Original Article

Clinical Evaluation of Pranoprofen Combined with Fluorometholone Eye Drops on Postoperative Reaction of Corneal Cross-linking

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Abstract

Purpose: To evaluate the efficacy and safety of pranoprofen eye drops for reducing postoperative ocular pain and inflammation after corneal cross-linking (CXL).

Methods: Twenty-seven patients (38 eyes) with keratoconus undergoing CXL were examined and randomly divided into control (12 cases; 18 eyes) and experimental groups (15 cases; 20 eyes). The patients in the control group were given fluorometholone eye drops, and those in the experimental group were administered with fluorometholone combined with pranoprofen eye drops. Corneal irritation and haze were compared between the two groups at 1 month postoperatively.

Results: At 1 to 3 days after surgery, the corneal irritation in the experimental group was significantly reduced compared with that in the control group ($P<0.05$), but there was no significant difference on 5 to 7 days postoperatively ($P>0.05$). The average degree of haze in the experimental group was significantly lower than that in the control group 1 month after surgery ($P<0.05$), but there was no significant difference in the best-corrected vision acuity and intraocular pressure between the two groups. There were 2 cases with >20 mmHg intraocular pressure in the control group.

Conclusion: The combined use of fluorometholone and pranoprofen can significantly reduce inflammatory response, alleviate corneal irritation at early stage after CXL, effectively prevent and control the average of haze, and reduce the incidence of steroid-induced ocular hypertension after surgery. (***Eye Science 2012; 27: 173-177***)

Keywords: pranoprofen; fluorometholone; corneal cross-linking; corneal irritation; haze

Recently, UV/riboflavin corneal cross-linking (CXL) has been used as a novel parasurgical treatment for keratoconus. It involves a one-time application of riboflavin solution to the eye, which is activated by illumination with UV-A light. The riboflavin causes new bonds to form across adjacent collagen strands in the stromal layer of the cornea, which recovers and preserves some of the cornea's mechanical strength, prevents the incidence of keratoconus[1], corneal ectasia after LASIK[2], and refractive keratitis[3]. It reduces the incidence of corneal transplantation and resolves the shortage of corneal donors in clinical practice. However, most patients showed corneal irritation during the early period postoperatively, affecting the willingness of patients to receive surgery and inhibiting postoperative visual recovery. Pranoprofen is a non-steroidal anti-inflammatory drug used in ophthalmology, which inhibits the synthesis of prostaglandin and maintains the membrane. A series of studies indicated that pranoprofen is efficacious in alleviating anterior segment inflammation and pain[4-6]. However, no investigations have reported the anti-inflammation effect of pranoprofen following CXL. This study investigated the safety and efficacy of pranoprofen regarding the reduction of corneal irritation after CXL. The results showed relatively good outcomes.

Materials and methods

Study subjects

Twenty-seven patients with keratoconus undergoing CXL surgery in our hospital between June and September 2012 were randomly divided into experimental (15 cases, 20 eyes; 3 females, 12 males; aged between 14 to 27 years, 19.00±3.85 years on average) and control groups (12 cases, 18 eyes; 2

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females, 10 males; aged between 16 to 26 years, 20.46±3.56 years on average). The inclusion criteria were as follows: diagnosis of keratoconus, the thinnest corneal thickness >400 μm. Patients with acute ocular inflammation, trauma and surgical history, diabetes, connective tissue illnesses, and mental illnesses were excluded from this study. The experimental procedures were approved by the Ethical Research Committee in our hospital, and informed consent was obtained from each participant.

Preoperative examination and drug administration

Preoperative tests, including visual acuity, best-corrected visual acuity, intraocular pressure, corneal topography, corneal thickness, slit-lamp, and fundus examinations were performed. All participants were given 0.5% levofloxacin eye drops 4 times/d from three days before surgery.

Surgical approach

Corneal epithelia with a diameter of 9 mm were removed mechanically. The handled corneal surface was covered by absorbent cotton containing 0.1% riboflavin (dissolved in 20% dextran). Riboflavin solution was added every 5 min for 30 min, and then the infiltration of riboflavin into anterior chamber was ensured under slit-lamp light. The corneal tissues were irradiated (3 mW/cm^2) by UV light at a wavelength of (370±5) nm and a beam diameter of 9 mm for 30 min, equivalent to 3.4 J. During irradiation, the corneal surface was washed by 0.1% riboflavin and topical anesthetics every 5 min. After radiation, the patients were told to wear contact lens (ACUVUE) until corneal epithelial healing.

