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The improvement of dry eye after cataract surgery by intraoperative using ophthalmic viscosurgical devices on the surface of cornea

The results of a consort-compliant randomized controlled trial

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Abstract

Backgroud: This study aimed to investigate the protective effect of intraoperative used hydroxypropyl methylcellulose (HPMC 2%) on the ocular surface after cataract surgery.

Methods: A total of 149 eyes (149 patients) diagnosed with age-related cataract, age 69.19±9.74 years, were enrolled in this prospective, parallel-design, continuous, randomised controlled study. Patients were randomly assigned to receive HPMC 2% (study group) or balanced salt solution (control group) during the surgery to moisturize the cornea surface. The Ocular Surface Disease Index, Schirmer test without topical anesthetics, tear break-up time, and corneal fluorescein staining were assessed preoperatively, 1 day, 1 week, and 1 month after the surgery, respectively.

Results: The Schirmer test value of male patients in the study group at 1 week postoperation was higher than that of male patients in the control group ($P = .019$). For patients diagnosed with dry eye before the surgery, Schirmer test value in the male patients in the study group at 1 month after surgery was higher than that in the male patients in the control group ($P = .037$). Furthermore, for the cluster of preoperative dry eye patients whose surgical time was longer than median, corneal fluorescein staining of the patients in the study group was superior to that of the patients in the control group ($P = .032$).

Conclusion: Intraoperative use of HPMC 2% on the cornea surface could improve clinical outcomes of tear film and ocular surface health to some degree, especially in the patients diagnosed with dry eye before the surgery, male patients, and patients whose surgical time was relatively longer.

Abbreviations: BSS = balanced salt solution, BUT = tear break-up time, HPMC 2% = hydroxypropyl methylcellulose, OSDI = Ocular Surface Disease Index, OVD = ophthalmic viscosurgical devices, ST-I = Schirmer test.

Keywords: cataract surgery, dry eye, ophthalmic viscosurgical devices

1. Introduction

Dry eye is a multifactorial disease of the tear film and ocular surface, classified as aqueous-deficient dry eye and evaporative dry eye.[1] According to the current epidemiological studies, the incidence of dry eye in China reached up to about 21% to 30%, which was similar to that in other Asian countries and higher than that in the United States and Europe.[2,3] Many factors, including ocular surgery, could induce or aggravate symptoms of dry eye. In recent years, phacoemulsification with intraocular lens implantation has been the main surgical treatment for cataract. Studies suggested that cataract surgery could aggravate the degree of dye eye.[4,5].

The surface of cornea is moist and smooth. It constitutes a part of the complete ocular refractive system. The poor condition of the tear film can exert an adverse influence on the visual quality of intraocular lens, which results in a decreased satisfaction degree after cataract surgery. Corneal protect (hydroxypropyl methylcellulose [HPMC 2%]; Croma-Pharma GmbH, Leobendorf, Austria) has the characteristic of viscosity, it had been confirmed to be safe and reliable in clinical application, and widely used as auxiliary lubricating substance during ocular surgery.[6] Meanwhile, it can also increase the transparency of refractive media and the comfort degree of patients.[7] However, whether HPMC

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2% exerts a protective effect on dry eye after cataract surgery remains unknown.

This study aimed to analyze whether the intraoperative use of ophthalmic viscosurgical devices (OVDs) on the surface of cornea could alleviate the dry eye after cataract surgery.

2. Materials and methods

2.1. General information

This study was a parallel-design, prospective, continuous, randomized controlled trial approved by the Ethics Committee of Beijing Tongren Hospital, and informed consent was obtained from all participants. Patients who were diagnosed with age-related cataract and underwent phacoemulsification and intraocular lens implantation between July 2015 and November 2015 were enrolled in this study.

2.2. Exclusive criteria

All patients were diagnosed with age-related cataract. The exclusive criteria were as follows: patients with systemic connective tissue disease and severe autoimmune disease; patients being combined with severe hypertension, diabetes, and other systemic diseases; patients who suffered from eye trauma, entropion or ectropion, uveitis, glaucoma, fundus oculi disease, and other eye diseases; patients used oral medications and eye drops within 6 months, which could influence tear secretion function such as antihistamines, antidepressants, contraceptives, and various kinds of artificial tears; patients with a history of intraocular and extraocular surgery within 6 months; and patients who underwent corneal refractive surgery.

2.3. Experimental group

All the eyes were randomized into the study group (using HPMC 2% during the surgery) and control group (using balanced salt solution [BSS] during the surgery) by computer-generated random number list.

The subjective symptom score (Ocular Surface Disease Index [OSDI]), Schirmer test (ST-I) without topical anesthetics, tear break-up time (BUT), and cornea fluorescein staining were assessed before the surgery, 1 day, 1 week, and 1 month after the surgery, respectively.

