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Efficacy of 4% tetracaine gel and lidocaine-prilocaine cream in reducing local anesthetic injection pain in upper eyelid blepharoplasty: a randomized, single-blinded, controlled trial

Hetian Sun[1†], Yingxue Mei[1†], Li Zhu[1], Zijing Sun[1], Jiacheng Yan[1], Don O. Kikkawa[2] and Wei Lu[1*]

Abstract

Background The injection of local anesthetics, an extremely painful procedure, leads to a reduction of patients' acceptance.

Objective To investigate the efficacy and adverse reactions of 4% tetracaine gel (TG) and lidocaine-prilocaine cream (LPC) on reducing the local anesthetic injection pain for upper eyelid blepharoplasty.

Methods Sixty participants were equally divided into three groups. Each patient in two treatment groups was assigned a pair of eutectic mixture of local anesthetics (EMLA) and 4% TG, and the blank control group did not receive any topical anesthetic. The primary outcome was the pain score associated with anesthetic injection. The secondary outcomes included the local cutaneous reactions and eyelid edema in 24 h postoperatively.

Results The NRS score in the control group was 6.65 ± 1.60, in the 4% TG and EMLA sides of 5.75 ± 1.62 and 6.25 ± 1.48 in group A, without statistically significant ($p = 0.334$, 0.067, respectively). While in group B, the injection pain scores in 4% TG and EMLA sides were 4.65 ± 1.66 and 5.5 ± 1.73 ($p < 0.001$ and $p = 0.031$, respectively). A negative correlation was observed between age and LAIP (regression coefficient = -0.022), whereas gender had almost no impact (regression coefficient = 0.368). The administration duration of 4%TG and EMLA had no statistically significant effect on the cutaneous reactions observed on the patients' eyelids ($p = 0.723$, $p = 0.507$, respectively). However, the incidence of cutaneous reactions was 35% for EMLA, significantly lower than 72.5% for 4% TG ($p < 0.001$). The postoperative edema score of the control group was 1.5 (1.0,2.0), while in group A both 4% TG and EMLA sides scored 2.0 (1.0,2.0) and in group B they scored 2.0 (1.0,2.0) and 1.0 (1.0,2.0), respectively. Neither group showed significant differences in postoperative edema score compared to the control group, and there's also no significant difference was revealed comparing the 4% TG or EMLA side with the paired side in one group or the same side in the other group.

[†]Hetian Sun and Yingxue Mei contributed equally to this work.

*Correspondence:
Wei Lu
drluweicn@163.com

Full list of author information is available at the end of the article

Conclusion In comparison to LPC, 4% TG showed a stronger anesthetic effect on reducing injection pain after 60-minute application. It also generally presented a higher frequency of cutaneous reactions but didn't affect the eyelid edema 24 h postoperatively.

Trial registration This study was registered at chictr.org (the first registration date is 03/04/2023, and the registration number is ChiCTR2300070153).

Keywords Tetracaine gel, Lidocaine-prilocaine cream, Local anesthetic injection pain, Upper eyelid blepharoplasty

Introduction

Local anesthesia is a routine pre-operation procedure in oculoplastic surgery. Compared to general anesthesia, local anesthesia poses no additional risks and does not necessitate the involvement of an extra anesthesiologist for administration [1]. However, the insertion of the local anesthetic needle and the subsequent ingress of medication into tissues can elicit significant pain [1], resulting in an unpleasant sensory and emotional experience for the patient, which decreases compliance. This effect is particularly pronounced without the aid of intravenous sedation by the anesthesiologist, and patients may not cooperate or even refuse treatment [2, 3].

Topical anesthetic creams provide anesthetic effects by applying anesthetics to the surface of the skin or mucous membranes, blocking the nerve endings of the skin through the penetrating effect [4]. Eutectic mixture of local anesthetics (EMLA), a mixture of lidocaine and prilocaine, with good anesthetic effect on superficial surgery and invasive operations, is widely employed in dermatological surgery, medication injection, and invasive operations for children [5–8]. Similar to EMLA, tetracaine gel (TG) is also a versatile topical anesthetic in clinics for decades, primarily for topical anesthesia of the cutaneous and mucous membrane [9, 10].

Both EMLA and TG exert a time-dependent depth of anesthesia effect. Studies have reported a duration of at least 60 min and 45 min or more to achieve a satisfactory level of anesthesia by the two anesthetics [8, 11]. The eyelid skin is considered the thinnest in the body, on which a topical anesthetic with good penetrating properties will provide adequate anesthesia for a shorter period of time [12]. However, few studies on the clinical application for eyelid have been carried out.

In the present study, we investigated the effect of reducing the local anesthetic injection pain (LAIP) by EMLA versus 4% TG at different application duration, as well as the local cutaneous reactions and the impact on postoperative eyelid edema (24 h after surgery), providing a reference for evaluating the safety and effectiveness in the eyelid environment.

Methods

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Review Committee of the Second Hospital of Dalian Medical University (NO. LCKY2023-101). This study has also been prospectively registered at *chictr.org* (the first registration date is 03/04/2023, and the registration number is ChiCTR2300070153). Written informed consents were obtained from all participants.

