groups in a roughly 1:1:1 ratio: 28 subjects in Group A (normal saline drops before and after surgery); 29 subjects in Group B (normal saline drops before and tetracaine 1% drops after surgery); 30 subjects in Group C (tetracaine 1% drops before and after surgery).

An observer masked to group assignment assessed each patient at 5, 10, 15, 30 and 45 minutes after arriving in the post-anesthesia care unit (PACU) using both an emergence behavior scale (EBS) and a modified behavioral pain scale (MBPS).

The MBPS contains 3 indicators (Cry, facial expression and movements). Cry is scored using a 0, 1, 2, 3 or 4 scale (0=laughing or giggling, 1=not crying, 2=moaning, quite vocalization or gentle whimpering, 3=full-lunged cry or sobbing and 4=full lunged cry, clearly more than baseline full-lunged cry). Facial and movements are scored using a 0, 1, 2 or 3. For facial (0=definite positive expression, 1=neutral expression, 2=slightly negative expression and 3=Definite negative expression). For movements (0=usual movements and activity, 1=resting and relaxed, 2=partial movement or attempt to avoid pain, 3=Agitation with complex movements). For each patient, based on the MBPS, at a given measurement time, the minimum pain score of 0 represented no pain and the maximum pain score of 10 represented high pain. For statistical analysis purposes, a MBPS score of 5 or greater was considered a child in pain. The study noted that the MBPS is a validated pain scale for infants, and that its accuracy in analyzing pain in older children has not been verified. The EBS is a 4-level scale (1=asleep or awake/calm, 2=slight agitation or fussy, 3=crying and 4=trashing and crying).

Note that, in this study, rescue medication (morphine, 0.05 mg/kg) was administered to any child who was crying at two consecutive 5-minute assessments, or whose MBPS ≥7, or who complained of eye pain. The primary endpoint of the study was the need for rescue using morphine. The study reported that there was no significant difference between groups in PACU morphine use. No summary data is provided regarding the number of subjects who received rescue therapy. There were no statistically significant differences in patient characteristics among the three arms.

The three treatment arms were also compared with respect to the percentage of children with MBPS score of less than 5, and the percentage of patients with an EBS score of 1 or 2 using the Kruskall-Wallis test at all measurement times. Additionally, pairwise comparisons with respect to the two endpoints were performed using the Mann-Whitney U-test.

Using the MBPS, the proportion of subjects with a post-operative pain score of less than 5 was statistically significantly lower in Group A (Placebo) when compared with Groups B or C at 5 minutes after arrival to the PACU. The differences however were not statistically significant at other measurement times (15, 30 and 45 minutes) (Table 14). Using the emergence behavior scale, a significantly lower proportion of patients in Group A, as compared with Groups B and C had behavioral scores of 1 or 2 (i.e. they were crying, or crying and thrashing more), at 5, 15, and 30 minutes after arrival to the PACU (5 minutes, $p < 0.019$; 15 minutes, $p<0.041$; 30 minutes, $p <0.021$; Table 15).

The authors stated that they expected significantly more patients in Group A would require rescue morphine when compared with Groups B and C, but this did not turn out to be the case. They stated that this suggests either that the tetracaine drops did not truly provide the pain relief described above or that the criteria for the administration of morphine were not sensitive enough to cause a difference in total medication given. A further consideration when applying the findings of this study to clinical practice is the fact that 1% tetracaine solution was used.

Table 14: Summary of proportion of subjects with post-operative pain score <5 (MBPS) (Anninger 2007)

Table 15: Summary of proportion of subjects with postoperative emergence behavioral score of 1 or 2 (Anninger 2007)

COPYRIGHT MATERIAL WITHHELD

Figure 14 : Summary of maximum MBPS score (Anninger 2007)

COPYRIGHT MATERIAL WITHHELD

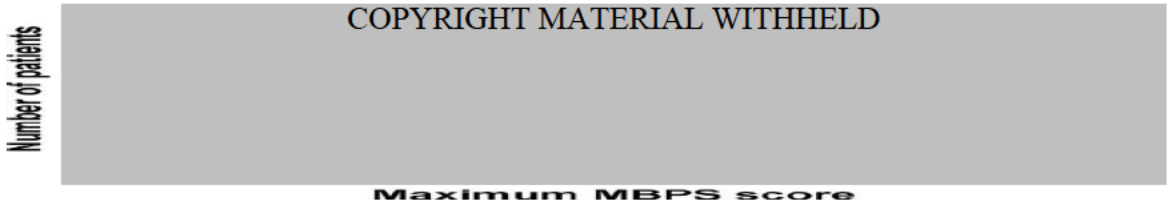


FIG 1. Maximum MBPS score by group. The number of patients who reached a given modified behavioral pain scale (MBPS) score in each group.

