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Tetracaine Effect on Pain Control within the First Day after Trans-Epithelial Photorefractive Keratectomy

Hamidreza Hasani *

Department of Ophthalmology, Shahid Madani Hospital, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

*** Corresponding author**

Hamidreza Hasani, MD
Department of Ophthalmology, Shahid Madani Hospital, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran
Tel: +98 21 8865 0450
Fax: +98 21 8865 0451
Email: hamidrezahasani@yahoo.com

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Abstract

Background: This study was carried out to evaluate the effect of non-preserved tetracaine 0.5% on pain alleviation in the first 24 *hr* after Trans-epithelial Photorefractive Keratectomy (TPRK) excimer laser surgery.

Methods: This quasi-experimental study was conducted on 50 patients who were candidates for TPRK surgery using SCHWIND AMARIS 1050RS (eye-tech-solutions, Germany) excimer laser. One eye randomly received standard treatment including the eye drops of betamethasone, chloramphenicol, artificial tear, diclofenac, and diclofenac tablet (25 *mg* daily), and the fellow eye received standard treatment plus non-preserved tetracaine 0.5% drop every 4 *hr*. Post-operative pain was the main outcome measure, and the secondary outcome measures including burning sensation, epiphora, foreign body sensation, and photophobia were compared using Fisher's exact test and ANOVA with a significance level of 0.05.

Results: Nineteen patients (38%) were male and 31 (62%) were female. Thirty patients (60%) reported no pain. The numeric scale of pain showed that the severity of pain was 4.4±0.8 for the cases' eyes and 4.5±0.6 for the controls' eyes, but the difference was not significant (p=0.75). Also, there was no difference regarding the burning sensation (p=0.49), epiphora (p=0.16), foreign body sensation (p=0.44), and photophobia (p=0.19). No significant difference was noted between the two groups.

Conclusion: Administering the eye drop of non-preserved tetracaine 0.5% every 4 *hr* had no significant effect on pain alleviation within the first day after TPRK surgery.

Keywords: Pain, Tetracaine, Trans-epithelial photorefractive keratectomy

Introduction

Trans-epithelial Photorefractive Keratectomy (TPRK) is one of the most common refractive surgeries throughout the world. Severe pain in the first 24 *hr* after surgery is one of the adverse effects of this procedure (1). Therefore, similar to any other elective surgical procedures, post-operative pain control is of crucial importance since it results in patients' satisfaction and increases their interest in this method of refractive surgery (2). The major mechanism through which post-operative pain develops is the release of the prostaglandins and direct stimulation of nerve endings in the margin of the ablated zone. Therefore, by repairing the epithelium in the periphery of the cornea (despite the epithelial defect in the center of cornea), the severity of the pain decreases considerably (2,3).

Although contact lenses, NSAID drops, and oral analgesics are now used to alleviate postoperative pain, a large percentage of patients still complain of post-operative pain (3). Installation of tetracaine drops has been recommended to decrease pain, but there are reports of a disturbance in the repair of the corneal epithelium and probable development of sterile wounds following the application of topical anesthetics, which are mainly due to their long-term uncontrolled use. It seems that if such medications are administered under the supervision of an ophthalmologist in combination with other treatments, they can efficiently control post-TPRK pain without leaving any adverse effects. The present study was conducted to evaluate the effect of non-preserved tetracaine 0.5% drops plus standard treatment on pain alleviation in the first 24 *hr* after TPRK surgery.

Material and Methods

This quasi-experimental study was conducted on 50 patients including 31 women and 19 men aged 20-49 years. Inclusion criteria were myopia less than 8 diopters, astigmatism less than 4 diopters, pachymetry more than 480 μ, and anisometropia less than 1/25 diopters. The participants had no other ocular diseases including glaucoma, keratoconus, or history of ocular surgery and were negative for systemic diseases such as collagen vascular diseases or diabetes. Also, they had never used medications such as isotretinoin, corticosteroid, chloroquine, and hydroxychloroquine.