2.4. Related examinations of the dry eye

(1) OSDI is a widely used questionnaire on subjective symptoms in patients with dry eyes, to assess the quality of life influenced by dry eye syndrome. It consisted of 12 questions on eye-related symptoms, vision-related function, and environment-related trigger symptoms.[8]
(2) BUT was measured using the sterile, BSS-soaked fluorescein detection test (Tianjin Jingming New Technological Development Co., Ltd, Tianjin, China). The patient was asked to blink several times. The time interval between the last blink and the appearance of the first desiccation spot was recorded as BUT. The examination was performed 3 times, and the mean value was recorded as the final result.
(3) Corneal fluorescein staining was examined using a slit-lamp microscope under the exposure of cobalt blue illumination. The corneal staining was scored according to the standard of Oxford program.[9]
(4) The ST-I was performed as follows: without anesthesia, a tear detection filter strip (Tianjin Jingming New Technological Development Co., Ltd, Tianjin, China) was placed in the lateral one-third junction of the lower conjunctival sac of the affected eye. The patient was asked to look downward or close eyes slightly. After 5 minutes, the filter strip was removed and the length of the wetting was measured. ST-I was measured only once at every time point.

The order of examination was as follows: the questionnaire was completed first, followed by BUT and corneal fluorescein staining. After at least 15 minutes, the ST-I examination was performed.

2.5. Surgical procedures

Every patient was prescribed with Gatifloxacin Eye Gel (Shenyang Xing Qi Pharmaceutical Co., Ltd. Shenyang, China) to clean the conjunctival sac 4 times daily for 3 days. All the operations were performed by the same surgeon (JW) using the same phacoemulsification machine (Infiniti Vision System with OZil Intelligent Phaco Torsional Technology; Alcon). After the placement of eye speculum before the surgery, povidone-iodine disinfectant (Shanghai Likang Disinfection Technology Co., Ltd, Shanghai, China) was used in the conjunctival sac, and about 20 mL of BSS was used to wash away povidone-iodine. During the washing process, the patient was required to keep rotating the eyeballs. Subsequently, the patients in the study group received 1 drop of HPMC 2% to cover the corneal surface. The HPMC 2% was used at 3 time points: just after povidone-iodine was washed away, before the implantation of intraocular lens, and before removal of eye speculum at the end of the surgery. The HPMC 2% was required to cover the corneal surface completely while using. However, the patients in the control group received only BSS to keep the corneal surface smooth and moist during the surgery. The intraoperative exposure time of the ocular surface (time interval between the placement and the removal of eye speculum) and the time of phacoemulsification were recorded. Eye drop used after cataract surgery for 2 groups was Tobramycin and Dexamethasone eye drop (TobraDex, Alcon, Puurs, Belgium) 4 times daily for only 1 week.

2.6. Diagnostic criteria for dry eye

So far, there has been no generally agreed "gold standard" for the diagnosis of dry eye; the diagnostic criteria for dry eye published by Chinese Medical Association Ophthalmology Group in 2013 was adopted in this study.[2] The patient had 1 of the following symptoms: irritation, discomfort, and vision fluctuations, and at the same time, BUT $\leq$5 seconds or STI $\leq$5 mm/5 min; or the patient had 1 of the aforementioned symptoms and 5 seconds $<$BUT $\leq$10 seconds or 5 mm/5 min $<$ST1 $\leq$10 mm/5 min. Meanwhile, corneal fluorescein staining was positive.

2.7. Statistical analysis

The data were arranged and input into Excel chart. The data processing and statistical

analysis were performed using SPSS 22.0 software (SPSS, IL) Categorical variables were shown by indicators of relative number, such as rate, percentage, and so on. The chi-square test was used for statistical inference. Numerical variables were analyzed by different statistical methods on the basis of data distribution. Student *t* test or nonparametric test was used for

Table 1

Comparison of the baseline characteristic of patients between the 2 groups (mean value ± standard deviation).

	Study group	Control group	*P*
Sex (male)	40% (29/72)	34% (26/77)	.410
Age, y	68.36 ± 9.20	69.43 ± 12.08	.549
Right eye	42% (30/72)	51% (39/77)	.272
Surgery time, s	311.06 ± 12.44	326.22 ± 17.88	.689
Surgery time ≥median	54% (39/72)	47% (36/77)	.366
Phaco time, s	23.96 ± 2.23	27.00 ± 2.34	.473
Nuclear hardness ≥NC4	56% (40/72)	66% (51/77)	.182
ST-I, mm	14.49 ± 1.19	13.85 ± 1.14	.699
BUT, s	3.89 ± 0.22	3.93 ± 0.17	.603
CFS	0 (39), 1 (18), 2 (15), 3 (3), 4 (1)	0 (40), 1 (15), 2 (12), 3 (5)	.691
OSDI score	20.44 ± 2.11	16.82 ± 2.04	.139
OSDI symptoms	17.24 ± 2.21	14.33 ± 2.07	.246
OSDI vision	29.80 ± 4.44	19.61 ± 3.69	.071
OSDI triggers	19.67 ± 3.39	18.38 ± 3,24	.139