Power calculation

As there were no previous studies evaluating the efficacy of two types of local anesthetic creams in alleviating local anesthesia pain during eyelid surgery, we conducted a pre-experiment to determine the necessary parameters. GPower 3.1 was used to calculate the sample size, with effect size $d=0.8$, $\alpha=0.05$, $1\text{-}\beta=0.8$, and the required sample size was 26 in each group.

Study design

The study was designed as a prospective, single-blind, randomized, controlled trial, as detailed in Fig. 1. Participants were recruited from April 2023 to May 2023 and written informed consent was obtained. Researchers could only access individual information after completing data collection and statistical analysis.

Materials

EMLA (Aspen Pharmacare Australia Pty Ltd, Australia), containing 25 mg of lidocaine with 25 mg of prilocaine per 1 g; 4% tetracaine hydrochloride gel (Zhen Ao Jin Yin Hua Pharmaceutical Co, Ltd, China), containing 70 mg of tetracaine hydrochloride per 1.5 g.

Participants

Patients in the ophthalmology department of the Second Hospital of Dalian Medical University for bilateral upper eyelid blepharoplasty were recruited as study participants. Exclusion criteria: (1) age < 18 years; (2) presence of skin wounds in the upper eyelids; (3) history of local anesthetic allergy; (4) preoperative long-term use of analgesics; (5) history of dermatosis; (6) pregnant women and lactating women; (7) history of upper eyelid surgery and (8) unable to cooperate with the investigation.

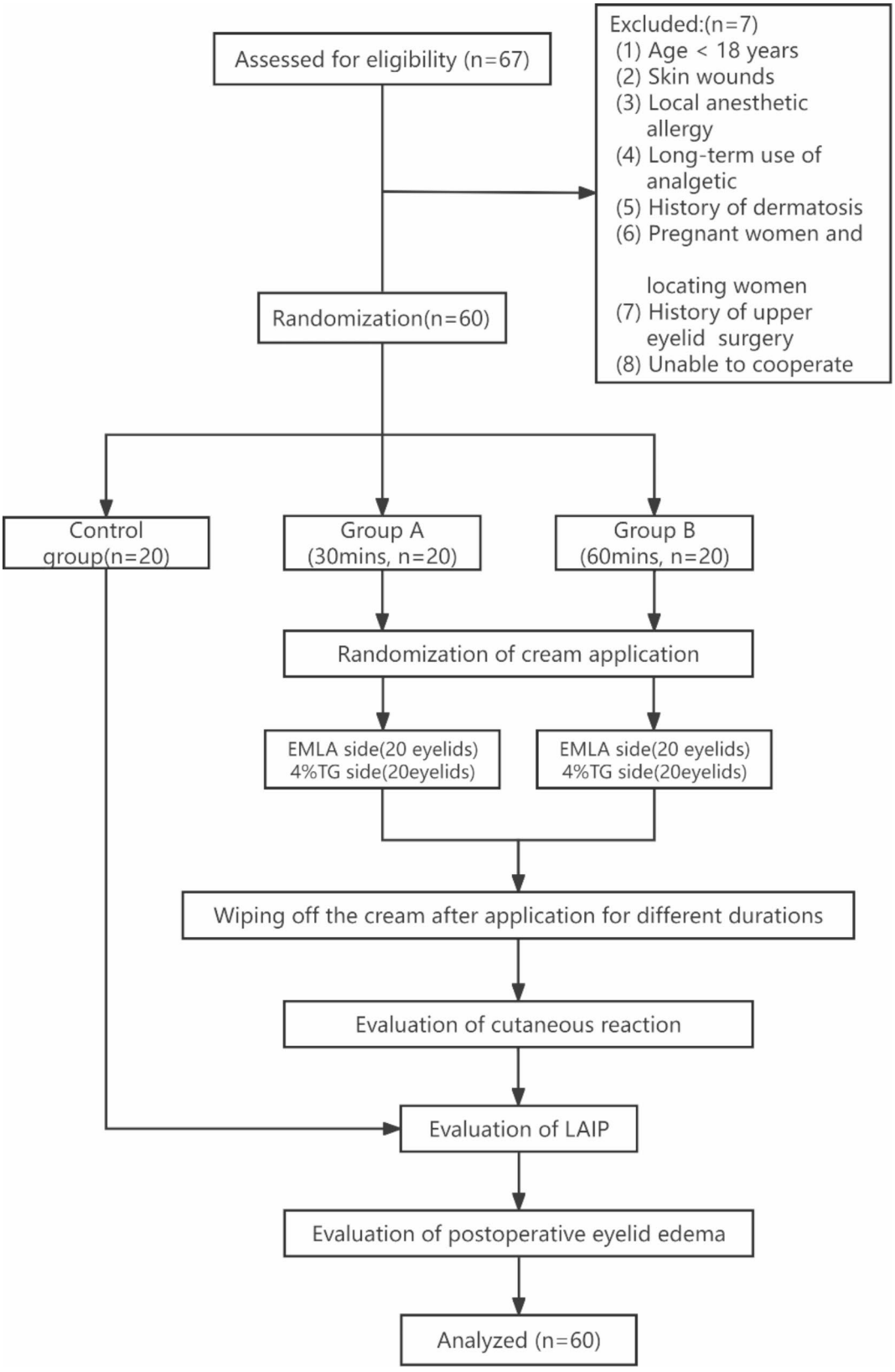

Fig. 1 The study flow diagram

Randomization, blinding, and intervention

Patients were randomized into a 30-minute group (group A), a 60-minute group (group B), and a blank control group that did not receive any topical anesthetic. The randomization process relied on SPSS 27.0 statistical software.

