

# Effects of sodium hyaluronate combined with rhEGF eye drops in patients with dry eye

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**Abstract:** To analyze the effects of sodium hyaluronate combined with recombinant human epidermal growth factor (rhEGF) eye drops in patients with dry eye. Totally 97 patients who suffered dry eye after cataract surgery in our hospital from March 2018 to June 2020 were selected and randomly assigned into control group (n=57, sodium hyaluronate eye drops) and intervention group (n=63, sodium hyaluronate combined with rhEGF eye drops). The clinical efficacy, Break Up Time (BUT), schirmer I test (SLt), fluorescent test (FL) and ocular surface disease index (OSDI), the scale of quality of life for disease with visual impairment (SQOL-DVI), interleukin-6 (IL-6), tumor necrosis factor (TNF- $\alpha$ ) level of the two groups were compared. The intervention group yielded remarkably higher effective rate than the control group ( $p<0.05$ ). Markedly higher BUT, SLt, SQOL-DVI scores and lower OSDI scores were witnessed among patients in the intervention group than the control group ( $p<0.05$ ). The clinical effect of sodium hyaluronate combined with rhEGF eye drops in the treatment of dry eye is superior to sodium hyaluronate alone, in terms of enhancing the stability of tear film, accelerating corneal healing, inhibiting the level of inflammatory factors and improving patients' quality of life.

**Keywords:** Clinical efficacy, inflammatory factors, quality of life, recombinant human epidermal growth factor, sodium hyaluronate.

## INTRODUCTION

Dry eye, a common disease, predisposes to abnormal tear and ocular surface function. Despite the considerable development of surgical technology, patients after surgery still experience dry eye related symptoms (Kato *et al.*, 2019). Studies have shown that patients are prone to dry eye at one week, one month and three months after cataract surgery with possibility of 42%, 15% and 9%, respectively. The burden of dry eye disease on affected patients is significant, with effects on visual function, activities of daily living, professional work, and quality of life. Systematic diagnosis and monitoring of dry eye disease can be achieved through the use of various validated measures of both signs and symptoms of disease. Sodium hyaluronate eye drops are the mainstay for the treatment of dry eye, which can enhance the stability of tear film, accelerate the repair of corneal epithelium, and promote the recovery of ocular surface function, but its outcome remains unsatisfactory (Ang *et al.*, 2017; Ishrat *et al.*, 2019). A prior study revealed that rhEGF can raise the amount of conjunctival goblet cells in patients who suffer dry eye, enhance the proliferation and division of tear film and corneal epithelial structure effectively, cut down the healing time of damaged cornea, advance the change of tear film quality, and alleviate the dry eye symptoms (Marquez *et al.*, 2011). However, despite its long track record and frequent use, active questions still surround the use of these methods. To this end, this study aimed to explore the effect of sodium hyaluronate combined with recombinant human

epidermal growth factor (rhEGF) eye drops in patients with dry eye after cataract surgery, so as to provide reference for the drug use in patients with dry eye after cataract surgery.

## MATERIALS AND METHODS

### Clinical data

This study is a prospective controlled study. 97 patients (120 eyes) with dry eye after cataract surgery treated in our hospital from March 2018 to June 2020 were selected.

**Inclusion criteria:** (1) Patients who met the diagnostic criteria of dry eye (Association, 2013); (2) Patients who successfully completed cataract surgery; (3) Patients who voluntarily participated in this study and provided an informed consent.

**Exclusion criteria:** (1) Patients with dry eye not caused by cataract; (2) With other eye diseases such as eye trauma, eyelid disease, lacrimal duct disease, keratoconjunctivitis, retinopathy, optic neuropathy, fundus disease; (3) With autoimmune diseases, endocrine system diseases, connective tissue diseases; (4) With history of eye surgery or trauma in recent three months; (5) Patients who have used drugs that affect tear secretion or tear film stability in the past month.

According to different treatment methods, patients were assigned into control group and intervention group. There were 46 patients (57 eyes) in the control group, including 21 males (26 eyes) and 25 females (31 eyes), aged from 42 to 77, with an average age of (60.28 $\pm$ 5.26) years; the course of disease ranged from 1 month to 5 years (mean,

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1.76±0.87). Meanwhile, there were 51 cases (63 eyes) in the intervention group, including 26 males (33 eyes) and 25 females (30 eyes), aged from 45 to 79, with an average age of (60.87±5.83) years; the course of disease ranged from 1 month to 5 years (mean, 1.91±0.98). The two groups of patients had no statistically significant differences in age, venereal disease, and course of disease.

### Methods

The control group was given sodium hyaluronate eye drops (Shenyang Xingqi ophthalmic Co., Ltd., approval number: H20183132, specification: 0.4ml/piece), 1 drop each time, tid; In addition to the treatment of control group, the intervention group was additionally given rhEGF eye drops (Guilin Huanuowei gene Pharmaceutical Co., Ltd., approval number: S20020016, specification: 2.0ml/piece), one drop each time, tid. Both groups were treated for 4 weeks.

