https://doi.org/10.31925/farmacia.2024.5.18 **ORIGINAL ARTICLE**

THERAPEUTIC OUTCOME OF SODIUM HYALURONATE EYE DROPS COMBINED WITH RECOMBINANT EPIDERMAL GROWTH FACTOR DERIVATIVE EYE DROPS ON POSTOPERATIVE XEROPHTHALMIA

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Abstract

Post-operative xerophthalmia is a frequent complication following eye surgery. This study aimed to assess the effectiveness of sodium hyaluronate (SH) eye drops combined with recombinant human epidermal growth factor (rh-EGF) derivative eye drops in treating this condition. First, the physicochemical properties of SH eye drops, at concentrations of 0.1% and 0.3% were analysed, evaluating viscosity, surface tension, pH and electrical conductivity. A randomised controlled trial was conducted with 85 patients, divided into three groups: Group A (SH eye drops), Group B (rh-EGF eye drops) and Group C (combined SH and rh-EGF eye drops). Postoperative outcomes were assessed using visual acuity, intraocular pressure and the Scale of Quality of Life for Disease with Visual Impairment (SQOL-DVI). Additionally, xerophthalmia severity was evaluated through clinical symptom scoring, Schirmer's test, tear break-up time (BUT), corneal staining and nerve density analysis. Results showed that Group C demonstrated significantly better outcomes compared to Groups A and B, with improved tear secretion, tear film stability, reduced inflammation and enhanced corneal nerve morphology. These findings suggest that combining SH and rh-EGF eye drops offers a more effective treatment for postoperative xerophthalmia, with notable therapeutic benefits in improving patients' ocular health.

Rezumat

Xeroftalmia postoperatorie este o complicație frecventă după chirurgia oculară. Acest studiu a urmărit să evalueze eficacitatea picăturilor oftalmologice de hialuronat de sodiu (SH) combinate cu picături oftalmologice derivate din factorul de creștere epidermal uman recombinant (rhEGF) în tratarea acestei afecțiuni. În primul rând, au fost analizate proprietățile fizico-chimice ale picăturilor oftalmice SH la concentrații de 0,1% și 0,3%, evaluând vâscozitatea, tensiunea superficială, pH-ul și conductivitatea electrică. A fost efectuat un studiu controlat randomizat cu 85 de pacienți, împărțiți în trei grupuri: Grupul A (picături oculare SH), Grupul B (picături oculare rhEGF) și Grupul C (picături oculare combinate SH și rhEGF). Rezultatele postoperatorii au fost evaluate utilizând acuitatea vizuală, presiunea intraoculară și Scala de calitate a vieții pentru boala cu deficiență vizuală (SQOL-DVI). În plus, severitatea xeroftalmiei a fost evaluată prin scorarea simptomelor clinice, testul Schirmer, timpul de rupere a lacrimilor (BUT), colorarea corneei și analiza densității nervoase. Rezultatele au arătat că grupul C a demonstrat rezultate semnificativ mai bune în comparație cu grupurile A și B, cu secreție lacrimală îmbunătățită, stabilitate a filmului lacrimal, inflamație redusă și morfologie îmbunătățită a nervului cornean. Aceste constatări sugerează că combinarea picăturilor oculare SH și rhEGF oferă un tratament mai eficient pentru xeroftalmia postoperatorie, cu beneficii terapeutice notabile în îmbunătățirea sănătății oculare a pacienților.

Keywords: SH eye drops, EGF, rh-EGF derivative eye drops, xerophthalmia, efficacy

Introduction

With the continuous development of ophthalmic surgery technology, various surgeries such as laser surgery, cataract surgery and corneal transplantation have been widely used in clinical practice, but the problems of postoperative xerophthalmia associated with these surgeries have gradually become more prominent [1-3]. The pathogenesis of xerophthalmia is extremely complex and mainly involves many factors such as corneal nerve damage, tear secretion dysfunction and changes in ocular surface tissue structure caused by surgery [4]. The disease usually manifests as pain, xerophthalmia, blurred vision and other symptoms, which greatly affect the daily life and work efficiency of patients [5].