The OSDI evaluates the effect of dry eye on quality of life items divided into 3 subscales: ocular symptoms, vision-related function, and response to environmental triggers.
BUT = tear break-up time, CFS = corneal fluorescein staining, was graded using the Oxford Scheme 6-point scale (from 0 to 5), NC4 = nuclear color, OSDI = Ocular Surface Disease Index, ST-I = Schirmer test.

comparison between groups. All statistical analyses were performed by bilateral hypothesis testing. A P value $\leq .05$ was considered statistically significant.

3. Results

A total of 149 eyes (69 right eyes and 80 left eyes; 149 patients) were used in the study. The age of the patients was 69.19 ± 9.74 years (55 males and 94 females). The baseline information of the patients was shown in Table 1. The control group had 77 eyes, whereas the study group had 72 eyes. No significant difference in patients' baseline data was observed between the 2 groups. The application frequency of BBS in the control study was 6.43 ± 1.26 times, and about 5 mL of BBS was used for each flush. The participant flow chart was shown in Fig. 1.

3.1. Changes in ocular surface indicators before and after surgery

No significant difference in OSDI, ST-I, BUT, and cornea fluorescein staining was observed between the 2 groups at 1 day, 1 week, and 1 month after the surgery. However, when the patients were stratified into 2 groups according to sex, the value of ST-I was 19.65 ± 9.14 mm in the male patients in the study group and 13.43 ± 9.26 mm in the male patients in the control group at 1 week after the surgery, with a significant difference ($P = .019$; Fig. 2), but there was no significant difference between the dry eye test values of the 2 groups of female patients at different time points after cataract operation (Fig. 3).

3.2. Changes in ocular surface indicators in patients with dry eyes before and after surgery

A total of 95 patients (33 males and 62 females, with 43 right eyes and 52 left eyes) were diagnosed with dry eye before the surgery. Among them, 45 patients were in the study group and 50 patients in the control group. No significant difference in the baseline data was found between the 2 groups. The patients diagnosed with dry eyes before the surgery were further analyzed separately. It was found that, for the male patients diagnosed with dry eyes before the surgery, the ST-I value was 21.91 ± 9.90 mm in the study group and 12.92 ± 9.07 mm in the control group at 1 month after surgery, and a significant difference was observed between the 2 groups ($P = .037$; Fig. 4). But we failed to find significant

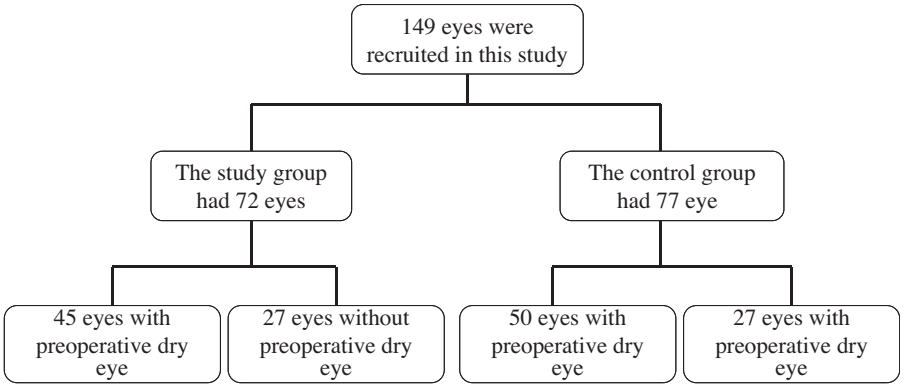

Figure 1. Participant flow chart for this study.

