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CLINICAL INVESTIGATION

Effect of topical steroid instillation on central corneal thickness in eyes with bullous keratopathy

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Abstract

Purpose To examine the effects of topical steroid instillation on central corneal thickness in eyes with bullous keratopathy (BK).

Study design Retrospective case series

Methods Consecutive patients with BK who did not wish to receive corneal transplantation and were treated with 0.1% betamethasone eyedrops were included. Patients with BK treated with 5% sodium chloride (hypertonic saline) eyedrops served as controls. Central corneal thickness (CCT), best-corrected visual acuity (BCVA), intraocular pressure (IOP), BK etiology, and clinical courses from medical records were retrospectively reviewed. We compared the two groups for differences in CCT, BCVA and IOP before treatment and 2 weeks, 1 month, and 3 months after treatment.

Results Eighteen eyes of 18 patients who were treated with betamethasone and 18 eyes of 18 patients who were treated with hypertonic saline were included. There was no significant difference in CCT between the two groups before treatment. The reduction of CCT in the betamethasone group was significantly larger than in the hypertonic saline group at 2 weeks ($p = 0.002$), 1 month ($p = 0.02$), and 3 months ($p = 0.001$) after treatment. Complications such as infectious keratitis and IOP rise did not occur during the observation period.

Conclusions Topical steroid instillation reduced central corneal thickness in eyes with BK.

Keywords Bullous keratopathy · central corneal thickness · betamethasone · hypertonic saline

Introduction

Bullous keratopathy (BK), induced by dysfunction of corneal endothelial cells, causes corneal edema and opacity, resulting in decrease in visual function and formation of epithelial bullae. BK is treated both by surgical and non-surgical approaches. As a surgical approach, penetrating keratoplasty is performed and many studies report good long-term prognosis [1, 2]. Recent progress in surgical instruments and techniques has led to new partial corneal transplantation methods, such as Descemet's stripping automated endothelial keratoplasty and Descemet's membrane endothelial keratoplasty. These new modalities have become prevalent with good prognosis after long-term postsurgical observation [3–5]. However, in some cases there is insufficient recovery of visual function owing to complications such as graft rejection and decompensation. Additionally, many patients with BK are often placed on long waiting lists for corneal transplantations due to the worldwide shortage of donor corneas. Hence, medical treatment is also necessary for patients with BK in order to recover visual function and lessen discomfort. Hypertonic saline and soft contact lenses are currently used for these purposes [6, 7]. The treatment effect of hypertonic saline is considered to involve reduction in intracorneal fluid and compaction of the cornea [8].

Because steroids have been shown to increase Na-K-ATPase activity and pump function of cultured corneal endothelial cells [9], topical steroid administration is likely

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to be an effective medical treatment for eyes with BK. Topical steroid administration has also been shown to promote the recovery of corneal thickness in eyes with Fuchs dystrophy after cataract surgery [10]. However, the effect of steroids on central corneal thickness (CCT) has not been sufficiently examined. In the present study, the effect of topical steroid administration on CCT in eyes with BK was investigated.

Patients and methods

This was a retrospective, observational study conducted in a single center. The institutional review board of Miyata Eye Hospital approved this study, and the study protocol adhered to the tenets of the Declaration of Helsinki. Consecutive patients who did not wish to receive corneal transplantation for BK and were treated with 0.1% betamethasone eyedrops (Shionogi Pharmaceuticals) four times a day between June 2011 and January 2014 were included. Age and sex matched patients treated with 5% sodium chloride (hypertonic saline) eyedrops during the same period served as controls. BK was defined as the inability to distinguish iris details and the inability to perform retinoscopy because of an opacified edematous cornea. CCT, best-corrected visual acuity (BCVA), intraocular pressure (IOP), BK etiology and clinical courses were reviewed from medical records. BCVA was measured with a 5-m Snellen chart and was converted to the logarithm of the minimum angle of resolution. IOP was measured with a non-contact tonometer (NT-4000, Nidek) and CCT was measured with optical coherence tomography of the anterior segment (SS-1000, Tomey). All examinations were performed between 9:00 and 17:30 on an outpatient basis.