With regard to the postoperative treatment of xerophthalmia, drug therapy has attracted much attention as an important intervention [6]. SH, also known as hyaluronic acid, is a polymeric polysaccharide naturally present in human tissues, mainly in the eyeball, joints, skin and other parts. Its unique biocompatibility and moisturizing properties make it an ideal vehicle for ophthalmic drug delivery [7]. Traditional ophthalmic treatment methods often have problems such as unstable drug effects, local irritation. Therefore, a new

ophthalmic treatment method is urgently needed to improve therapeutic outcomes and reduce patient discomfort [8]. As a new type of ophthalmic drug, SH eye drops have excellent hydration and adhesion properties, which can form a uniform lubricating film on the ocular surface and improve the retention time of the drug in the eye, thereby increasing the drug effect [9]. In addition, SH also has multiple biological activities, such as anti-inflammatory and antioxidant effects, which have an obvious effect on reducing ocular inflammation and promoting corneal healing [10]. A large number of clinical studies have shown that SH eye drops can not only rapidly relieve patients' ocular discomfort, but also maintain ocular surface wetness and improve patients' quality of life (QoL) during treatment [11-13]. Epidermal growth factor (EGF) is a type of cell growth factor that can regulate cell proliferation, differentiation and survival by binding to cell surface receptors and is essential for maintaining the normal function of corneal and conjunctival epithelial cells [14]. In some ocular surface diseases, such as xerophthalmia, keratitis and conjunctivitis, the structure and function of the ocular surface tissues are severely damaged, in which case the use of exogenous EGF or its derivatives is a potential treatment strategy [15-17]. As a novel treatment, rh-EGF derivative eye drops have attracted considerable attention in recent years. The present study shows that using genetic engineering technology, recombinant EGF derivatives can be efficiently synthesized and expressed, and have a longer half-life and stronger biological activity [18, 19]. These rh-EGF derivatives can not only promote the proliferation and repair of corneal and conjunctival epithelial cells, but also have multiple biological effects, providing a new direction for the treatment of ocular diseases [20].

However, there are few studies on the combined use of SH eye drops and rh-EGF derivative eye drops. The aim of this article was to evaluate the therapeutic outcome of SH eye drops combined with rh-EGF derivative eye drops in patients with postoperative xerophthalmia. By closely observing the effects of the combination therapy on clinical symptom scores, tear secretion, tear film BUT and healing efficacy, it was investigated whether this combination therapy can significantly improve postoperative dry eye conditions in patients. It is hoped that this will provide a scientific basis for the comprehensive management of post-surgical xerophthalmia, offering a new treatment strategy for clinical practice and improving patients' quality of life and therapeutic outcome.

Materials and Methods

Physical and chemical properties of SH eye drops

Determination of apparent viscosity. Apparent viscosity was measured using a rotational rheometer (HAAKE™ MARS™, Thermo Fisher, USA): 40 mm conical plate (2° angle), 0.1% SH eye drops (Hialid, J20090019, Santen Pharmaceutical CO., LTD., China), 0.3% SH eye drops (Hialid, H20173248, Santen Pharmaceutical CO., LTD., China) were dropped onto the plate, the pipetting gun was used to remove bubbles, making sure that the eye drop sample on the plate was free of bubbles, and then the button was clicked to lift the cone plate; the eye drop samples should be removed in areas other than between the plate and the cone plate with paper towels so that the wedge gap between the cone plate and the plate was filled with eye drop samples; according to the actual shear rate of eye drops on the ocular surface, the range of shear rate was set to 0 - 20/s. The start was clicked to measure the apparent viscosity between the shear rate of 0 - 20/s and the data was generated directly. The data of three consecutive measurements were scatter plotted and the measurement was stopped until the trend of the scatter plot of three consecutive measurements was consistent.

Surface tension measurement. A dynamic contact angle meter (CA200, Beidou Precision Instrument CO., LTD., China) was used to measure the surface tension. A sample of 30 mL eye drops (0.1% SH eye drops, 0.3% SH eye drops) was added to the sample cuvette, and the sample cuvette was placed in the centre of the sample table. The end of the platinum plate was clamped with tweezers, and the platinum plate was thoroughly rinsed with deionised water and then dried. Both sides of the platinum plate were heated to red under the outer flame of the alcohol lamp. After natural cooling, the platinum plate was clamped to the slit, and the glass door was closed. At 25℃, the computer automatically and continuously performed the measurement until the standard deviation of 50 consecutive readings was within the acceptable range of the system. The average and standard deviation of the recorded surface tension were displayed on the LCD screen.

Determination of pH value. The pH of the solution was measured using a pH meter (PHS-3C, INASE Scientific Instrument CO., LTD., China). After the calibration, the electrode head was rinsed with distilled water and then rinsed with eye drop samples (0.1% SH eye drops, 0.3% SH eye drops). The electrode was then immersed in the eye drop sample, the pH of the solution was read on the screen and the measurement was repeated three times.

Measurement of conductivity. The electrical conductivity meter (CON 150, Thermo Fisher, the United States) was used to determine the conductivity. The conductivity meter is composed of a conductance electrode and microprocessor chips, electronic units with appropriate frequency AC signal method. The signal was amplified and converted into electrical conductivity. The power supply was turned on and the samples of eye drops (0.1% SH eye drops, 0.3% SH eye drops) were measured 3 times after correction.