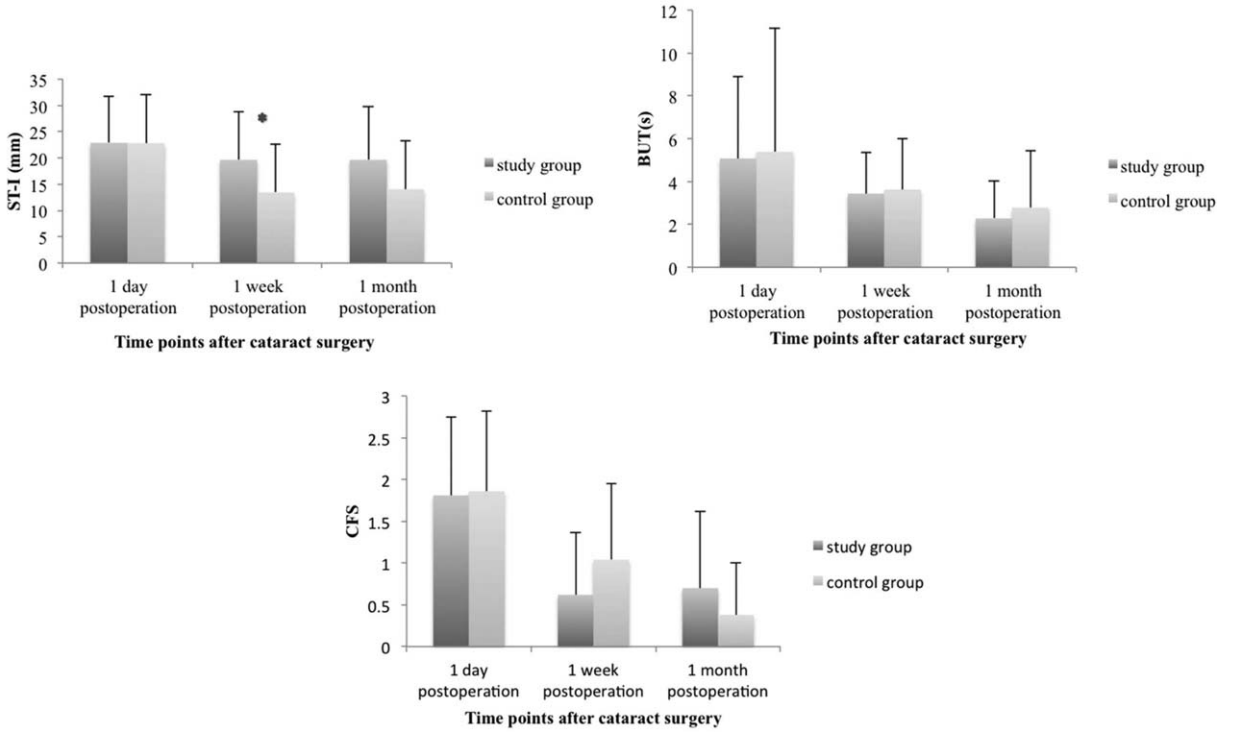

Figure 2. Comparison of dry eye measurements (ST-I, BUT, CFS) for the male patients between the 2 groups at different time points. The ST-I value of male patients in the study group at 1-week postoperation was higher than that of male patients in the control group ($^{*}P = .019$). BUT = tear break-up time, CFS = corneal fluorescein staining, ST-I = Schirmer test without topical anesthetics.

