



Preservative-Free Topical Anesthetic Unit-Dose Eye Drops for the Management of Postoperative Pain Following Photorefractive Keratectomy

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ABSTRACT

Introduction: Ocular pain is a common complication following photorefractive keratectomy (PRK). The level of patient satisfaction with current pain control strategies is not high. This study aims to assess the efficacy and safety of a novel regimen of preservative-free oxybuprocaine hydrochloride 0.4% unit-dose eye drops for post-PRK pain control.

Methods: In a contralateral eye study, 144 eyes of 72 patients who underwent bilateral transepithelial PRK (TransPRK) were stratified into experimental and control groups. The experimental group received preservative-free oxybuprocaine hydrochloride 0.4% unit-dose eye drops five times daily postoperatively until complete epithelial healing, while the control group received sodium hyaluronate 0.2% instead. The main outcome measures were pain scores assessed by the verbal rating scale and visual analogue scale (VRS, VAS), the corneal epithelial defect (CED) area, epithelial healing duration evaluated by slit-lamp biomicroscopy and anterior segment optical coherence tomography (AS-OCT), and endothelial cell

density (ECD) measured before and 1 month after surgery.

Results: Pain scores assessed by VRS and VAS were significantly lower in the experimental group 8 h after surgery, and 1, 2, and 3 days postoperatively ($P < 0.001$). The mean CED area showed no significant differences between the two groups at different follow-ups (P value > 0.05). The corneal epithelial healing had a mean duration of 3.32 ± 0.47 days in both studied groups and was parallel in both eyes of each patient. In each group, 49 eyes (68%) and 72 eyes (100%) had a fully epithelialized surface on the third and fourth postoperative days, respectively. No significant changes were observed in the mean ECD 1 month following surgery in both groups (P value > 0.05).

Conclusion: Preservative-free oxybuprocaine hydrochloride 0.4% unit-dose eye drops are effective and safe in controlling early postoperative pain following TransPRK. The availability of the single-dose unit preparation can overcome the problem of topical anesthetic abuse.

Trial Registration: ClinicalTrials.gov Identifier: NCT05733741.

Keywords: Preservative-free; Topical anesthetics; Oxybuprocaine hydrochloride; Trans-epithelial PRK; Post-PRK pain

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Key Summary Points

Why carry out this study?

Postoperative pain remains a major drawback of photorefractive keratectomy (PRK) surgery. Most of the current pain control practices are not satisfactory.

Many refractive surgeons had reservations about topical anesthetic prescription following PRK for fear of topical anesthetic abuse. We aimed to investigate the efficacy and safety of a treatment regimen that allows for topical anesthetic prescription following PRK, resolving the dilemma of topical anesthetic abuse.

What was learned from the study?

The prescription of preservative-free oxybuprocaine hydrochloride 0.4% unit-dose eye drops five times daily until complete corneal epithelial healing following transepithelial PRK is effective and safe for pain control post-PRK.

The availability of single-dose unit preparation of preservative-free topical anesthetic eye drops helps to prevent the possibility of topical anesthetic abuse by offering patients with PRK a limited number of unit-dose vials for single use according to a predetermined strict regimen.

INTRODUCTION

Photorefractive keratectomy (PRK) is a well-established surface ablation procedure for correction of refractive errors which involves the removal of corneal epithelium in a large diameter usually more than 6 mm, followed by stromal ablation [1]. Transepithelial PRK (TransPRK) is a less invasive PRK procedure that utilizes excimer laser phototherapeutic keratectomy (PTK) for corneal epithelial removal

instead of the conventional manual or alcohol-assisted techniques, resulting in faster epithelial healing associated with less postoperative pain [2].

Early postoperative ocular pain within the first few days after surgery is one of the commonest complications reported after PRK [3]. The cornea is a highly innervated structure in the human body [4]. Although the exact mechanism of post-PRK pain is not clear, it is postulated that PRK causes direct damage to the nerve endings of the photo-ablated epithelium and underlying anterior corneal stroma, with consequent release of inflammatory mediators, amines, cytokines, growth factors, and prostaglandins that modify the activity of sensory fibers (nociceptors) and stimulate the exposed stromal nerve endings, resulting in severe postoperative pain experienced by patients [5, 6].

