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Original Research Article

Effect of combined use of sodium hyaluronate and rhEGF on xerophthalmia in the elderly after cataract surgery

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Abstract

Purpose: *To determine the effect of combined use of sodium hyaluronate and recombinant human epidermal growth factor (rhEGF) on xerophthalmia in elderly patients after cataract surgery, as well as levels of serum inflammatory factors.*
Methods: *A total of 84 elderly patients diagnosed with xerophthalmia after phacoemulsification were retrospectively studied. The patients comprised two groups: control group consisting of 40 patients given basic therapy using anti-inflammatory drugs and sodium hyaluronate eye drops (1 drop 3 times a day), and combination group (n = 44) who additionally received rhEGF. The expression levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and tumor necrosis factor (TNF-α) in tears were determined using enzyme-linked immunosorbent assay (ELISA). After 4 weeks of treatment, clinical efficacy was assessed.*
Results: *There was significantly higher clinical efficacy in the combination group than in the control group ($p < 0.05$). The values of tear break-up time (BUT) and Schirmer test (Sit) in both groups increased significantly with time, while fluorescein corneal staining (FL), symptom score, and expression levels of IL-6, hs-CRP and TNF-α significantly decreased ($p < 0.05$). At 2 weeks and 4 weeks of therapy, the combination group had higher values of BUT and Sit than the control group ($p < 0.01$). However, FL value, symptom score, and levels of IL-6, hs-CRP and TNF-α were significantly lower in the combination group than in the control group ($p < 0.01$).*
Conclusion: *Sodium hyaluronate, in combination with rhEGF, improves treatment efficacy in elderly xerophthalmia patients after operation, reduces inflammatory reactions, and enhances disease alleviation. However, a multi-center prospective study will be required to validate the findings of this study.*

Keywords: *Sodium hyaluronate, rhEGF, Senile cataract, Xerophthalmia*

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INTRODUCTION

Cataracts is one of the primary causes of reversible visual impairment and blindness worldwide [1]. It is characterized by an abnormality in the lens due to decreased transparency and increased turbidity. Crystallin, the main protein of the lens and lens surface, is affected by many factors which cause irreversible damage to the lens and lead to the formation of

cataracts [2]. Cataracts often occur in the elderly, and China has gradually become a country with a high proportion of aging population [3].

According to current statistics, the proportion of elderly people aged over 65 years in China in 2022 is over 11 %, and it is expected to increase yearly [4]. Another survey showed a 3.23 % incidence of cataracts among male patients aged 45 - 49 years, while the incidence of cataracts in patients aged 85 - 89 years was 65.78 %. A similar trend was found in female patients [5]. Accordingly, it is the desire of medical experts to treat cataracts and make patients see again.

For now, phacoemulsification is the first choice in the clinical therapy of cataracts. However, cataract patients are relatively old, with many old age-related diseases which prolong postoperative healing time, in contrast to younger people. Moreover, patients experience short-run xerophthalmia after phacoemulsification [6]. Xerophthalmia is a multifactorial disease triggered by hyperosmotic tears, unstable tears film, inflammatory reaction on the ocular surface, and abnormal nerve sensation, with major characteristics of imbalance in tears film and ocular surface symptoms [7]. In the clinics, a growing number of cataract patients have been diagnosed with xerophthalmia before undergoing surgery. The symptoms of xerophthalmia become further aggravated after surgery, thereby triggering obvious discomfort which affects the healing of surgical wounds [8]. At the present, the most frequently adopted method for treating xerophthalmia is artificial tears supplementation. Sodium hyaluronate, an artificial tear, produces an artificial protective film on the surface of the eyeball, and it enhances the repair of tears film by keeping the eyes moist [9].

Epidermal growth factor (EGF) is also an effective component of human body fluids such as tears and aqueous humor. It quickly repairs corneal epithelium after corneal epithelium injury in patients, a property which makes it a crucial factor in ensuring normal visual function [10]. Recombinant human epidermal growth factor (rhEGF) is a multifunctional cell growth factor composed of 51 amino acid residues. When rhEGF binds to its receptor, the signal transduction pathway in corneal epithelial cells is activated. This leads to effective enhancement of synthesis of protein and nucleic acids in corneal epithelial cells, thereby contributing to corneal repair [10].