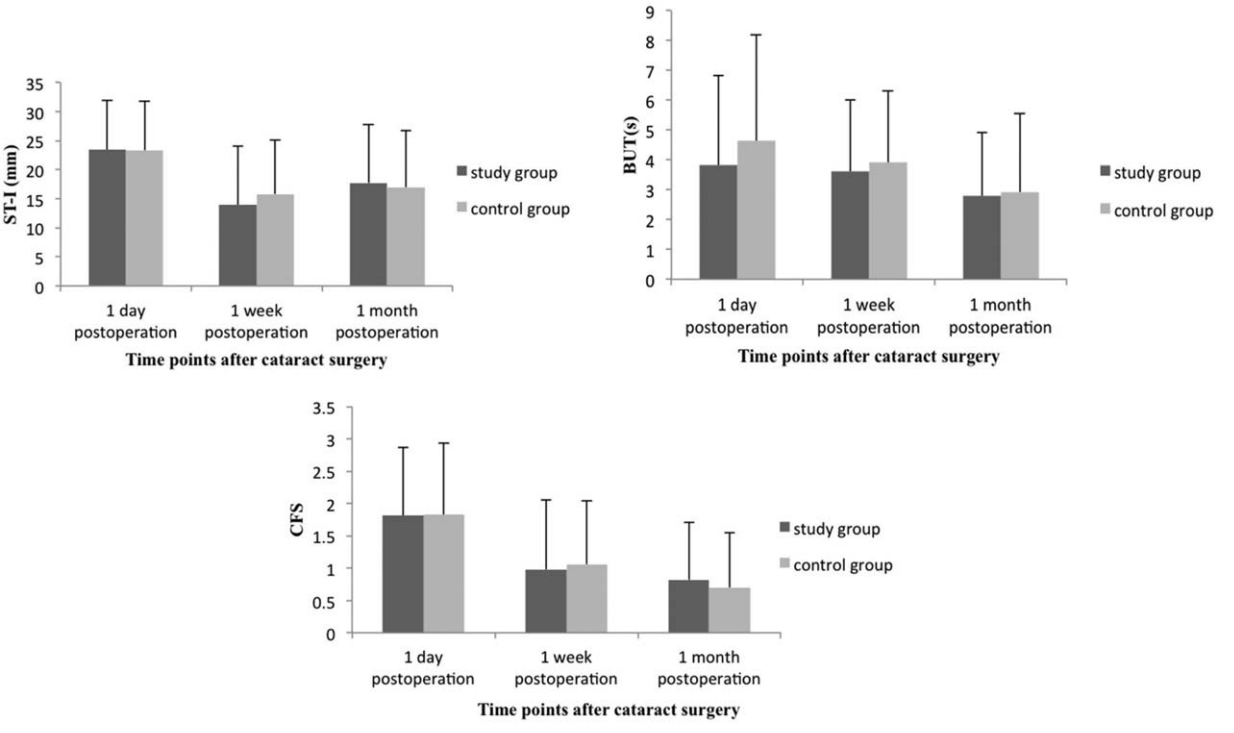

Figure 3. Comparison of dry eye measurements (ST-I, BUT, CFS) for the female patients between the 2 groups at different time points. There is no significant difference between the dry eye test values of the 2 groups of female patients on days 1, 7, and 30 after cataract operation. BUT = tear break-up time, CFS = corneal fluorescein staining, ST-I = Schirmer test without topical anesthetics.

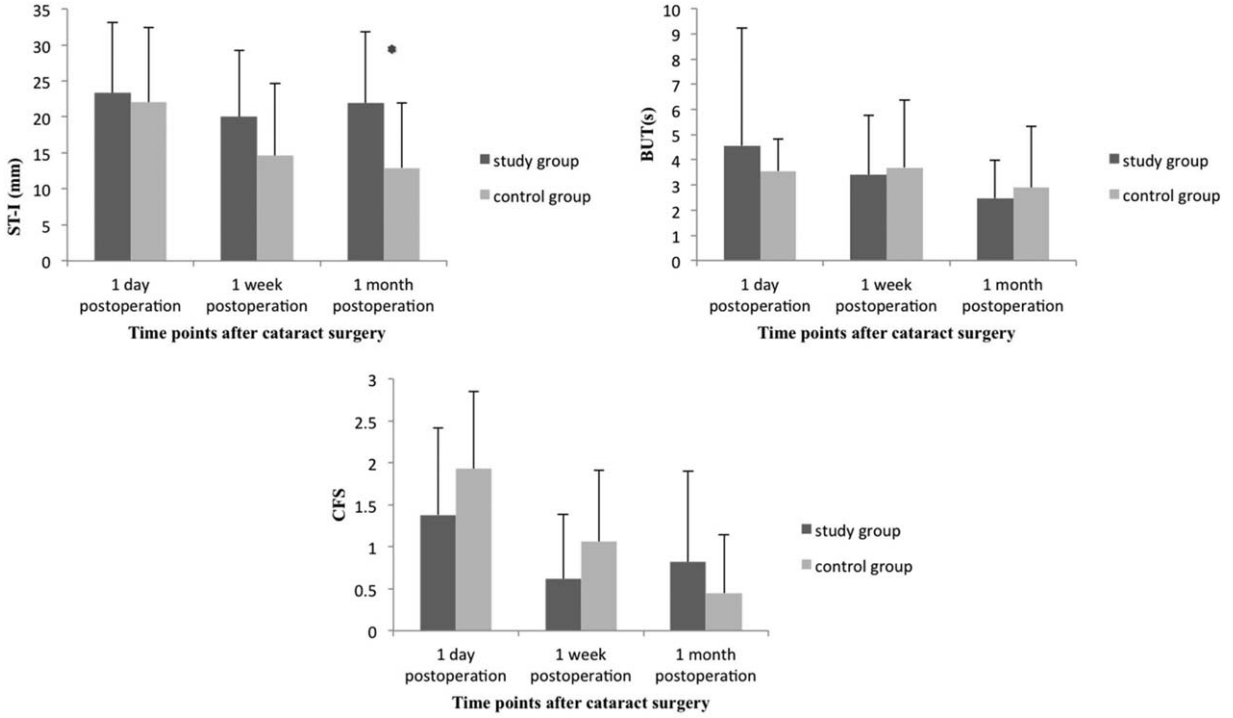

Figure 4. Comparison of dry eye measurements (ST-I, BUT, CFS) between the 2 groups of male patients with preoperative diagnosis of dry eye at different time points. The ST-I value of male patients in the study group at 1 month after surgery was higher than that of male patients in the control group ($^{*}P = .037$). BUT = tear break-up time, CFS = corneal fluorescein staining, ST-I = Schirmer test without topical anesthetics.

difference between dry eye test values of the 2 groups of female patients with preoperatively dry eye at different time points after cataract operation (Fig. 5).

Meanwhile, for the part of preoperative dry eye patients whose surgical time was longer than median, corneal fluorescein staining in the study group was superior to that of the patients in the control group. A significant difference was found between the 2 groups ($P = .032$; Fig. 6).