In the statistical analysis, the chi-square test was used to compare the sex ratio and etiologies of BK. The Mann-Whitney U test was used to compare age, corneal endothelial cell density, BCVA, IOP, and CCT between the groups. Statistical significance is reported at the p value < 0.05.

Results

Thirty-six eyes of 36 patients were included. Eighteen eyes of 18 patients received 0.1% betamethasone eyedrops and 18 eyes of 18 patients received 5% sodium chloride eyedrops. The demographic data of all patients before treatment are showed in Table 1. Corneal endothelial cell density was examined in 15 in the betamethasone group and 12 in the hypertonic saline group. There were no significant pre-treatment differences in CCT, IOP, and corneal endothelial cell density between the betamethasone and hypertonic-saline groups. However, BCVA was significantly better in the betamethasone group than in the hypertonic-saline group ($p = 0.02$). BK etiologies are summarized in Table 2. There was no association between groups and BK etiologies ($p = 0.52$).

Seven patients in the betamethasone group dropped out of the study because eyedrop instillation was withdrawn at their request although they did not complain of any side effects. In the betamethasone group, the number of eyes examined before and 2 weeks, 1 month, and 3 months after treatment was 18, 17, 16, and 9, respectively. In the hypertonic-saline group, 18 eyes were examined at all points.

The changes of CCT after treatment in the two groups are shown in Figure 1. In the betamethasone group, changes in CCT were -28.8 ± 29.3 μm after 2 weeks, -39.5 ± 40.4 μm at 1 month and -61.7 ± 54.1 μm at 3 months. In the hypertonic

Table 2 Etiology of bullous keratopathy

	Betamethasone (eyes)	Hypertonic saline (eyes)
Laser iridotomy	6	7
Cataract surgery	5	6
Corneal endothelitis	2	0
Peripheral iridotomy	1	0
Iridocorneal endothelial syndrome	1	0
Primary angle closure	1	3
Decompensation after penetrating keratoplasty	1	0
Corneal dystrophy	1	1
Trabeculectomy	0	1

Table 1 Demographic data of patients before treatment

	Betamethasone	Hypertonic saline	P value
Age (years)	77.6±5.1	75.8±7.6	0.66
Sex (male : female)	6 : 12	6 : 12	1.0
Central corneal thickness (μm)	673.1±90.8	699.6±124.3	0.60
Best-corrected visual acuity (logMAR)	0.76±0.69	1.37±0.88	0.02
Intraocular pressure (mmHg)	12.4±3.5	13.4±4.0	0.33
Corneal endothelial cell density (cells / mm^2)	558.5±222.7	592.6±186.5	0.58

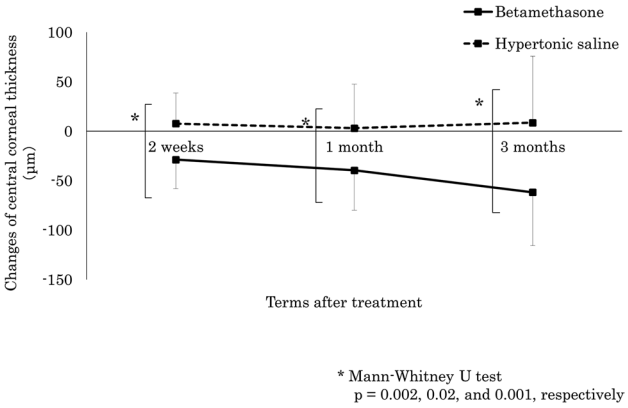

Fig. 1 Changes of central corneal thickness after treatment. There was a significant difference in changes of central corneal thickness between the betamethasone and the hypertonic saline groups at 2 weeks, 1 month, and 3 months after initiation of instillation (p = 0.002, 0.02, and 0.001, respectively)