The classic postoperative treatment following PRK surgery includes the prescription of topical antibiotics and frequent preservative-free lubricants to accelerate epithelial healing [7, 8]. The current treatment regimens also include topical steroids, topical nonsteroidal anti-inflammatory drugs (NSAIDs), and oral NSAIDs to reduce inflammation and post-PRK pain [9–11]. Although topical anesthetics are effective for controlling ocular surface pain, their postoperative prescription after open ocular surface corneal surgery is limited due to their known harms such as persistent corneal epithelial defects, stromal edema, stromal infiltration, and endothelial toxicity [12]. However, most of these side effects and reported complications were associated with topical anesthetic abuse [13, 14]. In addition, many topical anesthetics contain preservatives such as benzalkonium chloride, which is also known to disrupt the corneal epithelium barrier, interfere with tear film stability, and deplete goblet cells [15].

Earlier studies [16–18] suggested that prescribing topical anesthetics in diluted concentrations and fractional doses did not delay corneal epithelial regeneration after PRK, but their use failed to gain popularity due to problems with topical formulation, stability, preservation and, most importantly, the fear of abuse by patients at home. The aim of the current

study was to assess the efficacy and safety of a novel regimen of preservative-free oxybuprocaine hydrochloride 0.4% unit-dose eye drops for controlling early postoperative pain following single-step TransPRK surgery.

METHODS

Study Settings and Design

A prospective double-blind randomized controlled contralateral eye study was conducted at Tiba Eye Center (private practice).

Compliance with Ethics Guidelines

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of the Faculty of Medicine, Assiut University, Egypt (IRB: 04-2023-300046). Written informed consent was obtained from all individuals who participated in the study. In addition, they signed a written informed consent for the publication of their clinical data and/or clinical images.

Patient Selection

Patients older than 18 years, with mild to moderate myopia and/or myopic astigmatism with a maximum manifest spherical equivalent refraction (SEQ) of -6 diopters (D), and who were candidates for TransPRK were included. Exclusion criteria were patients with corneal scars, dry eye disease with a tear film break-up time (TBUT) less than 10 s, past ocular surgery, history of contact lens wear, corneal or ocular diseases, systemic diseases such as diabetes mellitus and autoimmune diseases, and those with history of abuse of oral analgesics or psychological disorders.

Preoperative Assessment

Routine ophthalmic examination for enrolled patients was carried out including visual acuity, manifest and cycloplegic refraction assessment,

anterior and posterior segment examination with slit-lamp biomicroscopy, intraocular pressure measurement with Tono-Pen AVIA (TPA, Reichert, Inc.), cotton wisp test for corneal sensitivity, TBUT for dry eye testing, and keratorefractive evaluation using a Pentacam Scheimpflug camera (Oculus® GmbH, Wetzlar, Germany). Preoperative clinical and investigative assessment was performed by the same ophthalmologist.

Surgical Technique

Single-step transepithelial PRK was the surface ablation technique of choice performed by one surgeon targeting emmetropia for all patients enrolled in this study. A drop of preservative-free oxybuprocaine hydrochloride 4% (Benoxidia® unit-dose vials [UD], Orchidia Pharmaceutical Inc., El Obour City, Egypt) was instilled in the lower conjunctival fornix of both eyes followed by sterilizing the eyelids and the periorcular area with povidone-iodine 10% solution (Betadine®, Mundi Pharma, Cairo, Egypt). In a single step, the StreamLight® software of WaveLight® EX500 (Alcon Laboratories, Fort Worth, TX, USA) removes the corneal epithelium in a predetermined depth between 45 and 65 μm based on anterior segment optical coherence tomography (AS-OCT) epithelial mapping and with an epithelial optical zone diameter of 8 mm (default setting for combined myopia and astigmatism correction) followed by the standard 6.5-mm optical zone stromal ablation. Following laser treatment, mitomycin C 0.02% (mitomycin C Kyowa®, Biochem Pharmaceutical Inc., Mumbai, India) was applied for 20 s and the cornea was then copiously irrigated with chilled balanced salt solution (BSS; Alcon Laboratories, Fort Worth, TX, USA). A soft bandage contact lens (CL) (Acuvue Oasys®, Johnson & Johnson Vision Care, Inc., Jacksonville, FL, USA) was applied for all cases until complete epithelial healing.

Postoperative Treatment

Our post-PRK treatment regimen includes the prescription of topical moxifloxacin 0.5% four

times daily for a week (Vigamox[®]; Alcon Laboratories, Inc., Fort Worth, TX), preservative-free lubricants five times daily for 3 months (Systane[®] Hydration; Alcon Laboratories, Fort Worth, TX, USA), topical fluorometholone 0.1% (Fluca[®]; Jamjoom Pharmaceuticals Company, Jeddah, Saudi Arabia) three times daily for 1 month followed by gradual tapering over the next 4 weeks (twice daily for 2 weeks, and then once daily for another 2 weeks), oral ascorbic acid 500 mg once daily for 7 days (C-Retard[®], Hikma Pharmaceuticals, Cairo, Egypt), and oral diclofenac potassium 50 mg once daily for 3 days (Cataflam[®]; Novartis, Stein, Switzerland).