3.3. Dry eye index influenced by lens hardness and incision site

According to the Lens Opacities Classification System III,[10] the patients were stratified based on cataract nuclear hardness ≥NC4. The related indicators of dry eye at each time point were not significantly different between the 2 groups. Because the main incision was close to the nasal side for the left eye and temporal side for the right eye, we also analyzed the results between the left eyes and the right eyes, and no significant difference was found in the measurements of dry eye between left and right eyes in the 2 groups.

4. Discussion

A number of factors influence the ocular surface during and after cataract surgery: intraoperative placement of eye speculum resulted in the persistent opening of the ocular surface,[11] damage induced by the operating microscope light and heat,[11] cleansing of the conjunctival sac and lid with povidone–iodine,[12] the corneal incision resulting in nerve tissue damage, local anesthetic and mydriatic drops used, and the ocular tissue damage induced by operative procedures[4]; and to keep the cornea from desiccation, BSS was frequently used to flush the ocular surface. Postoperative factors could exert adverse effects on the ocular surface function, including increased inflammatory mediators induced in response to inflammation, topical ophthalmic remedy containing preservatives, and so on.[5]

In recent years, owing to lubricating and corneal-wetting properties, the OVDs were widely applied to the corneal surface during ophthalmologic surgeries to maintain corneal moisture, clarity, and transparency. Also, the application of ocular lubricants to keep the ocular surface moistened is also 1 of the most common therapies for treating dry eyes.[13] Their ability to remain on the cornea surface and their effectiveness in protecting corneal epithelial cells against desiccation could decrease the dry eye exposure induced by persistent opening of the ocular surface through the placement of eye speculum. It could also effectively avoid the frequent BSS flushing of the ocular surface. Some studies suggested that frequent BSS flushing of the ocular surface during cataract surgery could result in a decline in goblet cell density.[5] The loss of goblet cells is a characteristic of dry eye, and it is also associated with decreased expression of mucoprotein MUC5AC.[14]

4.1. Dry eye influenced by sex

In this study, the results of subjective symptom questionnaire, ST-I, BUT, and corneal staining were compared between the 2 groups. No significant difference in the aforementioned indicators was found between the 2 groups. However, further analysis showed that the ST-I value in male patients in the study group was obviously higher than that in male patients in the control

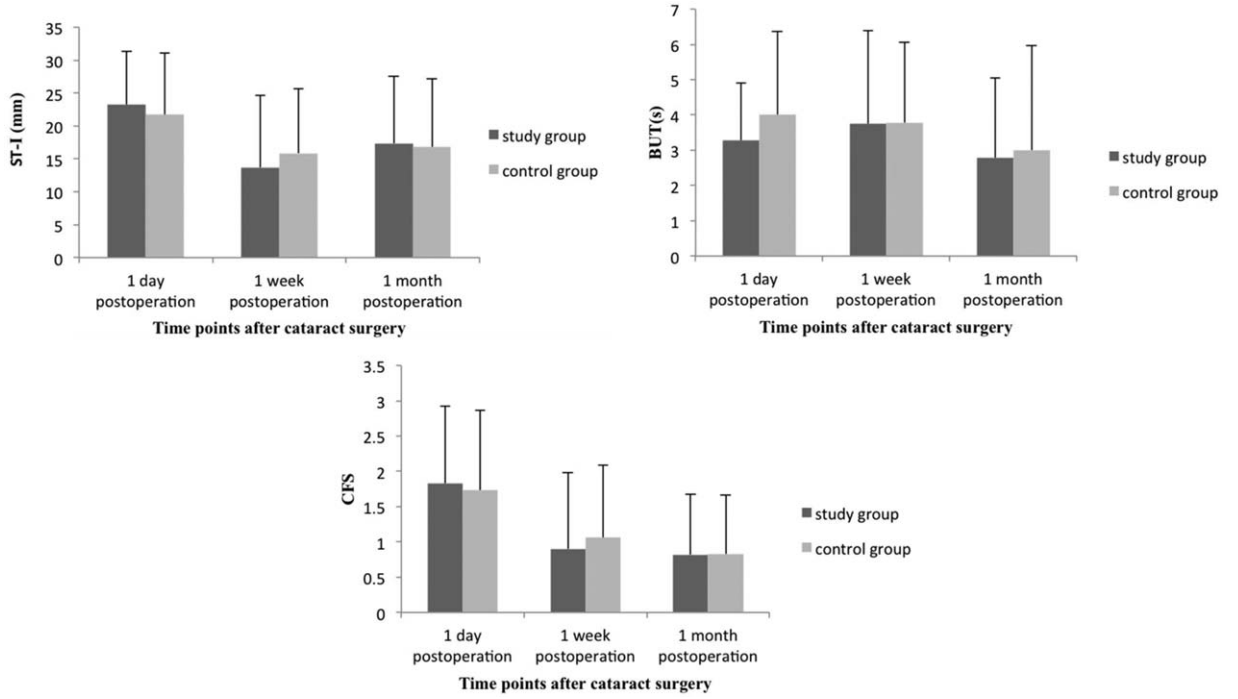

Figure 5. Comparison of dry eye measurements (ST-I, BUT, CFS) between the 2 groups of female patients with preoperative diagnosis of dry eye at different time points. There is no significant difference between the dry eye test values of the 2 groups' female patients on days 1, 7, and 30 after cataract operation. BUT = tear break-up time, CFS = corneal fluorescein staining, ST-I = Schirmer test without topical anesthetics.