### Outcome measures

(1) Curative effectiveness was classified into followings (Lei *et al.*, 2017). Cured: slit lamp examination is totally normal, and symptoms fully disappear; markedly effective: slit lamp examination is normal and symptoms mainly disappear; effective: Slit lamp examination has tiny cracks, and symptoms basically disappear; ineffective: Slit lamp examination has no advancement or degeneration. Total effective rate= (cured + markedly effective + effective)/total cases×100%. (2) BUT examination: A drop of fluorescein sodium solution was put into the lower conjunctival sac, the patient was asked to blink, and the time from opening eyes after the last blink to the first black spot on the cornea with slit lamp under blue light was observed. (3) Slit: The first end of the filter paper was folded in the outer 1/3 of the inferior conjunctival sac and the length of the filter paper soaked in tears at 5 minutes was measured without topical anesthesia. (4) FL: Four quadrants of the cornea were observed under slit lamp drilling blue light, which are classified into no staining (0 point), scattered punctate staining (1 point), diffuse punctate staining (2 points) and sheet staining (3 points) in the corneal epithelium, with a total score of 12 points. (5) OSDI questionnaire: the main symptoms of dry eye and their impact on visual function were evaluated, with scores ranging from 0 to 100. Higher scores indicate more severe dry eye symptoms. (6) SQOL-DVI: the quality of life of patients was investigated before and after treatment, and the levels of IL-6 and TNF- $\alpha$  were measured by ELISA

### Ethical approval

This study was approved by the ethic committee of the affiliated People's Hospital of Ningbo University.

## STATISTICAL ANALYSIS

All data analysis was conducted using SPSS20.0 statistical software. The measurement data were expressed

as ( $X\pm s$ ), and the t test was applied for the comparison between groups and the analysis of variance was applied for the comparison among multiple groups. The count data were investigated by  $\chi^2$  test. Significance was set at a  $p$  value of <0.05.

## RESULTS

### Treatment effectiveness

The intervention group produced remarkably higher effective rate as compared to the control group ( $\chi^2=8.209$ ,  $p=0.004$ ), as shown in table 1.

### THF-a and IL-6 levels

Prior to treatment, no significant difference was exhibited in the levels of THF-a and IL-6 between the two groups ( $p>0.05$ ). After treatment, the levels of THF-a and IL-6 in the two groups decreased, while much lower was observed in the intervention group (all  $p<0.05$ ), as displayed in table 2.

### Changes of BUT, SLt, FL

Prior to treatment, no significant difference was observed in BUT, SLt, FL between the two groups ( $p>0.05$ ). Whereas, both groups showed a markedly higher BUT and Slit but lower FL after treatment, and the changes in intervention group were more evident (all  $p<0.05$ ), as presented in table 3.

### Dry eye symptoms

The OSDI scores of the two groups both declined after 2 or 4 weeks of treatment, whereas the intervention group witnessed much lower score at each time point after treatment (all  $p<0.05$ ), as shown in table 4.

### Quality of life

The scores of SQOL-DVI in the two groups at 2 and 4 weeks after treatment increased ( $p<0.05$ ), with a higher score obtained in the intervention group ( $p<0.05$ ), see table 5 for details.

## DISCUSSION

Multiple factors such as anesthesia, mechanical injury and the release of intraoperative inflammatory factors during cataract surgery can lead to corneal epithelial damage and the decline of tear film stability and in turn the morphology of tear film lipid layer would be destroyed. Dry eye symptoms including irritation, eye redness, foreign body sensation and visual fatigue could result in a somber prognosis (Jing *et al.*, 2018). A previous study (Qiong and Jie, 2016) pointed out that the incision in cataract surgery causes corneal hypoesthesia, which leads to the weakness of blink movement and uneven distribution for tear on the corneal surface. Consequently, some patients could have dry eye symptoms and signs. To date, some artificial tears, epidermal growth factor and other drugs are predominantly used to promote the repair

**Table 1:** Comparison of treatment effectiveness [n,%]

Group	eyes	Cured	Markedly effective	Effective	Effective rate
Control group	57	19(33.3)	27(47.4)	11(19.3)	46(80.7)
Intervention group	63	41(65.1)	18(28.6)	4(6.3)	59(93.6)

**Table 2:** Comparison of THF-a and IL-6 levels (X±s, pg/ml)

Group	Eyes	THF-a		IL-6	
		Before treatment	After treatment	Before treatment	After treatment
Control group	57	265.39±31.27	176.56±22.61*	1261.72±135.65	983.62±111.68*
Intervention group	63	273.82±33.56	125.62±16.79*	1228.37±127.29	768.96±100.63*
<i>t</i>		1.419	13.821	1.389	9.775
<i>P</i>		0.158	0.000	0.167	0.000

**Table 3:** Comparison of BUT, SLt, FL (X±s)

Group	Eyes	BUT (s)		SLt (mm)		FL (score)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	57	5.67±1.38	9.28±1.85*	3.52±0.85	9.16±1.76*	2.61±0.85	1.07±0.51*
Intervention group	63	5.92±1.45	12.83±2.13*	3.63±0.96	12.65±2.31*	2.66±0.93	0.42±0.18*
<i>t</i>		0.965	9.700	0.662	9.235	0.306	9.488
<i>P</i>		0.337	0.000	0.509	0.000	0.760	0.000