However, there is controversy about the effect of combined use of sodium hyaluronate and rhEGF in xerophthalmia therapy after cataract surgery. Therefore, the present study was aimed at investigating the effect of combined application of sodium hyaluronate and rhEGF on xerophthalmia in elderly patients after cataract surgery.

METHODS

Clinical profile of patients

The clinical data of 84 elderly patients with xerophthalmia who received phacoemulsification in the Ophthalmology Department, of Leshan People's Hospital, Shizhong District between February 2019 and February 2021 were retrospectively analyzed. Forty (40) of the patients (control group) were given basic therapy involving anti-inflammatory drugs and sodium hyaluronate eye drops, while the remaining 44 patients (combination group) received rhEGF eye drops, in addition to sodium hyaluronate eye drops. This study was performed with permission from the Medical Ethics Committee of Leshan People's Hospital, Shizhong District, and was carried out in compliance with the guidelines of Declaration of Helsinki [11].

Inclusion criteria

Patients in the following categories were included in the study: patients with xerophthalmia after cataract surgery, those aged ≥ 60 years old, patients who had not received any drugs for xerophthalmia before enrolment, patients with complete clinical data, and those who provided signed informed consent forms after the objectives and protocols of the study were explained to them.

Exclusion criteria

The excluded patients were those with congenital lacrimal gland deficiency, those who had taken systemic antihistamines, anticholinergics, or other ophthalmic drugs orally in the previous month, and patients with comorbidities such as tumors, or serious diseases in vital organs such as heart, brain, liver, and kidney.

Therapeutic regimen for patients

After surgery, all patients received comprehensive care as well as conventional anti-inflammatory drugs. Moreover, all patients were given sulfacetamide sodium eye drops (Bengbu BBCA Tushan Pharmaceutical Co. Ltd, State Food and Drug Administration (SFDA) approval number: H34020141) at a dose of 2 drops 4 times per day. Patients in the control group were treated with sodium hyaluronate eye drops (Santen Pharmaceutical Co. Ltd, SFDA:

J20130150) at a dose of 1 drop thrice daily, while patients in the combination group received rhEGF eye drops (Guilin Pavay Gene Pharmaceutical Co. Ltd, SFDA: S20020016) at a dose of 1 drop given thrice daily, in addition to sodium hyaluronate eye drops. Treatment in both groups lasted 28 days.

Assay of levels of inflammatory factors

Serum levels of interleukin-6 (IL-6), hyper-sensitive C-reactive protein (hs-CRP), and tumor necrosis factor-α (TNF-α) in patients before therapy and after 28 days of therapy, were quantified using ELISA kits (Shanghai Biyuntian) in accordance with the manufacturer's protocols.

Indices of treatment

Primary indices

The two groups were compared with respect to tear break-up time (BUT), Schirmer test (Sit), and fluorescein corneal staining (FL) before and after therapy. In assessment of BUT, 1 % sodium fluorescein was dropped with a sterile glass rod into the conjunctival sac of the lower eyelid of the subject. The subject was required to blink several times and stare frontally. The time-lapse from uniform staining to the appearance of the first black spot on the cornea was recorded as BUT. Each subject was observed 3 times, and the average results were computed. In the Schirmer test (Sit), a tear detection filter paper folded 5 mm from the end, was placed in the conjunctival sac of the lower eyelid. The patient was required to gently close the eye for 5 min, after which the wetting length of the filter paper was measured. In FL test, the cornea was stained with fluorescein and examined under cobalt blue light. The corneal area was divided into four quadrants: supratemporal, supranasal, infratemporal, and infranasal areas. The corneal appearance was scored 0, 1, 2, and 3 points for no coloring, dot coloring, small flake coloring, and block coloring, respectively. The scores for each quadrant were summed up to get the final score.