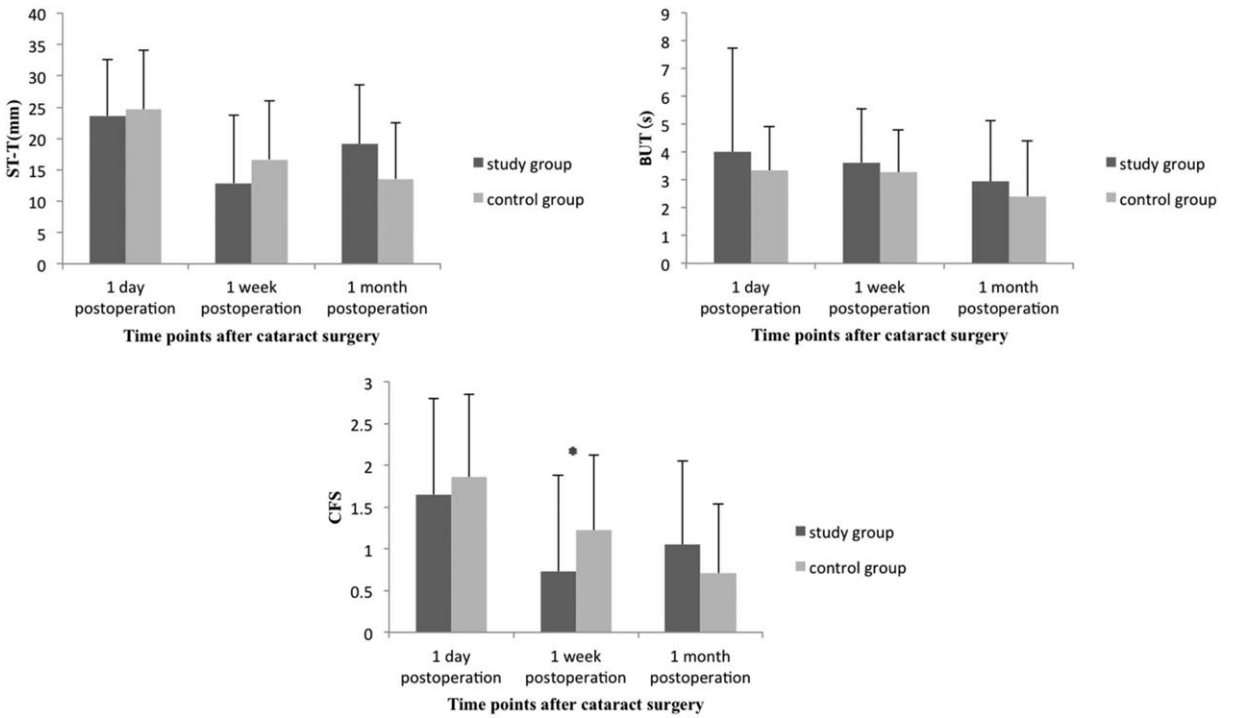

Figure 6. Comparison of measurements for the crowd of preoperatively dry eye patients whose surgery time is longer than median between the 2 groups at different time points. CFS values of the patients in the study group were superior to that of the patients in the control group 1 week after operation, and a significant difference was found between the 2 groups ($^{*}P = .032$). BUT = tear break-up time, CFS = corneal fluorescein staining, ST-I = Schirmer test without topical anesthetics.

group ($P = .019$). For the patients diagnosed with dry eye before the surgery, the ST-I value in the male patients in the study group was superior to that in the male patients in the control group at 1 month after the surgery ($P = .035$). The result suggested that the use of HPMC 2% during the surgery for male patients with and without dry eye could exert some protective effect on the ocular surface. Huge differences in incidences, etiology, risk factors, and response to treatment and prognosis could be observed between the female and male populations. Therefore, in recent years, a large number of basic and applied researches have been conducted to further investigate the sex differences. Women were found to have distinctly higher incidence and degree of severity of dry eye,[3,15] and the reduction in estrogen is related to the occurrence of dry eye.[16,17] Sex-based differences exist in the lacrimal glands and Moll glands in terms of anatomy, physiology, and pathophysiology, and this kind of difference is also reflected in conjunctival goblet cells.[18] The ocular surface tissues are 1 of the specific targets of sex hormones. It was confirmed that estrogen and androgen receptors existed in human conjunctiva, cornea, and Moll gland.[19] Therefore, sex hormones could influence a large number of cells and tissues in the ocular surface, and the pathways involved had sex-based differences also.[20] In this study, compared with the male patients in the control group, the male patients in the study group showed different results. However, no similar findings were observed in female patients. This might be related to the different roles of reproductive hormones in patients of different sexes.