Stratification, Randomization, Regimen, and Blinding

For each patient, one eye (experimental group) was treated with preservative-free oxybuprocaine hydrochloride 0.4% (Benoxidia[®] unit-dose vials [UD], Orchidia Pharmaceutical Ind., El Obour City, Egypt), and the other eye (control group) was treated with preservative-free sodium hyaluronate 0.2% (Polyfresh[®] unit-dose vials [UD], Orchidia Pharmaceutical Ind., El Obour City, Egypt).

The instillation of the topical anesthetic in one eye (right or left) and the topical artificial tears in the other eye was determined by computer-generated randomization. One of the investigators responsible for collecting data was unblinded and recorded which type of eye drops was prescribed in the right and left eyes of every patient.

TransPRK surgery was done in the early morning and the prescribed regimen for both types of eye drops was identical and consisted of the instillation of a single unit at a frequency of five times daily (every 3 h while awake). To avoid possible topical anesthetic abuse by patients at home, each patient was given five UD vials of each type (the anesthetic and the lubricant) immediately following surgery and on each daily follow-up visit until complete epithelial healing. Clear instructions were given to immediately discard each unit-dose vial after a single use. The discarded vials were collected on the next daily follow-up visit to ensure

meticulous adherence to the postoperative instructions. Strict compliance with the prescribed regimen was stressed to both the patients and their companions.

Blinding of patients to the type of unit-dose vials, which were similar in size and shape, was achieved by cutting the lower segment of the vial that contains the labels of these eye drops. The unit-dose vials were then marked as right and left for patients to avoid confusion. Blinding of the outcome assessor was applied by masking the author responsible for the assessment of the studied outcome measures (the outcome assessor was not involved in any of the steps of preoperative assessment, operative interventions or treatment planning).

Follow-Up and Outcome Measures

After surgery, patients were advised to remain under observation for 8 h. Follow-up visits were scheduled daily at the same time of the day (early morning) until complete epithelial regeneration. The main outcome measures were:

Pain Scores

Postoperative pain scores following single-step transepithelial PRK were assessed 8 h after surgery and 1, 2, and 3 days postoperatively. The verbal rating scale (VRS) consisted of a simple single-dimensional pain scoring system where the doctor asks the patient to choose the word that best describes his/her pain and then gives it a score from 0 to 4 (0 for no pain, 1 for mild pain, 2 for moderate pain, 3 for severe pain, and 4 for unbearable pain) [19]. The visual analogue scale (VAS) was assessed by a test in which the patient is asked to rate his/her pain by choosing a number on a scale from 0 to 10 considering 0 as no pain and 10 as the worst possible pain [20]. With regard to the average duration of anesthesia or analgesia, patients were asked to record the average duration of anesthesia or analgesia experienced after instilling either type of the preservative-free eye drops in each eye at a time, with answer options of less than 30 min, 30–60 min, 60–90 min, 90–120 min, and more than 120 min.

Corneal Epithelial Healing

The area of the corneal epithelial defect (CED) in each eye of every patient was recorded 8 h after surgery and 1, 2, and 3 days postoperatively through the contact lens. Images were captured using a slit lamp (Huvitz[®] HIS-5000, Huvitz Co. Ltd, Anyang-si, Gyeonggi-do, Republic of Korea) with a similar photography protocol for all eyes (transmit speed of 400 Mbps, frame rate of 15 frames per second [fps], and an image resolution of 1388 × 1036 pixels). Broad illumination was adjusted to accommodate the size of the epithelial defect at various follow-up visits with an oblique view at 45 degrees. The obliquity and width of the light beam were modified at the operator's discretion in order to obtain the best obtainable images of the epithelial defect. Some modifications of the standard technique were permissible to delineate the edges of the healing epithelium by obtaining the light reflection of the tear film straddling the healing edges. The area of the CED was then calculated in mm² after importing the corresponding image to ImageJ[®] software [21] version 1.8.0 (National Institutes of Health, Bethesda, MD, USA) taking the white-to-white corneal diameter as a reference distance and considering the mean measurements obtained by two separate observers. The number of days required for complete epithelial healing as documented by negative corneal staining using sterile fluorescein 2% strip (Medicare Inc., Mumbai, India) was reported. In addition, AS-OCT (Heidelberg[®], GmbH, Wetzlar, Germany) was used to monitor epithelial healing with the bandage contact lens in situ (to avoid epithelial trauma) 8 h following surgery and on daily follow-up visits until full corneal epithelialization.