**Table 4:** Comparison of dry eye symptoms (X±s, score)

Group	Eyes	OSDI			F	P
		Before treatment	2 weeks after treatment	4 weeks after treatment		
Control group	57	47.83±10.22	30.26±5.62*	28.53±5.16*	119.879	P<0.001
Intervention group	63	46.56±9.27	23.38±4.72*	21.65±4.18*	264.203	P<0.001
<i>t</i>		0.714	7.284	8.058		
<i>P</i>		0.477	0.000	0.000		

**Table 5:** Comparison of quality of life (X±s, score)

Group	Eyes	SQOL-DVI			F	P
		Before treatment	2 weeks after treatment	4 weeks after treatment		
Control group	57	88.22±17.25	101.26±20.23*	104.52±21.87*	10.734	P<0.001
Intervention group	63	86.98±16.39	115.65±22.71*	118.39±25.26*	40.217	P<0.001
<i>t</i>		0.358	4.230	2.902		
<i>P</i>		0.721	0.000	0.005		

Note: Compared with before intervention, \*P<0.05

and healing of the cornea and reduce the occurrence of dry eye.

Sodium hyaluronate eye drops play a crucial role in lubricating and water retaining, can promote corneal epithelial healing, stabilize tear film and prolong the duration on the ocular surface. For patients with dry eye following cataract surgery, sodium hyaluronate treatment based on conventional anti-inflammatory treatment has emanated apparently excellent outcome (Wen *et al.*, 2020). As a key component in tears, EGF can significantly regulate the growth, proliferation, differentiation, migration and metabolism of a variety of tissue cells *in vivo* and *in vitro* and promote the

regeneration of corneal epithelial cells and endothelial cells (Moon *et al.*, 2020; Peterson *et al.*, 2014). As the number of tears decreased, the content of EGF in tears of dry eye patients declined significantly, the healing of corneal epithelium slowed down with unsatisfying quality and even the dry eye disease aggravated (Lopez-Miguel *et al.*, 2014). Research by Sriwidodo *et al.* found that adding 25g/mL hEGF to eye drops can raise cell viability by up to 197%. rhEGF eye drops, a kind of exogenous EGF, has similar biological activity with natural EGF (Hu *et al.*, 2019; Sriwidodo *et al.*, 2020; Yan *et al.*, 2013). Moreover, it can promote the combination of exogenous ECF and endogenous ECF, activate the signal transduction pathway inside the cell, promote the synthesis of RNA, DNA and

protein, and stimulate corneal stromal fibroblasts and lacrimal gland cells proliferation and promote the repair of the corneal stroma, shorten the healing time of ocular surface damage. Hence, it is conducive to reducing the symptoms of dry eye, improving the stability of the tear film, tear secretion and corneal epithelial cell integrity and further cutting down inflammation.

BUT can reflect the stability of tear film and judge whether there is insufficient tear secretion or not. FL score can display the corneal surface defect. SlT is the main method to measure the amount of tear secretion and an important indicator of lacrimal gland function. In this study, after 2 and 4 weeks of treatment, the OSDI, SQOL-DVI score and BUT, SLt, FL examination results of the intervention group were superior to the control group, and the total effective rate was found to be higher in the intervention group beyond the control group, indicating that sodium hyaluronate combined with rhEGF Eye drops yielded a preferable therapeutic effect. Our findings are in agreement with Chen *et al.* (Yuhong *et al.*, 2021) who used rhEFG gel combined with Sodium Hyaluronate eye drops in treating patients with dry eye after phacoemulsification and found that the clinical symptoms improved significantly. Additionally, the clinical efficacy was more excellent than those using Sodium Hyaluronate eye drops alone, with higher safety profile.

Tear hypertonicity and inflammatory response are considered important factors that cause dry eye and the progress of the disease. Inflammatory responses play a major part in the course of various dry eye diseases (Yamaguchi, 2018). IL-6 and TNF- $\alpha$  are important members of the inflammatory mediators of dry eye, and the variations in their expression levels are closely related to the course of dry eye (Zhili *et al.*, 2016). The results of this study showed that the concentrations of TNF- $\alpha$  and IL-6 in the tears of the intervention group after treatment were remarkably lower than those of the control group, suggesting that sodium hyaluronate combined with rhEGF eye drops reduces the inflammatory reaction of the tear film of dry eye after cataract, which is in line with the study of Kim *et al.* (Kim *et al.*, 2013) who demonstrated that the mRNA levels of IL-6, EGF and EGFR decreased in the dry eye model to provide osmotic protection, and reduce apoptosis and increased proliferation.

## CONCLUSION

Collectively, rhEGF eye drops combined with sodium hyaluronate eye drops may be a preferable technique in the treatment of dry eye after cataract surgery in terms of improving the curative effect, reducing the postoperative inflammatory reaction and enhancing the stability of tear film, tear secretion as well as corneal epithelial cell integrity.

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