Subjects

Eighty-five patients with xerophthalmia after ophthalmic surgery from July 2017 to July 2022 were enrolled. According to the principle of randomised controlled trial, the patients were divided into two groups: A (28 cases): SH eye drops; B (28 cases): rh-EGF derivative eye drops; C (29 cases): SH eye drops and rh-EGF derivative eye drops. A: There were 11 males (39.29%) and 17 females (60.71%), age (43.61 ± 8.26) years, 10 (35.71%) cases of cataract surgery, 13 (46.43%) cases of myopia surgery and 5 (17.86%) cases of corneal transplantation. B: 13 (46.43%) males, 15 (53.57%) females, (43.22 ± 8.15), 9 (32.14%) cases of cataract surgery, 12 (42.86%) cases of myopia surgery, 7 (25%) cases of corneal transplantation; C: 13 males (44. 83%) and 16 females (55.17%), (44.73 ± 7.95), 12 (41.38%) cases of cataract surgery, 11 (37.93%) cases of myopia surgery and 5 (17.24%) cases of corneal transplantation. The demographics of the subjects were similar and comparable ($p > 0.05$). This study was approved by the hospital ethics committee.

Inclusion criteria: subjects with obvious xerophthalmia after ophthalmic surgery, such as dry eye, foreign body sensation, blurred vision; no obvious fundus lesions found by slit-lamp examination; subjects understood and followed the study protocol and were able to cooperate with treatment and follow-up; subjects did not accept any other xerophthalmia treatment intervention within two weeks; subjects were aware of the study content and gave voluntary informed consent.

Exclusion criteria: Patients with other eye diseases such as keratitis and glaucoma. Patients who were allergic to or intolerant of the drugs used in the study; patients with severe mental illness or cognitive impairment; medical conditions that affect xerophthalmia, such as diabetes and rheumatoid arthritis; pregnant or breastfeeding women.

Treatment methods

Group A: 3 days before surgery, Levofloxacin eye drops (H20093808, Chengdu Brilliant Pharmaceutical Co., Ltd., China) were routinely administered 4 times *per* day, 1 drop/time, to prevent infection. Patients with xerophthalmia, 0.3% SH eye drops, 5 times/day, 1 drop/time, for one month.

Group B: 3 days before surgery, Levofloxacin eye drops were given routinely to prevent infection, 4 times/day, 1 drop/time. Rh-EGF derivative eye drops (Yibei, S20020016, Guilin Pavay Gene Pharmaceutical Co., LTD., China) were given twice daily, 1 drop/time, for 1 month after the patient developed xerophthalmia.

Group C: 3 days before surgery, Levofloxacin eye drops were routinely administered to prevent infection, 4 times/day, 1 drop/time. Patients with xerophthalmia were given 0.3% SH eye drops, 5 times/day, 1 drop/time; rh-EGF derivative eye drops, 2 times/day, 1 drop/time, for one month.

Observation indicators

Evaluation of surgical efficacy

(1) Visual acuity examination: the international standard logarithmic visual acuity chart [21] was used to score according to visual acuity, 1.0 - 0.8 is 0; 0.7 - 0.5 is 1 point; 0.4 - 0.2 is 2 points; < 0.1 is 3 points.

(2) Intraocular pressure examination: a non-contact tonometer (CT-800, Beijing Tuopukang Medical Instrument CO., LTD.) was used to measure 3 times and the average value was taken.

(3) Quality of life (QoL) assessment [22]: The patients' QoL was assessed using the SQOL-DVI. The highest total score of all indicators in the scale was 200. Higher scores indicate better QoL.

Evaluation of postoperative dry eye efficacy

Clinical symptom score: The Ocular Surface Disease Index (OSDI) questionnaire [23] was used to assess the subjects' xerophthalmia and visual function, and the criteria were as follows: A score of 0 - 12 points means that the ocular surface is in good health, symptoms and QoL were not clearly affected; a score of 13 - 22 indicates that the subject has mild symptoms of ocular surface disease that may cause minor inconvenience in daily life. A score of 23 - 32 indicates that the symptoms of ocular surface disease are more obvious and have some impact on QoL, requiring attention and treatment. A score of 33 or more indicates that the symptoms of ocular surface disease are obvious and require active intervention and treatment.

Schirmer I test (SIt): The Cream of Schirmer test strip (RYM-010, Jiangsu Riyueming Medical Equipment Co., Ltd., China) was placed at the lower palpebral junction, ensuring that the other end of the test strip hung down. Subjects were asked to close their eyes for 5 minutes, during which time they were instructed to avoid blinking to minimise interference with tear production. At the end of the test, the wet part of the test strip was measured and the length of the wet part of the test strip (in mm) was measured with a ruler. Under normal circumstances, the tear production should be between 10 and 15 mm in 5 minutes.