4.2. Dry eye influenced by surgical time

In this study, the results of the patients whose surgical time was higher than median were further statistically analyzed; no significant difference was observed between the 2 groups. However, further stratified analysis found that, in the preoperatively diagnosed dry eye patients whose surgery time was longer than the median, the corneal staining in patients in the study group was superior to that in the patients in the control group ($P = .032$). Corneal staining is very important in the diagnosis of dry eye. It can show damage of ocular surface epithelial cells induced by dry eye visually and quantitatively.[9] During cataract surgery, the surgical procedure can cause inflammation and release of inflammatory mediators such as oxygen-free radicals, proteolytic enzymes, and cyclooxygenase [21]in the ocular surface. Thus, the ocular surface is damaged, resulting in decreased density of goblet cells.[21] Cataract surgery itself can aggravate dry eye. The patients diagnosed with dry eye before the surgery had abnormalities of ocular structure and function. Their eye symptoms and signs worsened postoperatively, and the relatively longer surgical time could exert a negative impact on the original presence of dry eye disease. The results of this study suggested that the use of HPMC 2% during cataract surgery could protect the vulnerable ocular surface of the patients with dry eye from the damage induced by surgical procedures.

4.3. Dry eye influenced by lens hardness and incision cite

The cornea is a highly innervated organ. The incision made by cataract surgery can result in nerve fracture, leading to neurogenic inflammation. The inflammatory mediators can change the role of corneal nerves and reduce corneal sensitivity.[22] After the change in normal corneal innervation, the rate of blinks and tears are reduced, resulting in unstable tear films, and a change in tear osmotic pressure.[1] However, for right eye surgery patients, the nerve fracture caused by temporal corneal incision not only influences the incision region, but also exerts an adverse effect on the corneal tissues remote from the incision region.[23] But in our study, no significant difference was found in the 2 groups in the measurements of dry eye between left and right eyes.

For a patient whose lens nucleus is hard, the surgeon should use relatively higher phacoemulsification energy and longer phacoemulsification time to smash the lens nucleus, further increasing the damage to the corneal nerve tissues.[23] The patients of the 2 groups were further stratified and statistically analyzed according to cataract nuclear hardness ≥NC4. However, no significant beneficial influence of the HPMC 2% was observed.

4.4. Dry eye influenced by medicines

Over use or improper use of drugs, which contained preservatives such as benzalkonium chloride, could trigger the expression of inflammatory cell markers on the ocular surface. Thus, this could result in epithelial cell injury and apoptosis, and also reduce the density of goblet cells.[24] Pisella et al observed 4107 patients with glaucoma. They found that compared with patients who used preservative-free eye drops, the patients who used eye drops containing preservatives were prone to have ocular surface changes, and the occurrence rate increased 2 or more than 2 times. Meanwhile, the symptoms and signs were dose-dependent.[25] This could significantly decrease the stability of the tear film and the number of mucin-expressing cells, which could be the reason for postoperative dry eye and corneal toxicity. In our study, the patients used only 1 kind of antibiotic and corticosteroid compound preparation 4 times every day for 1 week, which remarkably reduced the ocular drug use frequency and duration, and thus, greatly decreased the potential ocular surface damage caused by medicines and the results interference by long-term use of multiple drugs. There was only 1 male patient aged 51 years. He had an ocular inflammatory response 1 week after the surgery. The clinical manifestation showed that visual acuity was 0.6, intraocular pressure was 18 mm Hg, and mixed conjunctival hyperemia could be observed. The patient also had signs of positive keratic precipitate and aqueous flare. Then, he was administered TobraDex 4 times every day, and diclofenac sodium (Shenyang Xing Qi Pharmaceutical Co., Ltd. Shenyang, China) was also added 4 times every day. The patient was observed for 1 week. His visual acuity returned to 0.8, and intraocular pressure was reduced to16 mm Hg; also, the inflammatory response disappeared. This patient was not enrolled in this study. Also, other patients did not have any abnormal inflammatory response.

This study had certain limitations. First, the follow-up time of the present study was relatively short; it only lasted for 1 month after the surgery. Second, the patients of this study did not undergo examination of the morphology and function of the meibomian glands.

The results of this study indicated that the use of OVD on the surface of cornea during cataract surgery could reduce the ocular surface trauma induced by surgery and intraoperative BSS flushing, especially in the patients diagnosed with dry eyes before the surgery, male patients, and patients whose surgical time was relatively longer. To some extent, the use of OVD during cataract surgery could exert a protective effect on postoperative ocular surface function.

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