Postoperative drug administration and measured parameters

The patients in the control group were given fluorometholone eye drops on the first postoperative day 4 times/d for one month. In the experimental group, the participants received 1% pranoprofen eye drops from 1 d preoperatively to 7 d postoperatively, in combination with fluorometholone eye drops on 8 d postoperatively 4 times/d for 1 month. After surgery, all patients were given levofloxacin and sodium hyaluronate eye drops 4 times/d and carteolol twice daily. The patients were told to pay a return visit at 1, 3, 5, 7 days and 1 month, postoperatively. The degree of corneal irritation was graded on a scale of 0 to 4. The grading criteria was as follows: 0, no discomfort; 1, a slight sense of a foreign body; 2, moderate pain and discomfort; 3, pain influencing daily life but no need to take analgesics; 4, intolerable sense of irritation and needs analgesics to ease the pain. The degree of haze was graded according to the criteria proposed by Fantes[7]: grade 0, transparent cornea; grade 0.5, punctate opacity was observed under slit-lamp microscope; grade 1, a slight degree of haze could be noted through careful observation under slit-lamb microscope without any influence on observing iris texture; grade 2, a slight degree of haze could be easily noted under slit-lamb microscope and mildly affected the display of iris texture; grade 3, moderate degree of haze, unable to observe the fine structures of anterior chamber and iris; grade 4, severe degree of haze, unable to see the inside of eyes.

Statistical analysis

SPSS 19.0 statistical software was used for the data analysis. The data were expressed as means±SD. Measurement data between the experimental and control groups were analyzed by *t*-test, and enumeration data were statistically analyzed by *chi*-square test. $P<0.05$ was considered statistically significant.

Results

Comparison of general information between the two groups

No statistical difference was noted between the two groups regarding sex, age, corneal thickness, and maximum K (Table 1). No surgical complications, such as delayed healing of corneal epithelium, tight, loose placement, or dislocation of contact lens, etc. affecting the analgesic effect, were observed. Conditions of lacking or inadequate usage of medicine were noted. In addition, medicine-induced adverse events were not observed.

Table 1 Comparison of general information between the two groups

Group	Age(y)	Km(D)	Corneal thickness (μm)
Experimental group	19.00±3.85	55.79±13.78	459.70±33.57
Control group	20.46±3.56	54.75±9.51	464.06±38.71
t	0.98	0.26	0.37
P	0.34	0.79	0.71

Grading of corneal irritation at various postoperative time points

The degree of corneal irritation became the most serious at 1 to 3 days after CXL; 2 cases in the control group with grade 4 corneal irritation required analgesics; and all patients with < grade 3 of corneal irritation were in the control group. The grading of corneal irritation in the experimental group was significantly lower than that in the control group at 1 and 3 days, postoperatively ($P<0.05$), while no statistical significance was found at 5 to 7 days postoperatively ($P>0.05$), as shown in Table 2.

Postoperative recovery

In both groups, corneal epithelial wound was healed at 3 to 5 days postoperatively. The patients easily opened their eyes, and no obvious conjunctival hyperaemia was noted. The mean healing time was (3.00±0.66) d in the experimental group and (4.00±1.0) d in the control group. A significant statistical difference was noted between the two groups ($P<0.05$). At 1 month, postoperatively, the degree of haze between the two groups significantly differed ($P<0.05$), whereas no significant difference was found in best-corrected visual acuity and intraocular pressure ($P>0.05$). Two patients had intraocular pressure >20 mmHg, and carteolol eye drops were used, as shown in Table 3.

Discussion

Although the cornea does not contain blood vessels, it has abundant neuropil and extremely acute sensitivity. The incidence of corneal irritation post CXL may be caused by multiple factors. First, corneal surface with a diameter of 7 to 9 mm was removed during conventional CXL to facilitate the infiltration of riboflavin into the cornea. Second, after surgery, the movement of the eyeball caused the eyelid to exert mechanical friction force on the corneal wound. Third, removing the corneal epithelia exposed a substantial amount of nerve fiber endings. Fourth, inflammatory response and a large amount of inflammatory cells were induced by UV irradiation, which released an aggregated inflammatory medium[8]. Most patients presented with corneal irritation before the complete healing of the corneal epithelia. It has been suggested that wearing contact lenses is a common method to reduce the mechanical friction between the eyelid and the corneal wound. Moreover, some scholars applied local cortical hormone to decrease the release of prostaglandin-like inflammatory factors[9] or prescribed oral ibuprofen or codeine[1] to alleviate corneal irritation. However, these measures pose a potential risk of adverse events. For instance, contact lenses probably cause infectious or non-infectious corneal inflammation. The local use of cortical hormones might induce corticosteroid glaucoma or delay the healing time of the corneal wound. The oral intake of analgesics possibly causes adverse events in the respiratory, digestive and central nerve systems. In addition, some patients had postoperative discomfort in various degrees even though these measures were taken. Thus, it is recommended that surgeons adopt safer measures, topical administration of medicine, and low-toxic medicine as priorities to achieve alleviating effects and reduce adverse events as much as possible.