Preoperatively, EMLA and 4% TG were randomly applied to the bilateral upper eyelids, with a dosage of 2.5 mg per eyelid. Each eyelid received one of the two drugs separately according to the generated random sequence (www.randomnumbergenerator.com) (Fig. 2). Neither the patients nor the investigators were aware of the grouping and interventions, and the cream would be wiped away after applying for the corresponding duration.

All surgeries were performed under local anesthesia. After disinfecting the surgical area and draping, markings were made with a surgical marking pen at a distance of 7 to 10 mm above the lash line or at the site of the double eyelid line. The local anesthesia applied a mixture of 2% lidocaine and 1% ropivacaine 1:1 compounded with epinephrine. The two experienced physicians simultaneously performed the anesthesia procedure on patient's bilateral eyelids, inserting the needle (25G) from the temporal side of the eyelid and advancing towards the nasal side while administering the anesthetic. Each side received an injection volume of 2.5 ml, and the entire procedure was completed within 20 s (Fig. 2). After waiting for 5 min to allow adequate infiltration of the anesthetic, an 11-blade scalpel was used to incise the skin along the marked line. During the procedure, an electrosurgical unit was utilized for the excision of skin and subcutaneous tissue, as well as for hemostasis. For the suturing of subcutaneous tissue, 6−0 synthetic absorbable sutures were employed, while 6−0 non-absorbable sutures were used for skin closure.

Cutaneous reactions evaluation

Before the operation, the eyelids are photographed and documented to compare with the pre-intervention photographs, mainly referring to local changes in the cutaneous of both eyelids. Preoperative photography and assessment were conducted by a blinded investigator here.

Injection pain evaluation

After injection, eyelids were covered with gauze, and the LAIP was quantified by the Numerical Rating Scale (NRS), a tool for evaluating pain severity. Each patient was required to report a score for each eyelid, from 0 to 10, corresponding to the pain perception in a positive sequence. On the scale of 0 to 10, 0 indicates no pain, 1–3 indicates mild pain, 4–6 indicates moderate pain, and 7–10 indicates severe pain. To ensure the reliability of scoring, two questions were asked in sequence: (1) On which side do you feel more discomfort or pain? (2) What is the score on the more painful side? What about the other side?

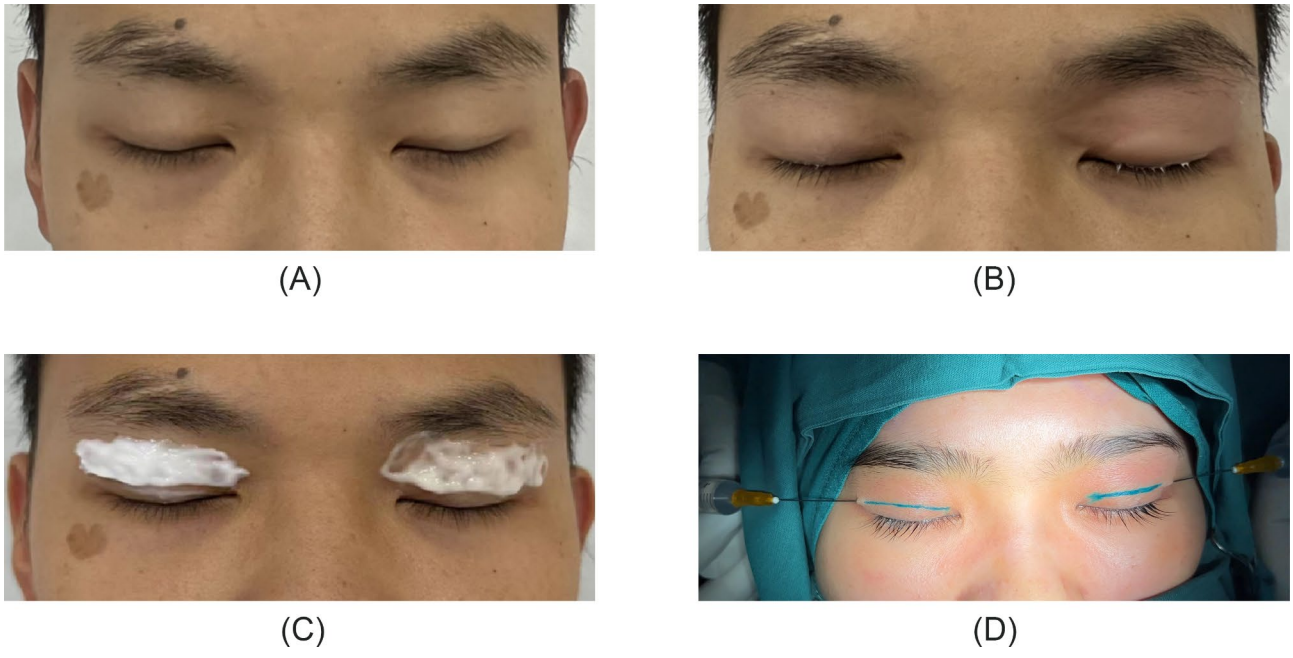

Fig. 2 A male patient treated with EMLA (L) and 4% TG (R). (**A**) Before the treatment. (**B**) Cutaneous reaction after 30 min of application. (**C**) The application area on the upper eyelids. (**D**) A female patient undergoing the injection procedure with bilateral upper eyelids performed simultaneously by two physicians