Break-up time (BUT) test: An eye drop containing fluorescein dye was instilled at the palpebral junction, and subjects applied the dye uniformly to the tear film by blinking. A corneal topography instrument (E300-USB, Nanjing Vedeng Medical Co., Ltd., China) was used to observe and record the time of first break-up of the fluorescein dye on the ocular surface under blue light, called BUT. Under normal circumstances, the BUT of the tear film is more than 10 seconds.

Corneal fluorescence staining examination (Fluorescent, FL): Sodium fluorescein solution was used. Through the dropper, 1 to 2 drops of the dye were applied to the conjunctival sac of the subjects, the subjects had to blink, and the dye was evenly coated on the corneal surface. According to the corneal fluorescein staining and the degree of symptom relief observed under the

slit lamp (SL-D701, Beijing Tuopukang Medical Instrument CO., LTD., China), the patients were divided into three grades: response rate = (marked efficacy + efficacy) cases/total cases × 100%. Clearly effective: corneal fluorescein staining was negative, and all symptoms were relieved; effective: corneal fluorescein staining was positive, showing punctate or scaly staining, and symptoms were partially relieved. Ineffective: corneal fluorescein staining was the same as before, with no improvement or worsening of symptoms.

The bulbar conjunctiva congestion degree grade: It is measured through the slit lamp to observe the degree of bulbar conjunctival congestion of the subjects for classification. Score 0 (normal): no conjunctival congestion, porcelain white ocular surface, no dilation of the conjunctival blood vessels; score 1 (very mild): a few small, reddish dilated blood vessels near the fornix or inner and outer canthus; score 2 (mild): only a slight increase in length near the fornix or inner and outer canthus: Only a small amount of elongation near the fornix or inner and outer can thus, bright red dilated conjunctival blood vessels, and the number was slightly higher compared to extremely mild; Score 3 (moderate): hyperaemic blood vessels involved 23 bulbar conjunctiva, and the blood vessels were thick, dense and dark red in colour. Grade 4 (severe): a large number of blood vessels in the bulbar conjunctiva were dilated and congested, the area involved was the whole bulbar conjunctiva, and the blood vessels were thick, numerous and dark red.

Corneal nerve examination

The examination was performed with a Heidelberg laser confocal corneal microscope using a 670 nm laser source tomography with 1μm resolution, 400 μm × 400 μm scan area, 380 × 380 pixels and 800× magnification. Confocal microscopy was performed in the central, superior, inferior, nasal and temporal positions of the cornea. Each position was arranged in a sequence and at least 100 images were collected for each sequence. Three random fibre images of corneal SBN with high resolution and contrast and less than 20% overlap from five directions and each position of each eye were selected for analysis. The average of the three images was calculated. ImageJ software was used for quantitative and qualitative analysis of SBN.

Statistical methods

All data are presented as mean ± standard deviation and analysed using SPSS23.0 software (IBM, USA). A t-test was used for contrast, and a value of $p < 0.05$ was considered statistically significant.

Results and Discussion

Evaluation results of physical and chemical properties

The results indicated that the apparent viscosity curve of 0.3% SH eye drops was visibly higher than that of 0.1%. The pH and surface tension of the two eye drops were similar ($p > 0.05$). The conductivity of 0.3% SH eye drops (10.22 ± 6.01) ms/cm was visibly lower compared to 0.1% ($p < 0.05$) (Figure 1).

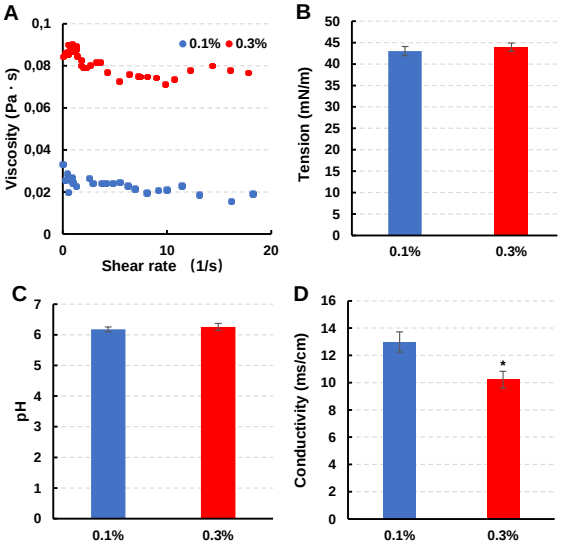

Figure 1.