5.3 Publications evaluating combinations of tetracaine ophthalmic solution 0.5% and other products

5.3.1 Tsoumani et al (2010): Tetracaine 0.5% eye drops with or without lidocaine gel 2% in topical anesthesia for cataract surgery

This was a prospective, randomized, controlled study. This study included 51 patients aged between 51-86 years who were undergoing phacoemulsification under topical anesthesia. Eligible subjects were randomized into two groups to receive either tetracaine eye drops (24 (47%)) or combined tetracaine eye drops and lidocaine gel (27 (53%)).

Preoperatively, all patients were asked to answer a questionnaire to collect information about factors which could influence the evaluation of pain. Patients were also asked to grade their pain intraoperative (immediately after surgery) and postoperative (one hour after surgery) on a visual analog scale (VAS: VAS1 for intraoperative and VAS2 for postoperative). The scale ranges from 0 to 10; with 0 = no pain, 10 = severe unbearable pain. The patients were also asked to differentiate the characteristics of pain or discomfort. Data recorded included eye conditions and systemic diseases, age, gender, and whether the patient was escorted to the hospital by friends and relatives. The Student's t-test was used to compare the groups for statistical purposes. The summary results for the pain scores are presented in Table 16.

The study reported that there were no statistically significant differences between the treatment groups with regard to patient age, education level, eye conditions, systemic diseases, and habitual use of analgesics. There was also no statistically significant difference between the two treatment groups in the mean intraoperative and postoperative pain score. The authors concluded that both tetracaine 0.5% eye drops alone and the combination of tetracaine 0.5% eye drops plus lidocaine 2% gel have good anesthetic properties for topical use in cataract surgery.

Table 16 : Summary pain scores (Tsoumani 2010)

COPYRIGHT MATERIAL WITHHELD

5.3.2 Sanabir et al (2010): Tetracaine 0.5% eye drops with or without lidocaine gel 2% in topical anesthesia for cataract surgery

This was a prospective, randomized, double masked, comparative study. The objective of this study was to evaluate the efficacy of different anesthetics and topical anti-inflammatory treatment in patients undergoing intravitreal injections. In his study 151 subjects were randomized to two different preoperative anesthetic regimes (regime A [0.5% tetracaine+naphazoline] versus regime B [5% lidocaine]) and two different post-injection topical protocols (protocol 1 [tobramycin qid] versus protocol 2 [tobramycin qid+diclofenac qid]). The study was conducted in two phases. In the first phase,

In this study the main outcome measures of interest were the amount of pain, the presence of conjunctival hemorrhage, intraocular pressure (IOP) and the presence of vitreous reflux. The patient's demographic characteristics are summarized in Table 17. There does not appear to be a noticeable difference in age and gender between the two treatment regimens.

The study reported that a numerical score evaluated pain immediately after the injection, 30 min and 24 h later. The study reported that there was no statistically significant difference between the two treatment regimens in average pain score immediately after the IVI (2.85 (2.23) tetracaine and 2.67 (2.00) with lidocaine; P=0.73; Table 18). The authors concluded that Average pain scores in the two groups showed that injection-related pain after IVI with topical anesthesia was mild and both anesthetic drugs were similarly effective.

Table 17 : Summary of demographic characteristics (Sanabria 2013)

COPYRIGHT MATERIAL WITHHELD

COPYRIGHT MATERIAL WITHHELD

Table 18 : Summary of main outcome efficacy measures (Sanabria 2013)

COPYRIGHT MATERIAL WITHHELD

Table 19: Publications evaluating analgesic efficacy of tetracaine ophthalmic solution 1%

Reference	Study Objectives	Total # of Patients	Dosing Regimen	Study Design
Watson 1991	To assess the effect of topical amethocaine 1% on post-operative analgesia requirements after strabismus surgery	40	2 drops of amethocaine 1% or 2 drops of saline	Single-blind Randomized
Anninger 2007	To test the hypothesis that topical tetracaine ophthalmic 1% drops can decrease the intensity and incidence of postoperative pain and emergence agitation	88	Single saline drops before and after surgery **or** single drop of saline drops before and single tetracaine 1% drops after surgery) **or** single tetracaine 1% drops before and after surgery.	Randomized, controlled, double- masked
Yu 2009	To compare the effectiveness of lidocaine 2% with amethocaine in terms of pain control in one-stage strabismus surgery	14	1 drop of amethocaine in one eye and 1 drop of lidocaine gel 2% in the other eye	Randomized

Source: Applicant's summary and the *reviewer's summary based on submitted publications