This study was carried out according to the Declaration of Helsinki after protocol approval of the Ethics Committee of the university under the code of IR.IUMS.REC.1397.1182. Preoperative examinations included Uncorrected Visual Acuity (UCVA), Best Corrected Visual Acuity (BCVA), refraction, complete slit lamp biomicroscopy, applanation tonometry, indirect ophthalmoscopy, corneal pachymetry, and topography using Sirius (SCHWIND eye-tech-solutions, Germany) was done in all the patients. After informing the patients and obtaining their written consent, they underwent surgery as the following:

First, tetracaine drop (Anestocaine, Sina Darou, Iran) was instilled in the eye. Then, a single-step laser-assisted corneal epithelium debridement eye was done followed by correction of the refractive error by SCHWIND excimer laser (eye-tech-solutions, Germany) with a 6.5 *mm* optical zone. Also, mitomycin-C (MMC) was used from 20 to 40 seconds based on ablation depth. After instilling ciprofloxacin 0.3% (Ciplex, Sina Darou, Iran) and chloramphenicol (Chlobiotic, Sina Darou, Iran) drops. Finally, bandage contact lens (Biofinity®, CooperVision, USA) was placed. The same procedure was regarded for the sound eye.

After surgery, the patients received operation standard treatment including betamethasone 0.1% eye drop (Betasonite, Sina Darou, Iran) every 6 hours, chloramphenicol 0.5% eye drop (Chlobiotic, Sina Darou, Iran) every 6 hours, artificial tear eye drop (Artipic advanced 0.15%, IPPC, Iran) every 6 hours, diclofenac tablet 25 *mg* (Sobhan Company, Iran) every 6 *hr*, and diclofenac drop (Dicloptin, Sina Darou Company, Iran) every 8 *hr* for up to three times. In one randomly selected eye, in addition to the standard treatment, drops of tetracaine 0.5% (Anestocaine, Sina Daru Company, Iran), and in the other eye, placebo drops were instilled every 4 *hr*. The patients were followed up and compared daily until the epithelium was completely repaired. The questionnaire was completed by an individual unaware of the prescribed medications one day after the surgery. The level of photophobia and foreign body sensation was assessed using a numeric scale scoring, defined as none (0), mild (1), moderate (2), or severe (3). To evaluate the level of pain, the Numeric Scale

of the Pain Questionnaire was used (4) as explained to the patients before surgery (Figure 1).

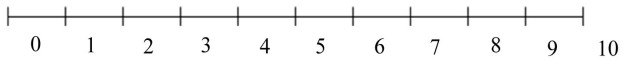

Figure 1. 0-10 numeric rating scale
Indications: adults and children (>9 years old) in all patient care settings who can use numbers to rate the intensity of their pain.

Statistical analysis

SPSS 22 (IBM Corp., Armonk, New York, USA) software was used for statistical analysis of data and the significance level was considered less than 0.05. The results obtained for qualitative variables are expressed as percentages and quantitative variables are expressed as mean with standard deviation (mean ± SD). To determine the parametric and normal distribution, the variables are subjected to the Kolmogorov-Smirnov test, and then data were analyzed using Fisher's exact test and ANOVA. The level of significance was set at 0.05.

Results

Thirty patients of the 50 participants (60%), including 10 men (20% of all patients) and 20 women (40% of all patients) reported no pain. Nine male patients (47.4%) and 11 female patients (35.5%) reported postoperative pain, but the difference was not significant (p=0.4). Also, there was no relationship between pain and the depth of ablation; the mean depth of ablation was 69.0 μ in patients who had pain and 60.2 μ in patients who did not, without a significant difference (p=0.19). Maximum pain was 4.44±0.81 in the eyes which had received tetracaine and 4.15±0.69 in the eyes which had received placebo, with no significant difference (p=0.75). Regarding photophobia, 38% of the patients in the tetracaine group and 40% in the placebo group expressed different levels of photophobia, but the difference between the two groups was not significant (p=0.09) (Table 1).

Regarding foreign body sensation, 77% of the eyes in the tetracaine group and 85% of the eyes in the placebo group had levels of foreign body sensation, but the difference was not significant (p=0.44) (Table 2).

Moreover, 57% of the eyes in the tetracaine group and 61% of the eyes in the placebo group experienced different levels of burning sensation, but the difference between the two groups was not significant (p=0.49) (Table 3).

54 percent of the patients reported no epiphora and in the rest of the patients, there was no significant difference between placebo and tetracaine groups in this regard (p=0.16) (Table 4). The mean duration of the epithelium defect repair was 3.56±0.1 days in the tetracaine group and 3.48±0.9 days in the placebo group, with no significant difference (p=0.3).

Table 1. Comparison of severity of photophobia between tetracaine and placebo group

Photophobia	Tetracaine	Placebo	p-value
No	62 *	60	0.19
Mild	26	20	
Moderate	6	12	
Severe	6	8	

* The values are presented in percent.