Postoperative eyelid edema evaluation

Postoperative eyelid edema was assessed 24 h after surgery, with a four-point scale applied: 0 for no edema, 1 for mild edema (imperceptible edema), 2 for moderate edema (significant eyelid edema), and 3 for severe edema (difficulty in opening the eyelid). Bilateral eyelids of patients in groups A and B were evaluated and recorded separately, and the mean value of each patient in the control group was recorded. A blinded investigator assessed postoperative eyelid edema in the patients.

Study outcome

The primary outcome was the LAIP score. The secondary outcomes included the following: incidence of local cutaneous reactions; eyelid edema score in 24 h postoperatively.

Analysis

The data were recorded and organized in an Excel sheet. IBM SPSS 27.00 statistical software was applied. The Shapiro-Wilk test was performed to verify the normality, and the Wilcoxon rank sum test was for paired design data. Inter-group differences of normally distributed variables were tested by independent samples t test, and the non-normal variables by Mann-Whitney U test. Count data were processed using χ^2 test, and the correlation analysis between variables was analyzed by multiple linear regression. Differences were considered statistically significant when $p<0.05$. Graphpad prism 9.0 software was used for plotting.

Results

A total of 60 patients were ultimately enrolled, with 7 excluded from the course of the investigation due to inability to cooperate with the pain scoring. The demographic data are provided in Table 1.

Local anesthetic injection pain

In the control group, the average value of NRS score on both eyelids was taken with the ultimate score of 7.0 (5.3, 8.0). There was no statistical difference when comparing the NRS score of bilateral eyelids in group A to those in the control group, neither when comparing within group A (All $p>0.05$). In group B, both the 4% TG side and the EMLA side showed significantly different NRS scores from the control group, respectively (All $p<0.05$), as well as comparing within group B ($p=0.017$). With the extended application duration, group A and group B exhibited a statistically significant difference in the NRS score on the side of 4% TG ($p=0.029$) while the EMLA side didn't ($p=0.138$) (Fig. 3; Table 2).

Table 1 The demographics data

	Control group	Experimental group	
		Group A (30 min)	Group B (60 min)
N (total patients)	20	20	20
Male	8	5	9
Female	12	15	11
Age (yrs)	46.3 ± 10.5	42.5 ± 12.7	39 ± 16.2
ASA-PS*			
I	15 (75%)	15 (75%)	14 (70%)
II	5 (25%)	4 (20%)	5 (25%)
III	0 (0%)	1 (5%)	1 (5%)

*ASA-PS: American Society of Anesthesiologists (ASA) physical status, a classification system according to patients' condition before surgery

The effect of age and gender on the LAIP

The age and gender of the 60 patients were enrolled in the regression model as independent variables while the different interventions were included as control variables. After excluding the confounding interference from topical anesthetics and application duration, the age was negatively associated with LAIP (regression coefficient = -0.022), while gender had almost no effect (regression coefficient=0.368) (Table 3).

Cutaneous reactions

The main cutaneous reaction to EMLA side was erythema with imperceptible edema, whereas local edema with slight erythema after 4% TG application (Fig. 2). In group A, 6 patients reported mild localized erythema on the eyelid of EMLA (30%) and 8 patients in group B (40%), without statistical difference ($p=0.507$). In group A, 15 patients reported cutaneous edema on the eyelid of 4% TG (75%), and 14 in group B (70%), without a statistical difference ($p=0.723$). This proved that there was no statistical difference in the effect of different duration of administration of the two drugs on the cutaneous reaction of the patients' eyelids. However, the total incidence of cutaneous reactions corresponding to the two drugs showed a significant difference ($p<0.001$, $\chi^2=11.314$) (Fig. 4; Table 4).

Postoperative eyelid edema

The median of bilateral eyelid edema in 24 h after operation in the control group was 1.5 (1.0,2.0). In group A, the postoperative edema score on the 4% TG side and the EMLA side were both 2.0 (1.0,2.0), while 2.0 (1.0,2.0) and 1.0 (1.0,2.0) in group B. In both experiment groups, no statistically significant difference was found comparing the 4% TG or EMLA side of the eyelid in postoperative edema with the control group, or with the paired side in one group or the same side in the other group (Table 5).