Clinical treatment effectiveness was compared between the two groups after therapy. Clinical treatment efficacy was divided into four grades: cured (C), remarkably effective (rE), effective (E), and ineffective (iE). If the clinical symptoms disappeared, with Sit >10 mm/5 min, and FL staining was negative, the patient was classified as cured. If the symptoms were alleviated significantly, with Sit = 5 - 10 mm/5 min, and FL staining was negative, the treatment was remarkably effective. If the symptoms were relieved, with Sit < 5 mm/5 min, and FL staining was positive, the treatment was deemed effective. However, if there was no improvement in clinical symptoms, and FI was strongly positive FL, with Sit < 5 mm/5 min, the treatment was ineffective. Total effectiveness (TE) was calculated using Eq 1.

$$TE\ (\%) = \{(C+rE+E)/Tn)\}100 \quad \ldots\ldots\ldots (1)$$

where Tn = total number of cases

Secondary indices

The clinical data of the two groups were analyzed. The symptom scores of the two groups were compared using the Ocular Surface Disease Index (OSDI) questionnaire. Moreover, the serum levels of IL-6, hs-CRP, and TNF-α were compared between the two groups before and after therapy.

Statistical analysis

This study used SPSS 20.0 (Shanghai Cabit Information Technology Co. Ltd) for statistical analyses of data, while Prism 8 (Shenzhen SOFTHEAD Software Technology Co. Ltd) was used for preparation of Figures. Counted data are expressed as numbers and percentages (n (%)), and were analyzed using the chi-square (χ^2) test. Measurement data are presented as mean ± standard deviation (SD). Two-group comparisons were done using an independent-sample *t*-test, while comparisons within groups before and after therapy were done with paired sample *t*-test. Values of $p < 0.05$ denoted significant differences.

RESULTS

Clinical data

The profiles of the two groups of patients were similar, with respect to age, sex, course of cataract, body mass index (BMI), history of hypertension, as well as history and severity of diabetes ($p > 0.05$; Table 1).

Serum levels of IL-6, hs-CRP, and TNF-α

As shown in Figure 1, the serum levels of IL-6, hs-CRP, and TNF-α in the two groups decreased significantly after treatment ($p < 0.05$). However, the post-treatment levels of these parameters were significantly lower in the combination group than in the control group ($p < 0.05$).

Table 1: Comparison of baseline data between the 2 groups

Variable		Control group (n=40)	Combination group (n=44)	χ2	*P-value*
Age				0.255	0.614
	≥65 years	31	32		
	<65 years	9	12		
Gender				2.160	0.142
	Male	21	30		
	Female	19	14		
Course of cataracts				0.426	0.514
	≥3 years	29	29		
	< 3 years	11	15		
History of hypertension				0.032	0.857
	Yes	28	30		
	No	12	14		
History of diabetes mellitus				0.392	0.532
	Yes	20	25		
	No	20	19		
Severity of illness				0.210	0.647
	Moderate	18	22		
	Serious	22	22		

Levels of BUT, Sit, and FL

After treatment, BUT and Sit levels significantly increased in the two groups, while the FL index was significantly reduced ($p < 0.0001$). However, there were higher levels of BUT and Sit, and a lower level of FL index in the combination group than in the control group ($p < 0.0001$). These results are shown in Figure 2.

Symptom scores

Symptom scores were compared between the two groups. After therapy, scores on photophobia, acid distension and foreign body sensation in the two groups were significantly decreased, but there were significantly lower scores in the combination group than in the control group ($p < 0.05$). These data are shown in Figure 3.

Treatment effectiveness

As shown in Table 2, there were significantly better clinical curative effects and higher treatment effectiveness in the combination group than in the control group ($p < 0.05$).

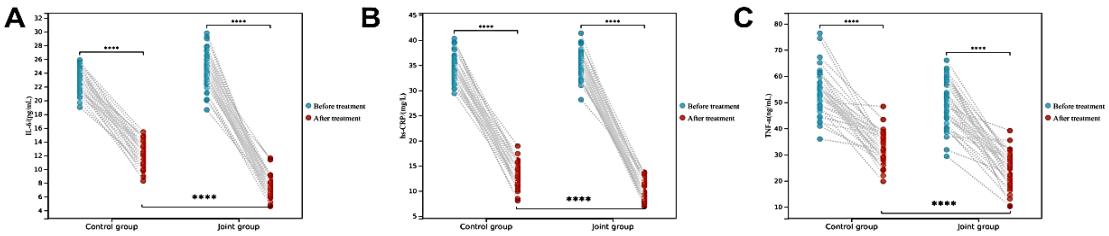

Figure 1: Serum levels of IL-6, hs-CRP, and TNF-α in patients before and after therapy. A. Comparison of serum IL-6 levels in patients before and after therapy. B. Comparison of serum hs-CRP levels in patients before and after therapy. C. Comparison of serum TNF-α levels in patients before and after therapy. ****$P < 0.0001$ (inter-group comparison)