Contrast of physical and chemical properties:
A: apparent viscosity; B: surface tension;
C: pH value; D: electrical conductivity
* $p < 0.05$ in contrast to 0.1 concentration

Evaluation of surgical efficacy

The mean visual acuity score of the subjects was low before surgery and increased visibly after surgery ($p < 0.05$) in all the groups. There were (2.52 ± 0.29) points, (2.53 ± 0.26) points and (2.56 ± 0.22) points in groups A, B and C respectively ($p > 0.05$) (Figure 2A).

The mean intraocular pressure of subjects was higher before surgery and decreased visibly after surgery ($p < 0.05$). In group A it was (11.46 ± 1.18) mmHg, while in B and C were (11.32 ± 1.15) mmHg and (11.72 ± 1.24) mmHg, respectively ($p > 0.05$) (Figure 2B).

The results of the scale evaluation suggested that the SQOL-DVI scores of the subjects were visibly higher than those before the operation ($p < 0.05$), and the scores were (124.33 ± 25.84) points, (125.76 ± 23.88) points and (122.48 ± 26.16) points, in groups A, B and C, respectively ($p > 0.05$) (Figure 2C).

Evaluation of dry eye efficacy

Clinical symptom score results. Before treatment, subjects' ocular symptom scores were similar ($p > 0.05$). After treatment, the symptom scores of the subjects were visibly reduced. The score in group C, (8.42 ± 2.79) was significantly lower compared to scores in group A (11.38 ± 3.24) and B (11.77 ± 2.71), respectively ($p < 0.05$) (Figure 3).

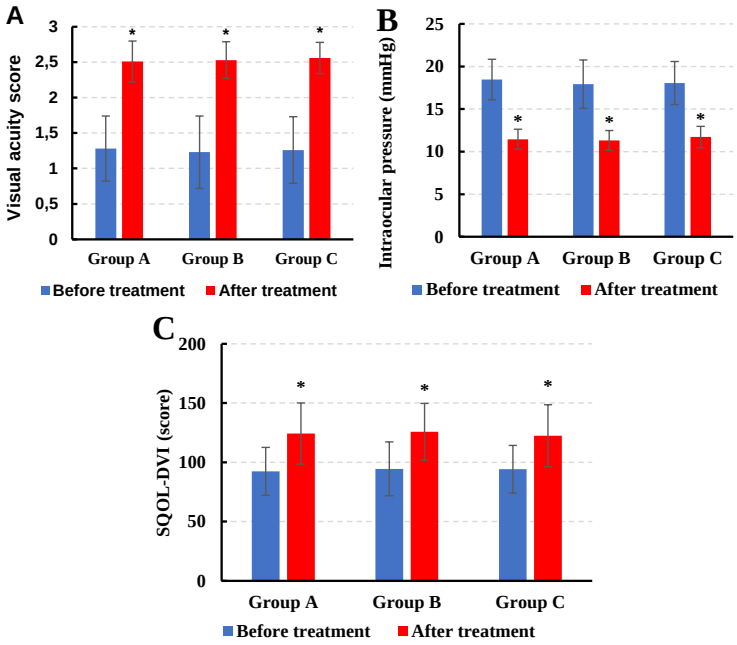

Figure 2.

The surgical curative effect comparison: A: visual acuity score; B: intraocular pressure; C: SQOL-DVI score

* $p < 0.05$ as against pre-operation

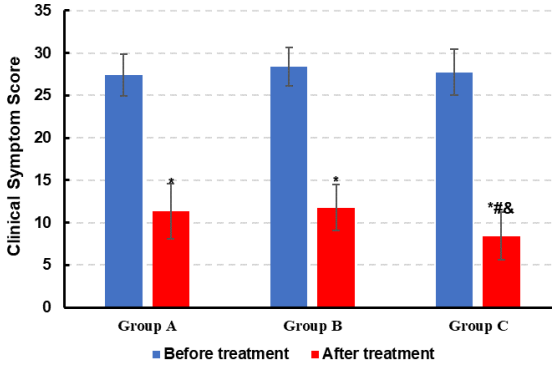

Figure 3.

Clinical symptom scores

* $p < 0.05$ compared with the pre-treatment levels, # $p < 0.05$ compared with group A, & $p < 0.05$ compared with group B

SIt results

The Schirmer secretion after treatment was visibly increased compared with the levels before treatment. The levels in Group C (10.87 ± 2.24) mm were significantly increased compared with the levels in group A (9.76 ± 2.31) mm and B (9.42 ± 3.18) mm, respectively (all $p < 0.05$) (Figure 4).