Discussion

It is the first trial to report the topical application of tetracaine gel as an effective method for reducing the LAIP in upper eyelid blepharoplasty. In the present study, 4%

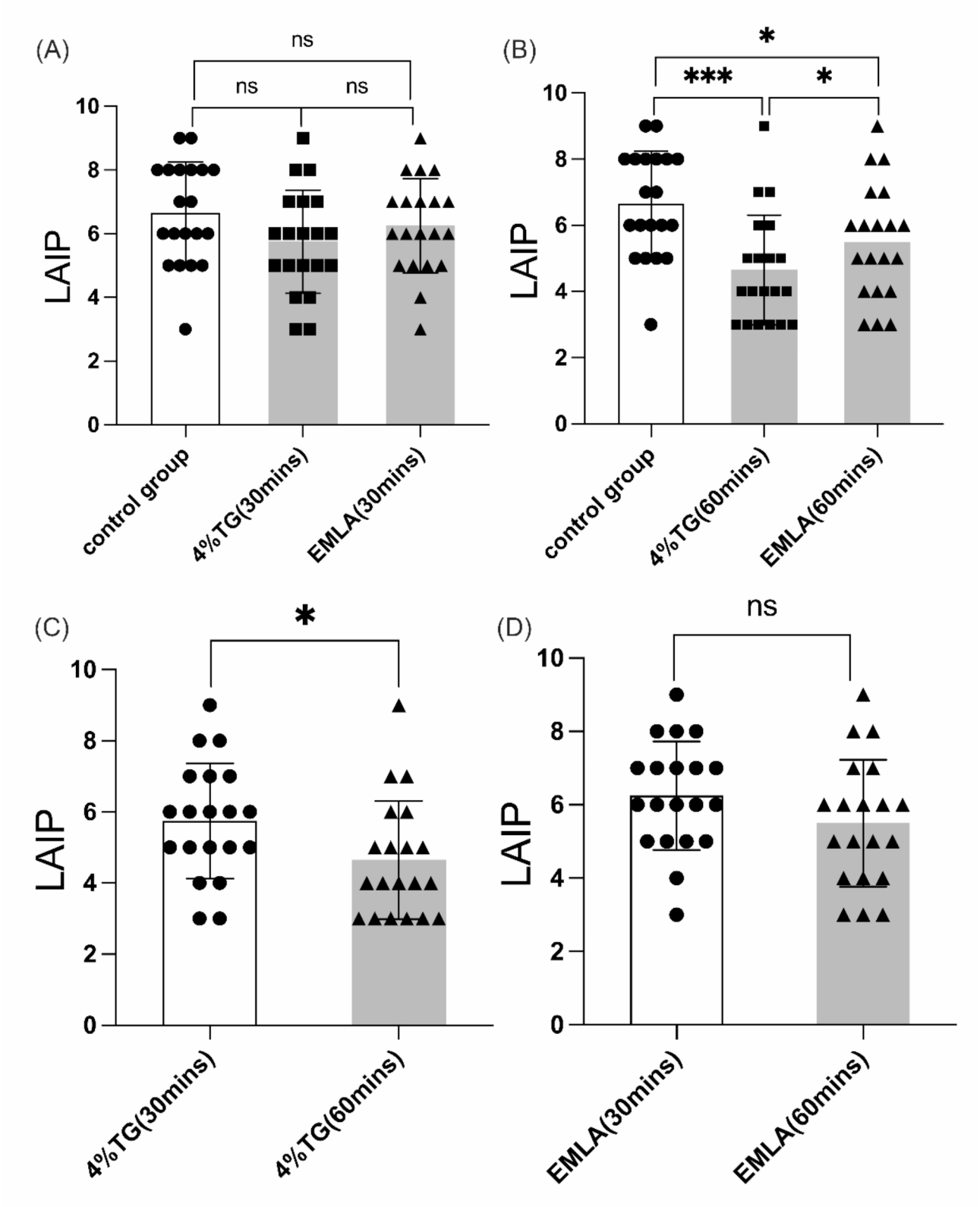

Fig. 3 Comparison of the NRS scores among the three groups. (**A**) The control group versus the 4% TG side of group A, the control group versus the EMLA side of group A, and comparison between the two sides of Group (**A**) (**B**) The control group versus the 4% TG side of group B, the control group versus the EMLA side of group B, and comparison between the two sides of Group (**B**) (**C**) Comparing the 4% TG side in group A to group B. (**D**) Comparing the EMLA side in group A to group B

Table 2 The NRS scores of LAIP among three groups (Shapiro-Wilk test)

	Control group		Experimental group			
			Group A(30 min)		Group B(60 min)	
	Right	Left	EMLA	4%TG	EMLA	4%TG
	6.6 ± 1.76	6.7 ± 1.59				
NRS score* (Avg ± SD) †	6.65 ± 1.60		6.25 ± 1.48	5.75 ± 1.62	5.5 ± 1.73	4.65 ± 1.66
NRS score* (Median; P25, P75) †	7.0 (5.3, 8.0)		6.0 (5.0, 7.0)	6.0 (5.0, 7.0)	5.5 (4.0, 6.8)	4.0 (3, 5.8)

*, Numerical Rating Scale score; †, the average is shown to help identify between the disparities across groups and due to the non-normality of some of the data, the quartile is also listed

Table 3 Regression model (multiple linear regression analysis)