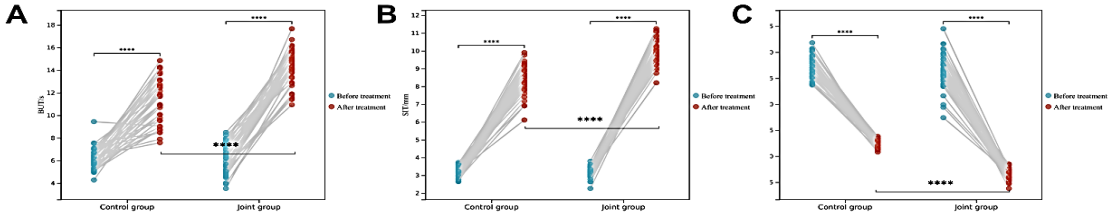

Figure 2: Levels of BUT, Sit, and FL in patients before and after therapy. A. Comparison of serum BUT levels in patients before and after therapy. B. Comparison of serum Sit levels in patients before and after therapy. C. Comparison of serum FL levels in patients before and after therapy. ****$P < 0.0001$ (inter-group comparison)

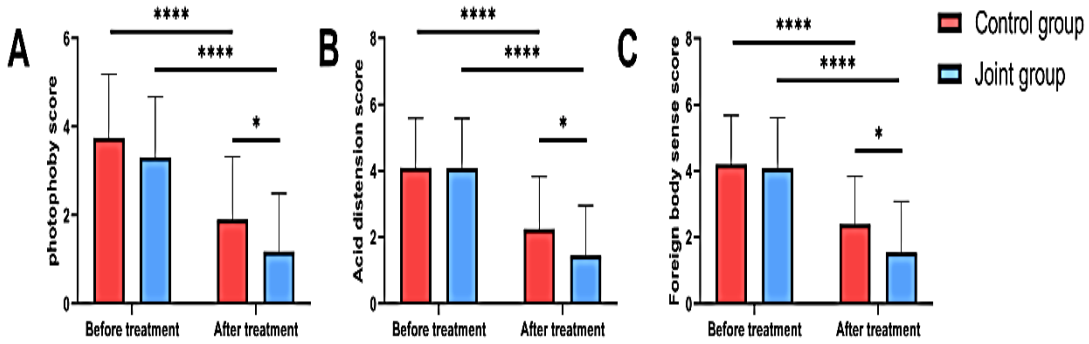

Figure 3: Comparison of symptom scores of patients before and after therapy. A. Comparison of photophobia scores in patients before and after therapy. B. Comparison of acid distension scores in patients before and after therapy. C. Comparison of foreign body sensation scores in patients before and after therapy. ****P < 0.0001 (inter-group comparison)

Table 2: Comparison of clinical treatment effectiveness between the 2 groups

Group	Cured	Remarkably effective	Effective	Ineffective	Total effectiveness {n (%)}
Control (n=40)	13	9	9	9	31 (77.50)
Combination (n=44)	22	10	9	3	41 (93.18)
χ^2/Z			-2.045		4.208
P-value			0.041		0.040

ISCUSSION

The problems associated with increases in global aging population have become increasingly serious over the past few years [12]. Cataracts occur frequently in the elderly. Phacoemulsification is a frequently-adopted therapeutic strategy for cataracts. It involves ultrasonic pulverization of the lens nucleus after suction, and implantation of the intraocular lens, and it has the advantages of a small incision, low tissue injury, and a favourable prognosis [13]. Xerophthalmia results from changes in tear film, injury to the corneo-conjunctival nerve, and inflammation [14]. Xerophthalmia not only worsens previous ocular surface diseases but also results in blindness [15]. Indeed, xerophthalmia occurs frequently after ophthalmic surgery. Moreover, with an increase in age, the symptoms of post-surgery xerophthalmia increase significantly, thereby compromising the effect of surgery and the quality of life of patients [16]. Therefore, the therapy for postoperative xerophthalmia is of particular medical importance.