Table 20: Summary of key findings from publication evaluating tetracaine 1%

Reference	Pain Measurement Scale	Summary of Key Results
Watson 1991	Pain scale (0-4): 1 = sleeping	A statistically significant difference in the mean total score in favor of the amethocaine group (11.4 (range 8-

	2 = awake and quiet 3=agitated 4=crying	19) versus 19.5 (range 8-32); P<0.001)
Anninger 2007	Modified behavioral pain scale: Cry (0-4: laughing, not crying, moaning, sobbing, full lunged cry) Facial expression (0-3:definite positive, neutral, slightly negative, definite negative) Movements (0-3: usual movement, resting, partial movement, agitation)	A statistically significantly (P=0.02) higher proportion of subjects randomized to tetracaine 1% drops alone (79%) compared to the saline only group (43%) reported a pain score less than 5 (less pain) at 5 minutes after surgery. The differences were not however significant at other time points (15, 30 and 45 minutes)
Yu 2009	Plain 10-cm line labeled "no pain or discomfort" on one side and "severe pain and discomfort" on the other	There was a statistically significant difference in favor of lidocaine gel 2% (p=0.01) in the mean pain score as reported by patients and mean discomfort score (P=0.01).

Source: Reviewer's summary based on submitted publications

6 References

1. Chalam KV., Murthy R., Agarwal S., Gupta S., Grover S. Comparative efficacy of topical tetraVisc versus lidocaine gel in cataract surgery. Biomedical Central Ophthalmology. 2009; 9(7).

2. Moshirfar M., Mifflin M., McCaughey M., Gess A.J. Prospective, randomized, contralateral eye comparison of tetracaine and proparacaine for pain control in laser in situ keratomileusis and photorefractive keratectomy. Clinical Ophthalmology, 2014; 8: 1213-1219.

3. Rifikin L., Schall S. Factors affecting patients' pain intensity during office intravitreal injection procedure. Retina, 2012; 32(4): 696-700.

4. Shafi T., Koay P. Randomized prospective masked study comparing patient comfort following instillation of topical proxymetacaine and amethocaine. Br Journal of Ophthalmology, 1998; 82(11): 1285-1287.

5. (b) (4)

6. Barequet S., Soriano E., Green R., O'Brien T. Provision of anesthesia with single application of lidocaine 2% gel. Journal of cataract referral surgery, 1999; 25(5): 626-631.

7. (b) (4)

8. Carden S., Colville D., Davidson A., McKenzie I., Mackey D., McKenzie J., Elder J. Adjunctive intra-operative local anesthesia in pediatric strabismus surgery. A randomized controlled trial. Australian and New Zealand Journal of Ophthalmology, 1998; 26: 289-297.

9. Kim J., Azavedo L., Bhananker S., Bonn G., Splinter W. Amethocaine or ketorolac eye drops provide inadequate analgesia in pediatric strabismus surgery. Obstetrical and pediatric anesthesia, 2003; 50(8):819-823.

10. Watson M. Topical amethocaine in strabismus surgery. Anaesthesis, 1991; 46: 368-370.

11. Anninger W., Forbes B., Quinn G., Schreiner MS. The effect of topical tetracaine eye drops on emergence behavior and pain relief after strabismus surgery. Journal of American Association of Pediatric Opthalmology and Strabismus, 2007; 11 (3): 273-276.

12. Yu CBO. , Wong VWY, Fan DSP., Yip WWK., Lam DSC. Comparison of Lidocaine 2% Gel versus Amethocaine as the Sole Anesthetic Agent for Strabismus Surgery. Opthalmology, 2003; 110: 1426-1429.

13. Shah Hr., Reichel E., Busbee BG. A novel lidocaine hydrochloride ophthalmic gel for topical ocular anesthesia. Local and Regional Aneshthesia, 2010; (3): 57-63.

14. Sinha R., Chandralekha, Batra M., Ray BR., Mohan VK., Saxena R. A randomised comparison of lidocaine 2% gel and proparacaine 0.5% eye drops in paediatric squint surgery. Anaesthesis, 2013; 68(7): 742-752.

15. Page M., Fraunfelder FW. Safety and efficacy, and patient acceptability of lidocaine hydrolic ophthalmic gel as topical ocular anesthetic for use in ophthalmic procedures. Clinical Opthalmology,2009; 3: 601-609.

16. McGee H., Fraunfelder FW. Toxicities of topical ophthalmic anesthetics. Expert opinion drug safety, 2007; 6(6): 637-640.

17. Weaver CS., Brizendine EJ., Abel S., Somerville GG., Howard JD., Root T. A prospective randomized double-blind comparison of buffered versus plain tetracaine in reducing pain of topical ophthalmic anesthesia. Annals of emergency medicine, 2003; 41: 827-831.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABEL T ESHETE
01/21/2016

YAN WANG
01/21/2016
I concur.