Corneal Endothelial Cell Density

Corneal endothelial cell density (ECD) as assessed by specular microscopy (CEM-530, Nidek Co., Ltd., Gamagori, Japan) was evaluated before and 1 month following surgery.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0 for

Windows. Qualitative data were expressed as frequency and percentage while quantitative data were tested for normality by the Shapiro–Wilk test and expressed as mean ± SD or SE. A paired-sample *t* test was used to compare the difference between the preservative-free topical anesthetic group and the preservative-free topical artificial tears group regarding the scales used in the study. A one-way repeated measures analysis of variance (ANOVA) test was used to identify changes over time within each group separately. Spearman's correlation was used to explore the correlation between VAS and VRS scales at each time point postoperatively. The level of significance was considered at a value of *P*-value < 0.05.

Sample size calculation: The sample size was calculated using G*Power software version 3.1.3, using a *t*-test for comparison between two dependent means. Effect size 0.4, alpha error probability 0.05, power (1 – beta error probability) 0.95. The minimum required sample size was 140 eyes of 70 patients (70 eyes in each group).

RESULTS

Demographic Data and Preoperative Baseline Characteristics

The study included 84 patients, of whom 12 patients failed to strictly follow the prescribed regimen and were excluded. One hundred forty-four eyes of 72 patients were finally enrolled in this fellow-eye study, where 72 eyes received preservative-free topical oxybuprocaine hydrochloride 0.4% UD as the experimental group and the contralateral 72 eyes received preservative-free sodium hyaluronate 0.2% UD as the control group. The mean age of patients was 23.66 ± 3.71 years, and the gender distribution was 25 male/47 female. All included eyes had myopia and astigmatism, with a mean manifest SEQ of −3.54 ± 1.23 D and a mean ablation depth of 63.48 ± 13.57 μm. The mean TBUT was 13.25 ± 0.98 s, and all eyes showed normal cotton wisp test. No statistically significant differences in these baseline parameters

were reported between the two groups ($P > 0.05$).

Verbal Rating Scale (VRS)

The VRS scores showed statistically significantly lower pain scores in the preservative-free topical oxybuprocaine hydrochloride 0.4% group (experimental group) compared with the preservative-free topical sodium hyaluronate 0.2% group (control group) 8 h after surgery, and 1, 2, and 3 days postoperatively ($P < 0.001$, paired-sample t -test). Pain scores of both studied groups are illustrated in Fig. 1.

Visual Analogue Scale (VAS)

Similarly, the VAS pain scores reported at all follow-ups were statistically significantly lower in the experimental group compared with the control group ($P < 0.001$, paired sample t -test). Pain scores of both studied groups are illustrated in Fig. 2.

For both the VRS and VAS scores, each study group showed a significant lowering of pain scores through the study follow-ups ($P < 0.001$, one-way repeated-measures ANOVA). A correlation between the scores of the two pain scales (VRS and VAS) was explored during the study course within each study group 8 h and on the first, second, and third postoperative days. A significant positive correlation was detected (Spearman's correlation, $P < 0.001$). Table 1 summarizes the detailed VRS and VAS scores in both studied groups.

Average Duration of Anesthesia

Forty-nine eyes (68%) in the experimental group reported an average duration of anesthesia ranging from 60 to 120 min after a single-dose-unit application, while all eyes in the control group had an average duration of analgesia of less than 30 min. The average duration of anesthesia/analgesia after a single-use unit-dose vial of either type of preservative-free eye drops is illustrated in Table 2.

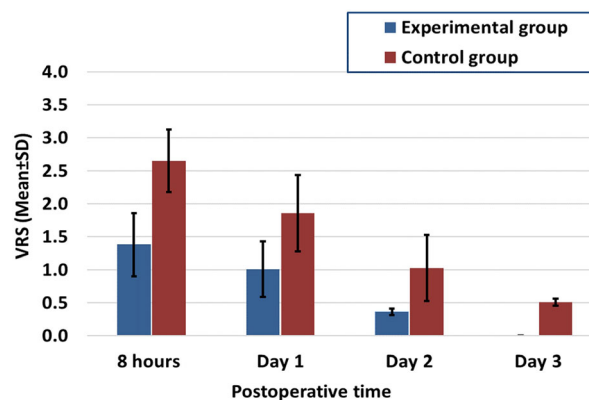


Fig. 1 VRS pain scale. Comparison of the mean postoperative VRS pain scores between the experimental and control groups. *VRS*: verbal rating scale