Sodium hyaluronate eye drops are artificial tears which prevent loss of water from the eye surface, in addition to providing a stable tear film and moistening the eyeball, all of which relieve the symptoms of dry eyes and foreign body sensation in patients [17]. However, sodium hyaluronate eye drops contain a small amount of desiccant which irritates the cornea, especially if the drug is used for a long time. Moreover, prolonged use of sodium hyaluronate induces drug dependence in patients, resulting in unsatisfactory overall therapeutic effect. Therefore, in the clinics, xerophthalmia is often treated with other drugs. Recombinant human epidermal growth factor (rhEGF), a derivative of human epidermal growth factor, is a crucial growth-regulating protein in the eyes. It increases the number of corneal endothelial cells, specifically acts on the damaged part of cornea, and adheres to the conjunctiva, thereby alleviating corneal tissue damage, enhancing tear film stability, and relieving clinical symptoms in patients [18]. As of now, the clinical effect of xerophthalmia treatment using a combination of sodium hyaluronate and rhEGF is still controversial. Therefore, this study compared the effect of the combined use of two drugs on therapy of xerophthalmia. Firstly, the serum expressions of inflammatory factors were compared between the two groups before and after therapy.

Previous studies have demonstrated that inflammatory reaction is implicated in the pathogenesis of xerophthalmia. Inflammatory cytokines released during the healing of corneal incision also led to tear film instability which decreases corneal sensitivity. Increases in the serum levels of the crucial inflammatory factors i.e., IL-6, hs-CRP, and TNF-α directly reflect the

degree of inflammatory reactions in patients. It has been reported that high levels of IL-1, IL-6, and TNF-α in patients with ocular surface diseases interfere with their ocular surface homeostasis [19]. In the present study, patients in the combination group showed significantly lower post-treatment serum levels of IL-6, hs-CRP, and TNF-α than those in the control group, which indicated that the combined use of sodium hyaluronate and rhEGF effectively suppressed inflammatory reactions in patients.

Moreover, the indices: BUT, FL and SI were used for evaluating eye function in patients before and after therapy. Tear break-up time (BUT) is an index which reflects the stability of tear film; Sit is an index of abnormality in quality of tear secretion, while FL is an index of corneal surface defect. In this study, there were higher levels of BUT and Sit, and a lower FL level in the combination group, which indicated that the combined therapy was more effective in improving ocular function in the patients. In addition, OSDI questionnaire scores were significantly lower in the combined treatment group than in the control group, indicating that the combined therapy significantly alleviated xerophthalmia symptoms and significantly lowered the severity of ocular surface diseases. There were higher clinical efficacy and higher curative effect in the combination group than in the control group. Compared with earlier reports [19,20], it was found that the combination of sodium hyaluronate and rhEGF improved clinical treatment effectiveness in patients. Thus, the combined treatment was better in improving the stability of tear film, correcting the abnormal tear dynamics, and alleviating corneal surface defects than sodium hyaluronate alone.

Limitations of the study

Firstly, it was done retrospectively. Thus, the results obtained might be biased. Secondly, being a retrospective study, the patients could not be followed up since all the data acquired were obtained through electronic medical records. Therefore, there is need to carry out prospective research in the future to validate the conclusion of this present study.

CONCLUSION

The combined use of sodium hyaluronate and rhEGF improves treatment efficacy in elderly xerophthalmia patients after surgery, reduces inflammatory reactions, and enhances the alleviation of symptoms of the disease. However, a multi-center prospective study will be required in the future to validate the findings of this study.

DECLARATIONS

Acknowledgements

None provided.

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None provided.

Ethical approval

This study was performed with permission from the Medical Ethics Committee of Leshan People's Hospital, Shizhong District, China.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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