Table 2. Comparison of severity of foreign body sensation between tetracaine and placebo group

Foreign body sensation	Tetracaine	Placebo	p-value
No	23/4 *	14/6	0.44
Mild	38/3	49/9	
Moderate	34	29/2	
Severe	4/3	8/3	

* The values are presented in percent.

Table 3. Comparison of severity of burning sensation between tetracaine and placebo group

Burning sensation	Tetracaine	Placebo	p-value
No	43 *	39	0.49
Mild	35	35	
Moderate	18	22	
Severe	4	4	

* The values are presented in percent.

Discussion

Decreasing post-TPRK pain, like any other surgery, is desired; On the other hand, the medications

Table 4. Comparison of severity of epiphora between tetracaine and placebo group

Epiphora	Tetracaine	Placebo	p-value
No	54 *	54	0.16
Mild	16	28	
Moderate	24	14	
Severe	6	4	

* The values are presented in percent.

which are used to control pain, should be effective and safe and have minimal side effects. In patients who undergo TPRK surgery, the epithelial barrier is lost and therefore, the stroma becomes exposed. Although nerve endings may be completely ablated with laser, confocal microscopy has shown that the nerve network of the anterior stroma remains intact and therefore causes severe pain in some patients (5). Various techniques are employed to alleviate pain following TPRK surgery, but no study has reported complete success in controlling pain.

It has been demonstrated that pain following photorefractive keratectomy surgery peaks within the first 24 hours (4,6) but then decreases in the next 2 days (7,8).

Nowadays, corneal surface ablation refractive surgery is widely performed throughout the world. According to a report from the USA, out of every 6 cases of refractive surgery, one person has tolerated surface ablation (10); Usually, the epithelial defect of the cornea takes approximately 3 days to repair (5,9). Therefore, post-operative pain control is very challenging. On the other hand, routine application of diluted corneal anesthetics has been decreased due to the possibility of corneal toxicity (11,12). The side effects of the topical anesthetics were investigated by Rosenwasser *et al* (13). Decrease of tear film break up time and stability with surface microvilli rupture occurs by the presumed mechanism of destruction of the cytoskeletal structure and decrease of epithelial adhesion, leading to inhibition of epithelial cell immigration (14-19). Also, it has been noted that proparacaine and tetracaine exert toxic effects on stromal keratocytes (20) and cause cell death (21). The reflex tear mechanism is also blocked which causes punctuate keratitis although intraepithelial hypersensitivity and precipitation are also proposed (13).

The most serious potential side effect of topical anesthetics for the cornea is bacterial keratitis, although there is no evidence that its risk increases when topical anesthetics are used for a limited time. However, since we routinely followed up with patients in the first 3-4 days after surgery until the cornea was repaired. Also, because we prescribed the drops of Tetracaine to be used every 4 *hr* and the patients had limited access to the drops, this side effect did not develop in our patients. However, the sample size was insufficient to determine a correlation between Tetracaine use and the incidence of bacterial keratitis post-PRK, due to the rarity of the condition.

Despite laboratory studies and case reports of keratopathy due to local corneal anesthetics, some reports confirm their efficacy and safety in relieving post-surgical pain. Brilakis *et al* performed a study on 69 eyes (22). They made 10 drops of non-preserved tetracaine 0.5% available to patients to use when they had pain and after TPRK, they only used the bandage soft contact lens and not NSAID drops or pain killer pills; in the end, 48% of the patients did not use the drops since they had no pain. This study showed that the limited use of tetracaine drops did not prolong the time for re-epithelialization (2).

Verma *et al* reported that utilizing tetracaine 1% drops every 30 *min* for 24 *hr* after surgery relieved pain without delaying re-epithelialization or disturbing visual function. This study was conducted on 44 patients, but they did not use NSAID drops or the contact lens. Thus, it confirmed the effect of tetracaine drops on reducing pain, but its definite effect could not be shown when used in combination with the contact lens and NSAID drops (1,5).