BUT test results

After treatment, the average BUT of subjects reached more than 10s. Group C (13.85 ± 2.01) s was visibly longer relative to group A (10.17 ± 1.92) s and group B (10.32 ± 1.88) s, respectively ($p < 0.05$) (Figure 5).

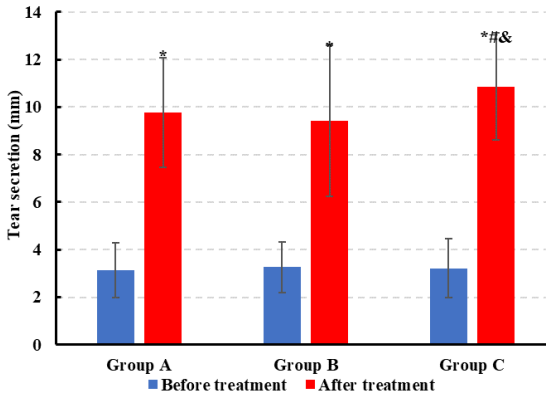

Figure 4.

Contrast of Schirmer secretion

* $p < 0.05$ compared to pre-treatment, # $p < 0.05$ compared with group A, & $p < 0.05$ compared with group B

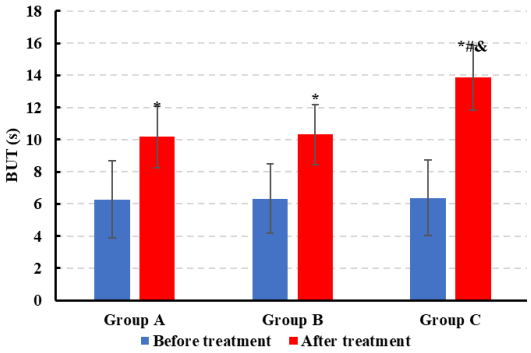

Figure 5.

BUT comparison

* $p < 0.05$ compared with pre-treatment, # $p < 0.05$ compared with group A, & $p < 0.05$ compared with group B

FL test results

In group A there were 9, 13, 6 cases markedly effective, effective and ineffective, respectively. In group B, there were 6, 14, 8 cases, respectively, while in group C, there were 16, 11, 2 cases, respectively. The response rate of treatment in group C (93.1%) was visibly higher compared to group A (78.57%) and B (71.43%), respectively ($p < 0.05$) (Figure 6).

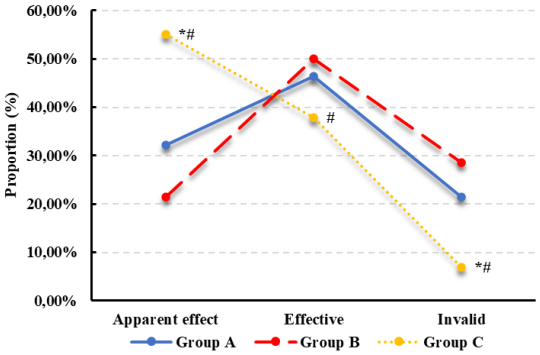

Figure 6.

Contrast of therapeutic outcomes

* $p < 0.05$ compared with group A;

# $p < 0.05$ compared with group B

Score results of bulbar conjunctiva congestion degree

It is showed that after the treatment, the scores of subjects decreased significantly ($p < 0.05$). The score of group C (1.25 ± 0.12) was markedly lower compared to group A (1.36 ± 0.14) and group B (1.28 ± 0.17) (Figure 7).

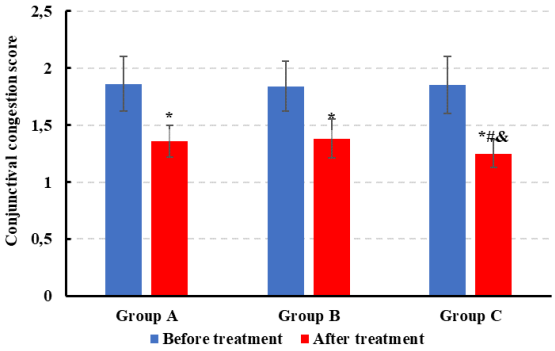

Figure 7.