Table 2 Comparison of the grading of corneal irritation at various time points between the two groups

Group	1 d postoperatively	3 d postoperatively	5 d postoperatively	7 d postoperatively
Experimental group	2.30±0.47	1.05±0.76	0.21±0.42	0.20±0.41
Control group	2.72±0.67	1.89±0.76	0.28±0.46	0.22±0.43
t	2.27	3.40	0.47	0.16
P	0.02	0.001	0.64	0.87

Table 3 Comparison of recovery conditions between the two groups

Group	Healing time (d)	BCVA at 1 m postoperatively	Haze at 1 m postoperatively	IOP at 1 m postoperatively (mmHg)
Experimental group	3.00±0.66	0.38±0.25	0.33±0.37	11.60±2.77
Control group	4.00±1.00	0.41±0.26	0.72±0.62	12.18±7.99
t	3.09	0.22	2.41	0.26
P	0.005	0.83	0.02	0.80

Non-steroidal anti-inflammatory drugs (NSAID) suppress the biosynthesis and release of prostaglandins by inhibiting cyclooxygenase. NSAIDs play a role in anti-inflammation and acetanilide by preventing injuries to eyes caused by inflammatory mediums. NSAIDs have been frequently applied to reduce and ease complications after LASIK and PRK[10,11]. In addition, unlike steroidal anti-inflammatory drugs, NSAIDs do not increase IOP[12]. The timely application of NSAIDs suppresses surgical complications, playing a major role in inhibiting the inflammatory medium, whereas glucocorticoid exerts a delayed effect[13]. Some scholars applied diclofenac sodium combined with fluorometholone eye drops to alleviate inflammation and relieve pain. Guidera et al. (2001) reported that 16 patients presented with severe corneal complications after the administration of NASID eye drops, 11 of whom were induced by diclofenac sodium eye drops[14]. Gokhale et al[15]. reported one case that had acute corneal melting post CXL and suggested that it was caused by diclofenac sodium eye drops. These underlying adverse events constrain the application of diclofenac sodium eye drops post CXL.

Because NSAIDs have disparate properties, a clear understanding of these properties is beneficial for clinical applications. Commonly used NASIDs include indomethacin, diclofenac sodium, ketorolac, and flurbriprofen. Verugno[16] suggested that flurbriprofen showed the highest efficacy with the least number of adverse events. The molecular structure of pranoprofen is similar to that of flurbriprofen. It can suppress the synthesis of prostaglandin by inhibiting the activity of cyclooxygenase to relieve corneal irri tation. Both pranoprofen and flurbriprofen are safe and efficacious in the treatment of corneal irritation and have good anti-inflammation and analgesia effects. In 1999, the Chinese Academy of Medical Sciences along with another five institutions conducted a study on the safety and efficacy of pranoprofen in the treatment of inflammatory responses and non-infectious inflammation in anterior segments after cataract extraction and IOL implantation. The results indicated that pranoprofen is efficacious in alleviating major inflammatory responses without systemic adverse events and liver damage. In addition, the incidence of adverse events was relatively low, and the administration of medicine could be continued[5]. Pranoprofen eye drops are superior to corticosteroid eye drops in terms of anti-inflammation, relieving ocular pain and hyperaemia, etc.

The results of the present study indicated that pranoprofen eye drops are safe and efficacious in alleviating corneal irritation following CXL. The grading of corneal irritation was significantly lower, and the duration was remarkably shorter compared with the control group at 1 and 3 days postoperatively, suggesting that pranoprofen relieves irritation and shortens reaction time. However, no statistical significance was noted at 5 and 7 days post-surgery between the two groups, indicating that corneal irritation was mainly caused by corneal epithelial defects. The inflammatory symptoms disappear when the wound is healed.

Furthermore, pranoprofen eye drops effectively reduced ocular pain after CXL, but had no significant effect on the healing time of corneal epithelia. In the experimental group, the mean healing time of corneal epithelia was 3.00±0.66 d, and it was 4.00± 1.00 d in the control group. These results were consistent with 4 d in previous studies[18]. The healing of the corneal wound was not delayed in either group. In the experimental group, the symptom of corneal irritation almost disappeared at 8 d, postoperatively, in combination with the use of fluorometholone eye drops. No significant difference was found between the two groups regarding BCVA and IOP (P>0.05). The degree of haze in the experimental group was significantly relieved compared with that in the control group, suggesting that the combined administration of pranoprofen and fluorometholone eye drops is more efficacious in alleviating haze after CXL. Since glucocorticoid and NASIDs take effect in different sections of anti-inflammation activity, the two substances can have a synergistic effect[19]. Apart from the synergistic effect, they can also decrease the dose and duration of glucocorticoid medicine and reduce the incidence of infectious keratitis and hormone-induced glaucoma, etc.

In this study, no topical or systemic adverse events were observed during the use of 0.1% pranoprofen, indicating safety and efficacy in easing

corneal irritation. Moreover, the combined treatment of pranoprofen and fluorometholone eye drops played a vital role in anti-inflammatory response, alleviating early corneal irritation and preventing the incidence of haze and steroid-induced ocular hypertension. However, the underlying mechanism and optimal administration time remain to be further elucidated.

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