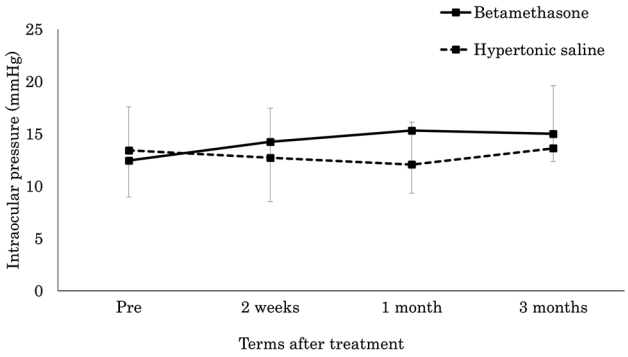

Fig. 3 Changes of intraocular pressure after treatment. There was no significant difference in intraocular pressure between the betamethasone and the hypertonic saline groups at 2 weeks, 1 month, and 3 months after initiation of instillation

saline group, changes in CCT were 7.8 ± 30.1, 3.1 ± 44.5, and 8.6 ± 67.1 μm, respectively. There was a significant difference in changes of CCT between the two groups at 2 weeks (p = 0.002), 1 month (p = 0.02), and 3 months (p = 0.001) after treatment.

The time-course changes in BCVA are shown in Figure 2. BCVA was 0.74 ± 0.68, 0.67 ± 0.68, and 0.61 ± 0.70 in the betamethasone group and 1.40 ± 0.95, 1.40 ± 0.93, and 1.36 ± 0.99 in the hypertonic saline group at 2 weeks, 1 month, and 3 months after treatment, respectively. There was a significant difference in BCVA between the two groups at 2 weeks and 1 month after treatment, but no difference at 3 months after treatment (p = 0.03, 0.01, and 0.06, respectively).

The time-course changes of IOP are shown in Figure 3. IOP was 14.2 ± 5.7, 15.3 ± 6.0, and 15.0 ± 2.6 mmHg in the betamethasone group and 12.7 ± 4.8, 12.1 ± 4.0, and 13.6 ± 6.0 mmHg in the hypertonic saline group at 2 weeks, 1 month, and 3 months after treatment, respectively. There was no difference in IOP between the two groups at each observation point (p =0.52, 0.12, and 0.07, respectively).

Infectious keratitis and IOP rise higher than 25 mmHg were not observed. No participant complained of pain at any examination point.

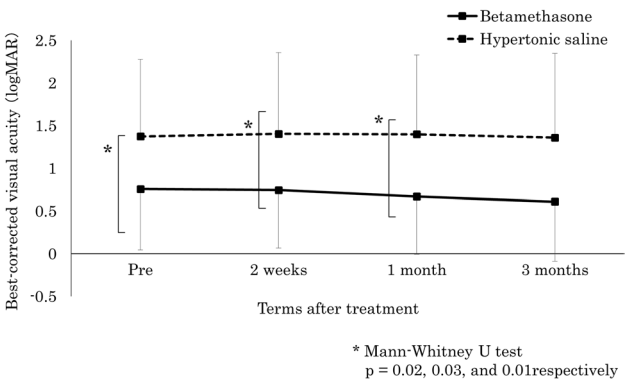

Fig. 2 Changes in best-corrected visual acuity after treatment. There was a significant difference in best-corrected visual acuity between the betamethasone and the hypertonic saline groups before, at 2 weeks, and 1 month after initiation of instillation (p = 0.02, 0.03, and 0.01, respectively)

Discussion

This study shows that 0.1% betamethasone was more effective than 5% sodium chloride in reducing CCT in eyes with BK. Five percent sodium chloride, which is effective compared to other hypertonic agents, has been used as a standard treatment for BK for a long time and it is reported that CCT in BK was reduced by more than 15% between 0.5 and 6 hours after 5% sodium chloride ointment application [11]. Therefore, we considered that patients who were treated with 5% sodium chloride four times a day would maintain their CCT without exacerbation in this study. Conversely, betamethasone reduced CCT more than 5% sodium chloride over 3 months. The other treatments for BK such as amniotic membrane transplantation, bandaged contact lens, and corneal cross-linking reportedly reduce occurrence of epithelial bullae and relieved pain [6, 12, 13]. Bandaged contact lens use reduces symptoms of BK, such as pain and foreign body sensation, but its long-term usage can cause infectious keratitis [14]. Steroid instillation may reduce the occurrence of epithelial bullae and relieve pain, but its long term safety needs to be confirmed by future studies.