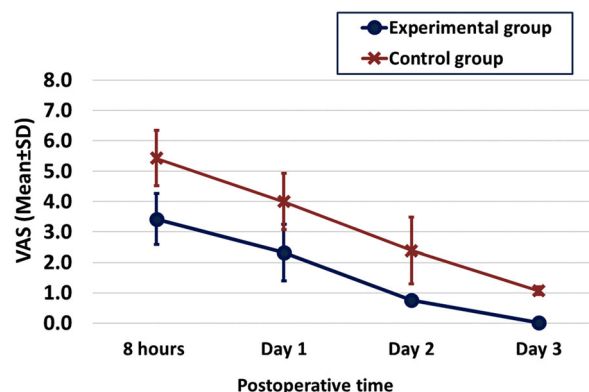


Fig. 2 VAS pain scale. Comparison of the mean postoperative VAS pain scores between the experimental and control groups. *VAS* visual analogue scale

Corneal Epithelial Healing

No significant differences were observed between the experimental and control groups regarding the mean CED area recorded 8 h after surgery and 1, 2, and 3 days postoperatively ($P > 0.05$) (Table 3, Fig. 3). The mean CED area showed a significant decrease during the study course in both studied groups ($P < 0.001$, one-way repeated measures ANOVA).

The mean number of days until complete epithelial healing was 3.32 ± 0.47 in both studied groups, and the documented epithelial healing was parallel in both eyes of each patient. In each group, 49 eyes (68%) had a fully epithelialized intact corneal surface on the third

Table 1 Pain scores for the experimental and control groups

Variables	Experimental group (<i>n</i> = 72)	Control group (<i>n</i> = 72)	<i>P</i> -value*
Pain score (VRS), mean ± SD			
8 h	1.38 ± 0.48	2.65 ± 0.47	< 0.001
Post-op day 1	1.01 ± 0.42	1.86 ± 0.58	< 0.001
Post-op day 2	0.36 ± 0.05	1.04 ± 0.50	< 0.001
Post-op day 3	0.00 ± 0.00	0.51 ± 0.05	< 0.001
<i>P</i> -value**	< 0.001	< 0.001	
Pain score (VAS), mean ± SD			
8 h	3.43 ± 0.85	5.43 ± 0.91	< 0.001
Post-op day 1	2.33 ± 0.93	4.00 ± 0.93	< 0.001
Post-op day 2	0.75 ± 0.12	2.39 ± 1.09	< 0.001
Post-op day 3	0.01 ± 0.01	1.07 ± 0.13	< 0.001
<i>P</i> -value**	< 0.001	< 0.001	

P values that are less than 0.05 (*P* value < 0.05) were considered significant and provided in bold
SD standard deviation; *VRS* verbal rating scale; *VAS* visual analogue scale

* Paired-sample *t*-test to compare means between the two groups

**One-way repeated measures ANOVA to compare change in means over time postoperatively within each group

Table 2 Duration of anesthesia/analgesia after a single-use unit-dose vial

Variables	Experimental group (<i>n</i> = 72)	Control group (<i>n</i> = 72)
Duration of anesthesia (min)		
< 30 min	8 (11.1%)	72 (100%)
30–60 min	10 (13.9%)	0
60–90 min	29 (40.2%)	0
90–120 min	20 (27.8%)	0
> 120 min	5 (7%)	0

Data expressed as number (*n*) and percentage (%)

postoperative day and all eyes (100%) on the fourth postoperative day. AS-OCT images of contralateral eyes showed no differences in the characteristics of the healing epithelial edges with regard to reflectivity, adherence to the underlying bed, or the absence of epithelial edge edema. Figure 4 illustrates image series of a study participant showing the daily progression

of corneal epithelial healing captured with slit-lamp biomicroscopy and AS-OCT.

Endothelial Cell Density

No significant differences were observed in the mean corneal ECD before and 1 month after TransPRK either in eyes that received preservative-free topical oxybuprocaine hydrochloride 0.4% unit-dose eye drops (*P* = 0.185) or in eyes that received topical artificial tears (*P* = 0.387). ECD changes in both studied groups are shown in Table 3.

Complications

At the end of the follow-up period (1 month), none of the included eyes in both the experimental and control groups developed persistent epithelial defects, stromal infiltrates, or post-PRK haze, and no other corneal or ocular complications were reported.