Model		Unstandardized coefficient		Standardized coefficient	t	*P*	VIF
		B	Standard Error	β			
(Constant)		7.497	0.606		12.369	<0.001*	
Independent variable	Age	-0.022	0.011	-0.179	-1.998	0.048*	1.148
	Gender	0.368	0.323	0.101	1.138	0.258	1.138
Control variable	EMLA in groupA	-0.449	0.446	-0.096	-1.008	0.316	1.293
	EMLA in groupB	-1.316	0.444	-0.280	-2.966	0.004*	1.283
	4%TG in group A	-0.949	0.446	-0.202	-2.130	0.035*	1.293
	4%TG in group B	-2.166	0.444	-0.461	-4.881	<0.001*	1.283
	Blank control group	0					
R^2				0.214			
F				5.122			
P				<0.001*			
Dependent variable: LAIP†							

*, statistical significance (*P*<0.05). †, local anesthetic injection pain

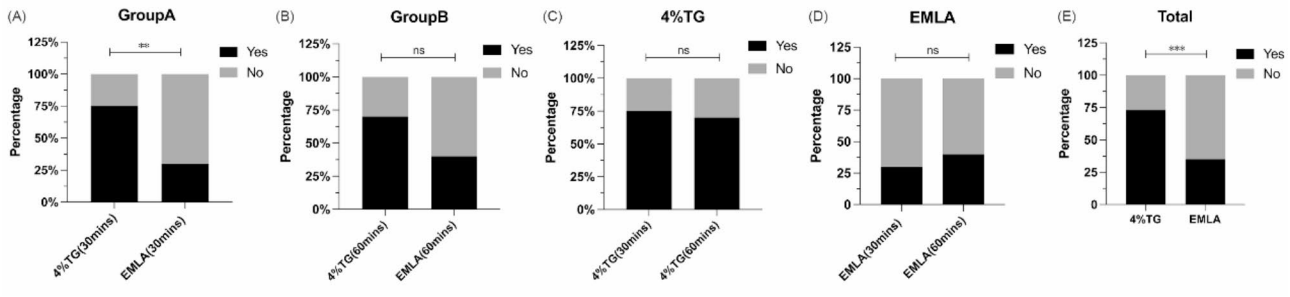

Fig. 4 Comparison of the incidence of cutaneous reactions. (**A**) (**B**) Comparison in group A and group B. (**C**) Comparing the 4% TG side in group A and group B. (**D**) Comparing the EMLA side in group A and group B. (**E**) Comparison of the total incidence of cutaneous reactions

TG was more efficient in reducing LAIP but eliciting high-frequency cutaneous edema, which didn't affect the eyelid edema 24 h after operation.

The role of LPC in anesthetizing eyelids has been demonstrated by several studies [13, 14], but few have investigated the anesthesia effect at shorter application durations. Our study indicated both LPC and 4% TG obviously showed effective anesthesia only at 60 min, although 4% TG tended to affect LAIP negatively at 30-minute application according to regression model (Table 3). This implied the time-dependent depth of anesthesia effect [15], and the necessity of sufficient pre-procedure application duration even if in upper eyelid environment.

After 60-minute application, 4% TG could more effectively anesthetize eyelids than LPC, corresponding to the previous studies [16–18], which could be attributed to the high lipophilicity of 4% TG [19]. Firstly, stratum corneum could be penetrated more easily by tetracaine due to the tens of times greater lipophilicity, leading to a deeper level of blockage in the same period. Secondly, the lipophilicity of the anesthetic is directly proportional to its potency [9, 10]. Finally, TG is considered to provide longer anesthesia due to a higher rate of plasma protein binding [18]. Additional potential benefits, such as less postoperative pain and opioid consumption, could result from a longer anesthesia period.

Table 4 Comparison of cutaneous reaction rate in two experimental groups (χ^2 test)

Cutaneous reaction	Group A (30 min)		χ^2	*P*
	EMLA	4%TG		
yes	6 (30%)	15 (75%)	8.120	0.004*
no	14 (70%)	5 (25%)		
	Group B (60 min)			
	EMLA	4%TG		
yes	8 (40%)	14 (70%)	3.636	0.056
no	12 (60%)	6 (30%)		
	Total			
	EMLA	4%TG		
yes	14 (35%)	29 (72.5%)	11.314	0.0008*
no	26 (65%)	11 (27.5%)		

*, statistical significance ($P<0.05$)

Table 5 Comparison of postoperative eyelid edema in two intervention groups (rank sum test)

	Group A	Group B	Z	*P**
4% TG	2.0 (1.0,2.0)	2.0 (1.0,2.0)	-0.270	0.787
EMLA	2.0 (1.0,2.0)	1.0 (1.0,2.0)	-0.937	0.349
Z	-0.632	-1.000		
P	0.527	0.317		

*, statistical significance ($P<0.05$)

Kemp et al. found longer latencies and reduced interpeak amplitudes in A-δ fiber evoked potentials in older patients compared to the younger, while no significant difference in C-type fiber evoked potentials [20], indicating that ageing may reduce the function of myelinated A-δ fibers and the sensitivity of their pain perception pathways, also revealed by a meta-analysis covering 1284 studies, suggesting the older individual was less sensitive to their injurious receptors for a given pain stimulus, even the more susceptible trigeminal system to the effects of age than the spinal nociceptive system [21]. Here, a trend towards lower LAIP scores with increasing age was also found, which may be related to age-related reductions in pain sensitivity. In various studies, females are considered more sensitive to pain [22–25]. A more in-depth conclusion states that females did not significantly differ from males in terms of sensitivity to chemical pain, but showed prominently less tolerance regarding pressure pain [26]. Although local anesthetic injections involve the two previously described types of pain, this study suggests that gender differences do not significantly affect LAIP, potentially due to the predominance of chemical pain or gender-related sample size disparities.