Bulbar conjunctiva congestion degree score

* $p < 0.05$ compared to pre-treatment, # $p < 0.05$ compared to group A, & $p < 0.05$ compared to group B

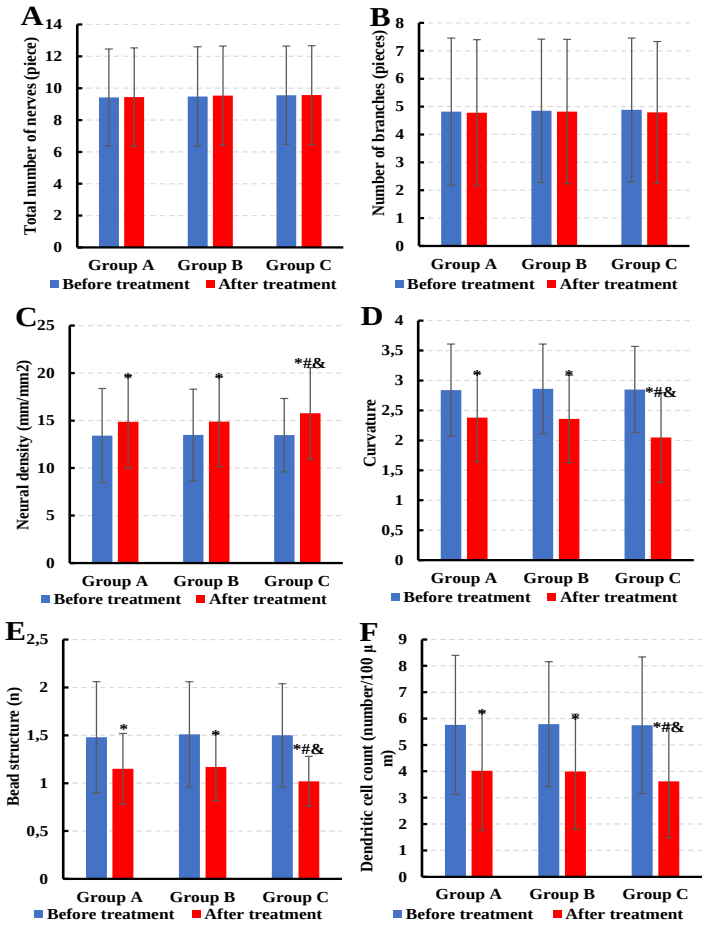

Figure 8.

Contrast of corneal nerve-related indexes: A: Total number of SBN nerves; B: number of SBN branches; C: nerve density; D: tortuosity; E: number of beaded structures; F: number of dendritic cells

* $p < 0.05$ compared with the pre-treatment values, # $p < 0.05$ compared with group A, & $p < 0.05$ compared with group B

Test of corneal nerve-related indicators

The total number of nerves and the number of branches in the SBN were similar before and after treatment in all the groups. SBN nerve density increased significantly after the treatment in all the groups and bending, bead structure and dendritic cell density decreased significantly after the treatment in all the groups. The effects in group C were significantly different compared with the other two groups in an additive protective manner (all $p < 0.05$) (Figure 8).

The occurrence of postoperative dry eye is closely related to ocular surgical trauma, corneal nerve damage and the use of postoperative medications and other factors. These factors lead to a decrease in tear secretion, and it appears to be unstable, which affects the function of the ocular surface wetting, leaving the patient in a state of chronic tear deficiency [24]. Ophthalmic surgery, especially common eye surgeries such as refractive surgery and cataract surgery, is not only an effective means to improve patients' vision but may also cause the occurrence of postoperative dry eye [25]. The clinical manifestations of postoperative xerophthalmia include ocular discomfort, pain, decreased visual acuity and inadequate tear secretion, which have an obvious negative impact on patients' quality of life and visual experience [26]. Currently, the methods used to treat post-operative xerophthalmia include the use of artificial tears, topical application of anti-inflammatory drugs and drugs that stimulate tear secretion. As a polymer, SH has excellent moisturizing and lubricating properties. It can form a uniform lubricating film to cover the ocular surface and reduce ocular surface dryness and discomfort. Its biocompatibility is strong and preservative-free, making SH eye drops an ideal choice for the treatment of xerophthalmia [27]. EGF can promote epithelial cell growth, wound healing and cell regeneration. Recent studies have shown that abnormal metabolism and dysfunction of epithelial cells play an important role in the pathogenesis of xerophthalmia [28, 29]. Therefore, the use of rh-EGF derivatives *via* topical eye drops is expected to exert its biological effect in xerophthalmia, thereby improving the health of the corneal surface. This article investigated the effect of the combination of these two drugs in post-operative xerophthalmia.

There are currently two concentrations of SH eye drops on the market, 0.1% and 0.3%. This article first compares these two concentrations of eye drops. The pH and apparent tension of the two eye drops were similar. Compared to 0.1% SH eye drops, the apparent viscosity curve of 0.3% SH eye drops was significantly higher and the electrical conductivity was significantly lower ($p < 0.05$). Apparent viscosity may affect the distribution of eye drops on the surface of the eye; xerophthalmia requires drugs to be more widely distributed on the surface of the eye, and the high apparent viscosity of eye drops may be more likely to achieve this; on the other hand, high apparent viscosity is more advantageous to maintain drug contact for a long time [30]. Electrical conductivity is commonly used to assess the salinity or solute concentration of a fluid, and higher electrical conductivity is associated with higher salinity, which can cause irritation or discomfort to the eye [31]. To reduce the influence of other factors, 0.3% SH eye drops were selected for the follow-up study after careful consideration.