Table 3 Corneal epithelial defect area, epithelial healing duration, and endothelial cell density for the experimental and control groups

Variables	Experimental group (<i>n</i> = 72)	Control group (<i>n</i> = 72)	<i>P</i> -value*
CED area (mm ²), mean ± SD			
8 h	46.69 ± 4.28	46.43 ± 3.95	0.127
Post-op day 1	26.88 ± 3.17	26.68 ± 3.13	0.286
Post-op day 2	7.50 ± 2.30	7.54 ± 2.46	0.677
Post-op day 3	0.71 ± 1.12	0.66 ± 1.05	0.081
Post-op day 4	0.00 ± 0.00	0.00 ± 0.00	--
<i>P</i> -value**	< 0.001	< 0.001	
Epithelial healing duration			
No. days, mean ± SD (range)	3.32 ± 0.47 (3–4)	3.32 ± 0.47 (3–4)	--
ECD, mean ± SD			
Preoperative	2796.38 ± 176.66	2793.18 ± 168.81	0.316
One month post-op	2795.15 ± 176.34	2791.81 ± 170.33	0.342
<i>P</i> -value*	0.185	0.387	

P values that are less than 0.05 (*P* value < 0.05) were considered significant and provided in bold
SD standard deviation, *CED* corneal epithelial defect, *ECD* endothelial cell density

*Paired-sample *t*-test to compare means between groups

**One-way repeated-measures ANOVA to compare change in means over time postoperatively within each group

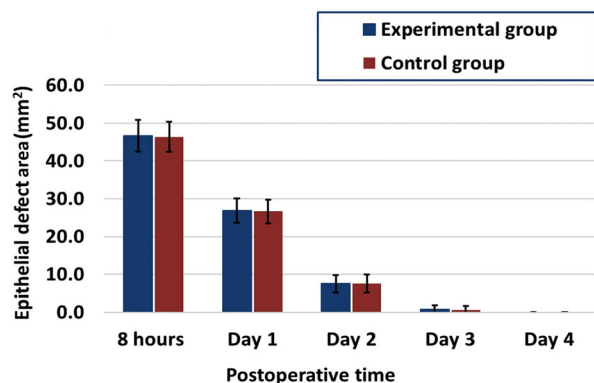


Fig. 3 Corneal epithelial defect area. Comparison of the mean corneal epithelial defect (CED) area (mm²) between the experimental and control groups

DISCUSSION

PRK surgery has been associated with acceptable visual and refractive outcomes, in particular after the introduction of the new

transepithelial technology [22]. Many studies consider PRK to be safer than flap-based corneal refractive surgery in terms of corneal biomechanical stability and postoperative dry eye disease [23, 24]. However, the occurrence of intense postoperative pain during the first 72 h following surgery presents the main limitation of this refractive procedure [25].

A variety of medications and techniques have been proposed in an attempt to control PRK pain during and after surgery, starting from the preoperative instillation of topical anesthetics, the intraoperative copious irrigation with cold BSS [26, 27], the application of soft bandage contact lenses at the end of surgery that can be soaked with analgesics or anesthetics [28–30] and the postoperative prescription of topical and oral anti-inflammatory analgesic medications including NSAIDs and steroids up to the use of systemic opioids in very severe pain [31–33]. Despite the relative analgesia achieved with these therapeutic agents or