In this study, the different incidence of cutaneous reactions may attribute to the different vasculature effect. LPC has a transitorily bidirectional effect on the cutaneous vessels, presenting with localized skin blanking and erythema, and both states can exist at the same time [27, 28]. As for TG, Wiles et al. found the strong property of TG in vasodilatation and decreasing vascular reactivity, which induces increased permeability, eliciting persistent edema and even a wheal [29]. In contrast, LPC has certain antihistamine effects, demonstrated to effectively reduce the neurogenic component of inflammation and the flare response to histamine, thus reducing the degree of cutaneous edema [28].

Eyelid edema is a common postoperative manifestation of blepharoplasty leading to adverse outcomes such as ptosis, blepharochalasis, and tissue fibrosis in severe cases [30]. East Asians tend to suffer from severe postoperative edema and a correspondingly higher rate of reoperation [31]. This study also investigated the effect of both drugs on postoperative eyelid edema to determine the exacerbation of subcutaneous tissue fluid leakage, which may lead to delayed recovery and other adverse events. Our findings suggest that even for TG, a 30- or 60-minute application was not sufficient to affect local microcirculation for a prolonged period.

This study has some limitations. Firstly, the assessment of LAIP is somewhat subjective, and patients may give scores based on different experiences and ways of understanding. Secondly, the lack of patients from other racial groups in this study limits the universal applicability of our research findings across diverse populations. Then, the amount of skin and subcutaneous tissue excised during the surgery varies among individuals, which may contribute to differing degrees of postoperative eyelid edema. In addition, the design of surgical incision is a critical first step in upper eyelid blepharoplasty, although eyelid edema due to 4% TG did not affect the surgical procedure here, the experience of the surgeon should be considered. Finally, the actual sample size failed to meet the expectations of the calculated sample size, and bias due to insufficient sample size may occur.

Conclusion

In conclusion, 4% TG showed a better effect on reducing LAIP when applied to the upper eyelid for 60 min of application. In comparison to LPC, 4% TG generally presented a higher frequency of cutaneous reaction, but didn't affect the degree of eyelid edema 24 h after operation. As for females in the younger, the benefits of applying 4% TG before surgery may be more pronounced.

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Author contributions
Conceptualization, H.S., Y.M.; methodology, H.S., Y.M., D.K., W.L.; investigation, H.S., Y.M., Z.S., L.Z., J.Y.; data curation, D.K., W.L.; writing—original draft preparation, H.S.; Y.M., writing—review and editing, H.S., Y.M., D.K., W.L. All authors have read and agreed to the published version of the manuscript.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Review Committee of the Second Hospital of Dalian Medical University (NO. LCKY2023-101). Written informed consents were obtained from all participants.

Consent to publish
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Ophthalmology, The Second Hospital of Dalian Medical University, Dalian, Liaoning Province, China
[2]Shiley Eye Institute, San Diego, CA, US