Some studies have used other medications for pain control. In a study by Nissman *et al* on 141 patients, in addition to antibiotic, steroid, and tetracaine, oral gabapentin 300 *mg* was prescribed three times daily for three days but no significant difference was observed in pain control after photorefractive keratectomy when compared to the patients who had received Percocet (oxycodone 5 *mg*+acetaminophen 325 *mg*) instead of gabapentin (23). Shahinian *et al* demonstrated that administration of proparacaine 0.05% drops every 15 *min* in the first 12 *hr* after

surgery and then every hour for one week was not toxic to the cornea (24). Each study has used a different concentration of tetracaine or proparacaine for controlling pain after TPRK and therefore, the maximum safe dose is not clear. Despite these numerous reports on the positive effects of Tetracaine on post-PRK pain, the findings of this study did not reflect similar results. Also, other secondary outcomes measure like photophobia, tearing, foreign body sensation, burning sensation, and epiphora did not decrease statistically significantly in the current survey. This discrepancy can be related to low dose, concentration, or duration of application".

Kim *et al* reported keratitis following drug abuse, radial keratotomy, laser-assisted subepithelial keratectomy, and photorefractive keratectomy, but the majority of the cases were due to drug abuse (25). NSAIDs have also been used to control post photorefractive keratectomy pain, but contradictory findings have been reported regarding their analgesic effect in comparison with topical corneal anesthetics. In a study conducted by Cherry *et al* (9), no significant difference was observed between patients who received tetracaine and those who received diclofenac. To control postoperative pain following photorefractive keratectomy surgery, they used the additive effect of the contact lens, tetracaine drops, and diclofenac drops and indicated that adding tetracaine drops every half an hour more effectively controlled pain. They also reported that the contact lens homogenized the effect of tetracaine and diclofenac drops on relieving pain, confirming the sponge effect of the contact lens (26). In this study, topical drops of diclofenac were only used on the first day after surgery up to 3 times; it was not routinely used for 3-4 days following photorefractive keratectomy surgery since stromal infiltrations have been reported in 1/250 to 1/300 of the patients who use NSAID drops (8,27).

Application of the bandage soft contact lens following photorefractive keratectomy surgery is safe and does not prolong re-epithelialization (8,9,28,29). Moreover, it is suggested that such lenses have a sponge effect that allows them to absorb the drops and then release them slowly (10), which prevents excessive drug release or low serum concentration. Although subepithelial infiltrates (29,30) and also keratitis (31,32) following the use of the contact lens after photorefractive keratectomy surgery has been reported, none of our patients developed these side effects. Though, the small sample size was not sufficient to determine a cause-effect correlation between Tetracaine use and post-PRK bacterial keratitis. Overall, TPRK has been reported as a successful procedure in all refractive error corrections (33). The cumulative effect of tetracaine and the contact lens has been determined by scale-rated surveys on pain (9). Although this was not our objective, we noted that less amount of tetracaine could alleviate the pain following TPRK during re-epithelialization when used together with the contact lens. With the correct application of non-preserved tetracaine, prolongation of re-epithelialization is not likely and patients benefit from sufficient pain control in a self-determined way.

Conclusion

Our study showed that administration of 0.5% non-preserved tetracaine every 4 *hr* exerted no clinically significant effect on pain alleviation after TPRK surgery. Moreover, no clinical benefit was noted in improving other variables such as epiphora, photophobia, foreign body, and burning sensation. Also, it was found that administration of the tetracaine drops, according to the above-mentioned protocol, did not prolong the time for re-epithelialization.

In the current study, we did not give our patients any narcotics, since it could interfere with daily activities during re-epithelialization. On the other hand, our issue is that we administered tetracaine drops every four hours which may account for its reduced analgesic effect, as compared to other studies that used it in shorter intervals, given the short half-life of tetracaine (2). Also, some patients did not feel pain even with administering this amount of tetracaine which shows different pain thresholds in different individuals.

Our study had some limitations including a small sample size, non being a randomized clinical trial, and the patients were included in the study only based on inclusion and exclusion criteria. Also, patients were not followed up continuously in an hourly fashion and therefore, the exact time needed for re-epithelialization could not be determined. Although epithelial repair of all eyes was completed within the

time frame expected for an untreated eye, it would have been better if the duration of complete epithelial repair had been documented in a more precise format for further comparison. Finally, tetracaine drops were administered every four hours in our study which could be the reason for insufficient pain control in our patients due to its rather short half-life; therefore, it is suggested that tetracaine drops be administered at shorter intervals in future studies. As a conclusion, local non-preserved tetracaine 0.5% every 4 *hr* did not have clinically significant effects on pain alleviation within the first day after trans-epithelial photorefractive keratectomy excimer laser surgery.

Ethics approval and consent to participate

This study was done according to the Declaration of Helsinki after protocol approval of the Ethics Committee with code IR.IUMS.REC.1397.1182.

Conflict of Interest

The authors declare that there is no conflict of interest.

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