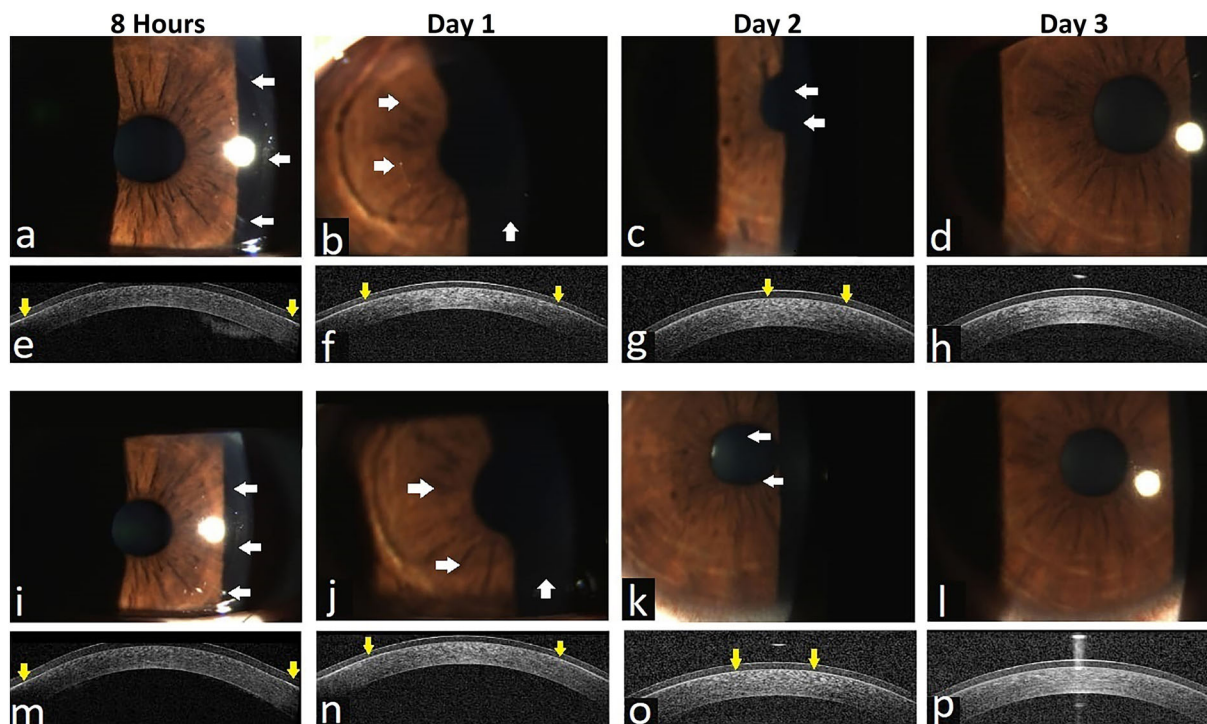


Fig. 4 Corneal epithelial healing image series by slit-lamp biomicroscopy and AS-OCT. Slit-lamp and anterior segment optical coherence tomography (AS-OCT) image series of a 25-year-old female patient who underwent bilateral transepithelial photorefractive keratectomy (TransPRK) and received preservative-free oxybuprocaine hydrochloride 0.4% in her right eye for post-PRK pain control and preservative-free sodium hyaluronate 0.2% in her left eye. Slit-lamp photos of the right eye (a–d) and left eye (i–l) showing progressive reduction of the size of the

epithelial defect (white arrows) 8 h after surgery, and 1 and 2 days postoperatively until complete epithelial healing on day 3. AS-OCT images of the right eye (e–h) and the left eye (m–p) marking the healing epithelial edges (yellow arrows) 8 h after surgery, and 1 and 2 days postoperatively until complete epithelial healing on day 3. Note: A highly reflective uniform linear pattern of bandage contact lens can be seen clearly anterior to the epithelium in AS-OCT images

techniques, the level of patient satisfaction with post-PRK pain control strategies is still not high [34].

Oxybuprocaine hydrochloride 0.4%, also known as benoxinate (ester-type local anesthetic), acts rapidly within 1 min by binding to neuronal sodium channels and decreasing their permeability to sodium ions, thus preventing the conduction of nerve signals along the corneal nerve axons that may last up to 60 min or more [35].

To the best of our knowledge, this is the first study to assess the efficacy and safety of preservative-free oxybuprocaine in controlling post-PRK pain. A research scarcity in the

literature was found when investigating the prescription of topical anesthetics for control of postoperative pain following PRK.

The results of the current study showed that the use of preservative-free oxybuprocaine hydrochloride 0.4% unit-dose eye drops significantly reduced early postoperative pain following TransPRK surgery. Previous studies [16–18] demonstrated the efficacy of other topical anesthetics in controlling pain after PRK, but their prescription as part of the routine post-PRK treatment protocols was restricted for various reasons. Verma et al. conducted two studies [16, 17] comparing non-preserved tetracaine 1% to placebo (saline) in one study

and to bupivacaine 0.75% in the other and concluded that tetracaine was significantly more effective at pain control than placebo or bupivacaine. However, the two studies had limitations such as the lack of a contralateral design, the need to use tetracaine eye drops every 30 min up to a frequency of 30–40 drops per day, which is impractical for many patients, and the limited prescription of tetracaine eye drops for the first 24 h only following PRK for fear of topical anesthetic abuse for longer periods. A study by Montard et al. [36] found that the use of topical diclofenac 0.1% four times daily for 3 days following PRK surgery was more effective in controlling PRK pain than instilling topical tetracaine 1% at 30-min intervals for the first 24 h only. In another study, Ripa et al. [37] identified a consistent trend in which pain scores after PRK were highest at 24–72 h, suggesting the need for an extended pain control regimen beyond the first 24 h following surgery. Shahinian et al. [18] investigated the use of diluted topical proparacaine 0.05% to control pain after PRK and found that proparacaine at such a low concentration produced a corneal analgesic rather than an anesthetic effect that would be beneficial to preserve some corneal sensation and to prevent abuse by patients if administered at higher anesthetic concentrations of 0.5% or 1%. Nevertheless, the presence of preservatives in proparacaine was not discussed. The unavailability of a ready diluted form of proparacaine and the need for preparation from the 0.5% ophthalmic solution is a major limitation. In addition, the frequent use when needed by patients for 7 days and the supply of this diluted anesthetic in bottles in the form of extended-use ophthalmic drops may increase the risk of contamination [38, 39].