There are a couple of possible mechanisms through which topical steroid administration could reduce CCT in eyes with BK. First, topical steroid administration increases Na-K-ATPase activity and pump function of corneal endothelial

cells. Na-K-ATPase is present on the membrane of corneal endothelial cells as a solute pump that imports 2 K^+ and export 3 Na^+ using one ATP molecule. Through this action, corneal endothelial cells are believed to release Na^+ in the extracellular environment. Na-K-ATPase is utilized as an index of corneal endothelial function [15]. Another glucocorticoid, dexamethasone, was found to increase Na-K-ATPase activity by regulation of subunit synthesis of Na-K-ATPase in cultured corneal endothelial cells [9]. Another report shows that dexamethasone increases Na-K-ATPase activity at a certain concentration although it suppresses corneal cell proliferation at high concentrations [16]. Similarly, it is likely that topical betamethasone administration increased Na-K-ATPase activity and pump function of corneal endothelial cells. The second possible mechanism pertains to the anti-inflammatory effect of steroids. Glucocorticoids could regulate various cytokines and clinically work as immunosuppressants. Yamaguchi et al. report that IL-1α, IL-6, IL-8, IL-17A, TNF-α, GM-CSF, MIP-1α, and IFN-γ were increased in the anterior chamber of patients with BK [17]. Yagi-Yaguchi et al. also report that reduction in corneal endothelial cells was correlated with an increase in cytokines in the anterior chamber [18]. These studies reveal that there was elevation of cytokine levels in the anterior chamber regardless of the absence of signs of inflammatory changes. Glucocorticoids, capable of suppressing IL-6, TNF-γ, and TNF-α, may reduce inflammation in the anterior chamber, protecting against corneal endothelial cell damage. To confirm this, further studies should measure cytokine levels both before and after steroid instillation.

Hypertonic sodium chloride in the form of eyedrops or ointment is reported to improve corneal thickness and visual acuity in patients with BK [7, 8, 19, 20]. Because it has a higher osmotic pressure than viable cells, fluid in the corneal stroma moves to the extracellular environment due to osmotic pressure difference that causes osmotic water flow [8]. However, hypertonic sodium chloride instillation was not therapeutic in eyes with moderate BK with CCT of 670 μm or higher [7]. The mean CCT of the two groups in this study was higher than 670 μm before treatment. Thus, it is likely that hypertonic saline did not reduce corneal edema in this study.

The possible adverse effects of long-term use of topical steroids include IOP increase, cataract formation, and infection. In the betamethasone group, IOP increase of higher than 25 mmHg was not observed. The average IOP in the betamethasone group was similar to that in the hypertonic saline group during the 3-month observation period. Although it is difficult to examine for cataracts through an opacified cornea, the BCVA of the betamethasone group was almost similar to that of the hypertonic saline group, suggesting that cataract progression was not significant during the 3-month observation period. No infectious keratitis was observed in this study. Long-term usage of steroids has been shown to be associated with infectious keratitis in eyes after penetrating keratoplasty [21]. Hence, meticulous care should be taken when topical steroids are used in eyes with BK. Furthermore, in eyes with BK in which corneal bullae rupture and corneal epithelium defects remain, topical steroid use should be avoided because infectious keratitis is prone to occur in such eyes. Usage of topical antibiotics may also be helpful to avoid the occurrence of infection. Betamethasone instillation could be a supportive treatment for BK patients, but corneal endothelial transplantation is recommended to treat the main cause of BK, dysfunction of corneal endothelial cells, if the patient agrees to undergo the procedure. Indeed, 2 of the 18 patients in the betamethasone group underwent corneal transplantation during the follow-up period.

This study has a couple of limitations. First, the number of subjects in each group was not sufficiently large for analysis. Future studies with larger samples should be performed to confirm the results of this study and examine the effects of topical steroids on visual function in order to avoid selection bias. Second, the time of measurement of visual acuity and CCT after the final instillation was not standardized among patients. The interval between last drop instillation and measurement could be related to visual acuity and changes of CCT. Third, due to the study's retrospective nature, the observation period in the betamethasone group varied between 2 and 3 months, resulting in dropout bias. Certain patients discontinued the treatment possibly because visual acuity improvement did not meet their expectations. A future prospective study with a lower dropout rate is warranted with better management of patient expectations.

In conclusion, CCT in eyes with BK was reduced to a greater extent by betamethasone than by hypertonic saline. No complications such as infectious keratitis and IOP elevation were observed. These results suggest that topical steroid instillation can extend the periods until the time when patients need to undergo corneal transplantation.

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