Patients with postoperative xerophthalmia after ophthalmic surgery were selected and randomly grouped according to the methods of postoperative xerophthalmia treatment. It was found that there were similarities in the general clinical data and postoperative efficacy evaluation indicators of the subjects ($p > 0.05$), which were comparable. After the evaluation of the postoperative xerophthalmia remedy in the subjects, the ocular symptom scores in group C were significantly lower, suggesting that the combined use of two drugs can help promote the improvement of patients with post-operative xerophthalmia compared to a single drug remedy. The significantly higher Schirmer secretion in group C suggests that the combination of the two drugs may have a positive effect on improving Schirmer secretion in patients. Tear film BUT greater than 10 seconds usually indicates good tear film stability, *i.e.* the ocular surface can be covered by tears for a long time without dryness or abnormalities [32]. The significantly higher BUT in group C meant that the combination of products had a synergistic effect and helped to improve tear film stability. Cagini *et al.* [33] found that SH eye drops could effectively reduce the signs and symptoms of xerophthalmia and improve the stability of the tear film. Ren *et al.* [34] pointed out that the clinical effect of SH plus rh-EGF derivatives eye drops is superior to SH alone in improving stability, accelerating corneal healing, inhibiting inflammatory factor levels and improving patients' quality of life. The ocular surface of patients with xerophthalmia is inadequately lubricated and protected, leading to ocular surface inflammation and conjunctival hyperaemia [35]. The degree of bulbar conjunctival congestion in group C (1.25 ± 0.12) was significantly lower compared to the other two groups ($p < 0.05$), which means that SH combined with rh-EGF derivative eye drops can help reduce the inflammatory response of the ocular surface. Gong *et al.* [36] also suggested that SH combined with rh-EGF-derivative eye drops could help alleviate the clinical symptoms and inflammation of xerophthalmia patients undergoing cataract surgery. The efficacy rate in group C was 93.1%, which was significantly higher compared to groups A and B ($p < 0.05$). Fan *et al.* [37] used rh-EGF eye drops to intervene in patients with xerophthalmia after cataract surgery, and the results also showed that the efficacy rate was significantly increased.

The corneal nerve plays a key role in maintaining the health and sensory function of the ocular surface, and one of the characteristics of xerophthalmia is nerve

damage and changes on the ocular surface [38]. The nerve density of the SBN in the three groups was significantly increased, while the tortuosity, beaded structure and dendritic cell density were significantly decreased, and there were clear differences between group C and the other two groups ($p < 0.05$). Previous studies have shown that the distribution of corneal nerves in xerophthalmia patients is markedly abnormal compared with normal subjects, the number and density of nerves are decreased, and the tortuosity of nerves is increased, which is associated with clinical severity [39, 40]. Therefore, this article shows that SH combined with rh-EGF derivative eye drops can help to improve corneal SBN morphology. In conclusion, the combined application of the two drugs may have a synergistic effect and help to improve the remedy effect in patients with postoperative xerophthalmia. However, the study sample was relatively small, which may affect the generalizability and reliability of the results.

In the future, further expansion of the sample size to include more types of surgery and more detailed classifications of xerophthalmia may be considered. In addition, a more comprehensive evaluation of side effects, long-term efficacy and quality of life will be helpful to understand the safety and practical effect of the combination. In addition, a more in-depth investigation of the mechanism of the combined remedy can be considered to better guide clinical practice. Overall, this article provides useful information on the treatment of postoperative xerophthalmia, but further research is needed to strengthen its practicality.

Conclusions

The combination of SH eye drops and rh-EGF derivatives can promote the improvement of post-operative xerophthalmia symptoms, promote tear secretion, improve tear film stability, reduce ocular surface inflammation and improve corneal SBN morphology, thereby improving the therapeutic outcome of post-operative xerophthalmia. It has practical value. However, the study sample was relatively small, the type of surgery was few, the time was short, and the classification of different degrees of dry eye was not investigated, which may affect the universality and reliability of the results. It can consider further expanding the sample size, and the patients were followed up for a more comprehensive understanding of the safety of the combined remedy and the actual application effect. It can explore the specific mechanism of the combination remedy. Overall, useful information is provided on the remedy for post-operative xerophthalmia, but further studies are needed to strengthen its reliability.

Conflict of interest

The authors declare no conflict of interest.

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