Most of the topical anesthetic-treated eyes in our study reported an average duration of anesthesia between 60 and 120 min after single-use application of the preservative-free oxybuprocaine, a finding that would help to reduce the need for frequent instillation described with tetracaine and proparacaine. The durability and less irritating adverse effects of topical oxybuprocaine hydrochloride 0.4% compared with other topical anesthetics have been shown in veterinary research studies [40–42].

Corneal cytotoxicity of topical anesthetics suggested by *in vitro* studies [43, 44] is one of the main concerns that impedes their postoperative prescription after PRK. Fan et al. [45] investigated the cellular and molecular mechanisms of corneal epithelial cytotoxicity of oxybuprocaine and found that it causes corneal epithelial cell apoptosis and disruption of the mitochondrial transmembrane potential, resulting in dose- and time-dependent cytotoxicity to human corneal epithelial cells. The current study supports the safety of the short-term use of preservative-free topical anesthetics for managing early postoperative TransPRK pain from both an experimental and clinical perspective. From an experimental perspective, *in vitro* studies [46, 47] have reported epithelial cytotoxic effects of different topical eye drops prescribed as part of the standard PRK treatment regimen, such as preservative-free moxifloxacin, fluorometholone with and without benzalkonium chloride ophthalmic solutions, and topical diclofenac. Also, the corneal cytotoxicity of topically applied drugs suggested by *in vitro* studies cannot predict clinical inferences without the support of *in vivo* studies, which usually help clinicians in adjusting the optimal dose, concentration, and duration of topical drug therapy. Furthermore, the presence of preservative-free formulations of these eye drops has significantly reduced their corneal epithelial and endothelial toxicity [48]. From a clinical perspective, the results of the current clinical trial supported the safety of administration of preservative-free oxybuprocaine for early post-PRK pain control as evidenced by the absence of any corneal epithelial, stromal, or endothelial complications. Moreover, recent studies [49, 50] addressing the use of topical anesthetics for corneal abrasions concluded that the appropriate and even frequent administration of these agents in a strict regimen and dosage for short periods was safe, with no reported adverse effects. It should be mentioned that the safety of prescribing topical anesthetic eye drops in aseptic, clean, surgically induced corneal abrasions as in PRK is expected to be higher than with traumatic corneal abrasions.

In summary, the findings of the current study would encourage surgeons performing

refractive procedures to prescribe preservative-free topical anesthetics supplied in single-dose units for the control of early postoperative pain following PRK, for a variety of reasons. First, these formulations are available for direct ophthalmic use without the need for preparation or dilution. Secondly, the absence of preservatives in these preparations helps to avoid a delay in epithelial healing as a result of lower corneal epithelial cytotoxicity. Third, the single-use eye drops decrease the possibility of contamination reported with multi-dose droppers. Finally, and most importantly, offering patients with PRK a limited number of topical anesthetic unit-dose vials in a predetermined regimen for a short period of time with clear instructions to discard after single use can resolve the dilemma and overcome the fear of abuse of these topical anesthetics (especially at home) resulting in the previously reported serious corneal complications and ocular morbidity.

Applying a contralateral eye study design enhances the internal validity of the current study, especially when evaluating objective interocular comparisons such as corneal epithelial healing and endothelial cell density changes.

Our study has some limitations, such as its single-center design with short follow-up as well as the known limitations of the subjective pain scoring scales. Other important limitations to consider are the probable lack of an anesthetic or analgesic effect with the instillation of artificial tears in the control group and the spillover effect from the experimental to control eyes and vice versa.

CONCLUSIONS

The present study revealed a significant decrease in post-PRK pain scores with the topical application of preservative-free oxybuprocaine hydrochloride 0.4%. No drug-induced corneal complications were reported following surgery. The availability of single-dose unit preparations of these topical anesthetics can overcome the problem of topical anesthetic abuse. Further studies are needed to investigate the safety of prescribing preservative-free

topical anesthetics unit-dose eye drops at higher daily frequencies and to evaluate their efficacy in controlling postoperative pain following other open ocular surface surgeries such as corneal collagen cross-linking (CXL).

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Mahmoud Abdel-Radi, Zeiad Eldaly, Sara Alattar and Islam Goda declare that they have no competing interests.

Ethical Approval. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of Faculty of Medicine, Assiut University, Egypt (IRB: 04–2023-300046). A written informed consent was obtained from all individuals who participated in the study. All

patients signed a written informed consent for publication of their clinical data and/or clinical images.

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