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References

1. Icoz M, et al. Comparison of Pain between First and Second Operated eyelids after Upper Eyelid Blepharoplasty. Korean J Ophthalmol. 2023;37(3):201–6. https://doi.org/10.3341/kjo.2023.0011.
2. Strazar AR, Leynes PG, Lalonde DH. Minimizing the pain of local anesthesia injection. Plast Reconstr Surg. 2013;132(3):675–84. https://doi.org/10.1097/PRS.0b013e31829ad1e2.
3. Raja SN, et al. The revised International Association for the study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–82. https://doi.org/10.1097/j.pain.0000000000001939.
4. Kaweski S. Topical anesthetic creams. Plast Reconstr Surg. 2008;121(6):2161–5. https://doi.org/10.1097/PRS.0b013e318170a7a4.
5. Ruetzler K, et al. Lidocaine/tetracaine patch (Rapydan) for topical anaesthesia before arterial access: a double-blind, randomized trial. Br J Anaesth. 2012;109(5):790–6. https://doi.org/10.1093/bja/aes254.
6. Greveling K, et al. Comparison of lidocaine/tetracaine cream and lidocaine/prilocaine cream for local anaesthesia during laser treatment of acne keloidalis nuchae and tattoo removal: results of two randomized controlled trials. Br J Dermatol. 2017;176(1):81–6. https://doi.org/10.1111/bjd.14848.
7. McNaughton C, et al. A randomized, crossover comparison of injected buffered lidocaine, lidocaine cream, and no analgesia for peripheral intravenous cannula insertion. Ann Emerg Med. 2009;54(2). https://doi.org/10.1016/j.annemergmed.2008.12.025. 214 – 20.
8. Lycka BA. A new and effective topical anesthetic. J Dermatol Surg Oncol. 1992;18(10). https://doi.org/10.1111/j.1524-4725.1992.tb02917.x. 859 – 62.
9. Adriani J, Dalili H. Penetration of local anesthetics through epithelial barriers. Anesth Analg. 1971;50(5):834–41. https://doi.org/10.1213/00000539-197150050-00027.
10. Tucker GT, Mather LE. Pharmacology of local anaesthetic agents. Pharmacokinetics of local anaesthetic agents. Br J Anaesth. 1975;47:213–24.
11. Browne J, et al. Topical amethocaine (Ametop) is superior to EMLA for intravenous cannulation. Eutectic mixture of local anesthetics. Can J Anaesth. 1999;46(11):1014–8. https://doi.org/10.1007/bf03013194.
12. Pratchyapruit W, et al. Functional analyses of the eyelid skin constituting the most soft and smooth area on the face: contribution of its remarkably large superficial corneocytes to effective water-holding capacity of the stratum corneum. Skin Res Technol. 2007;13(2):169–75. https://doi.org/10.1111/j.1600-0846.2007.00183.x.
13. Lähteenmäki T, et al. Topical analgesia for the cutting of split-skin grafts: a multicenter comparison of two doses of a lidocaine/prilocaine cream. Plast Reconstr Surg. 1988;82(3):458–62. https://doi.org/10.1097/00006534-198809000-00015.
14. Henrici K, Clemens S, Tost F. [Application of EMLA creme before upper lid blepharoplasty]. Ophthalmologe. 2005;102(8):794–7. https://doi.org/10.1007/s00347-005-1193-7.
15. Junputipong N, et al. Comparison of the onset, depth, and duration of cutaneous anesthesia between topical 10% lidocaine and EMLA creams: a randomized, intraindividual, comparative trial. J Dermatolog Treat. 2022;33(7):3047–52. https://doi.org/10.1080/09546634.2022.2109566.
16. Lawson RA, et al. Evaluation of an amethocaine gel preparation for percutaneous analgesia before venous cannulation in children. Br J Anaesth. 1995;75(3):282–5. https://doi.org/10.1093/bja/75.3.282.
17. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. Arch Dis Child. 2000;82(4):309–10. https://doi.org/10.1136/adc.82.4.309.
18. Rømsing J, et al. Tetracaine gel vs EMLA cream for percutaneous anaesthesia in children. Br J Anaesth. 1999;82(4):637–8. https://doi.org/10.1093/bja/82.4.637.
19. Taddio A, Gurguis MG, Koren G. Lidocaine-prilocaine cream versus tetracaine gel for procedural pain in children. Ann Pharmacother. 2002;36(4):687–92. https://doi.org/10.1345/aph.1A138.
20. Kemp J, et al. Differences in age-related effects on myelinated and unmyelinated peripheral fibres: a sensitivity and evoked potentials study. Eur J Pain. 2014;18(4):482–8. https://doi.org/10.1002/j.1532-2149.2013.00388.x.
21. Lautenbacher S, et al. Age changes in pain perception: a systematic-review and meta-analysis of age effects on pain and tolerance thresholds. Neurosci Biobehav Rev. 2017;75:104–13. https://doi.org/10.1016/j.neubiorev.2017.01.039.
22. Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nat Rev Neurosci. 2012;13(12). https://doi.org/10.1038/nrn3360. 859 – 66.
23. Mogil JS. Qualitative sex differences in pain processing: emerging evidence of a biased literature. Nat Rev Neurosci. 2020;21(7):353–65. https://doi.org/10.1038/s41583-020-0310-6.
24. Riley JL 3, et al. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain. 1998;74(2–3):181–7. https://doi.org/10.1016/s0304-3959(97)00199-1.
25. Unruh AM. Gender variations in clinical pain experience. Pain. 1996;65(2–3). https://doi.org/10.1016/0304-3959(95)00214-6. 123 – 67.
26. Racine M, et al. A systematic literature review of 10 years of research on sex/gender and experimental pain perception - part 1: are there really differences between women and men? Pain. 2012;153(3):602–18. https://doi.org/10.1016/j.pain.2011.11.025.
27. Russell SC, Doyle E. A risk-benefit assessment of topical percutaneous local anaesthetics in children. Drug Saf. 1997;16(4). https://doi.org/10.2165/00002018-199716040-00005. 279 – 87.
28. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream. A review of the topical anaesthetic/analgesic efficacy of a eutectic mixture of local anaesthetics (EMLA). Drugs. 1993;46(1):126–51. https://doi.org/10.2165/00003495-199346010-00008.
29. Wiles MD, Dickson E, Moppett IK. Transient hyperaemic response to assess vascular reactivity of skin: effect of topical anaesthesia. Br J Anaesth. 2008;101(3):320–3. https://doi.org/10.1093/bja/aen164.
30. Sami MS, et al. Eyelid edema. Semin Plast Surg. 2007;21(1):24–31. https://doi.org/10.1055/s-2007-967744.
31. Zhang-Nunes S, et al. Demographic and physiological factors associated with clinically significant eyelid edema in patients following upper eyelid surgery. J Plast Reconstr Aesthet Surg. 2023;78:4–9. https://doi.org/10.1016/j.bjps.2022.12.007.

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