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Original Research Article

Efficacy of the combination of cyclosporine and sodium hyaluronate eye drops on dry eye syndrome

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Abstract

Purpose: *To investigate the efficacy and adverse effect of cyclosporine combined with sodium hyaluronate (SH) eye drops on dry eye syndrome (DES).*
Methods: *148 patients with DES treated in Nanjing Drum Tower Hospital Group Suqian Hospital, Jiangsu Province, China between January 2022 and February 2023 were randomly assigned to control (70 cases) and study groups (78 cases). Control group was treated with SH eye drop (1 drop each on both eyes 5 - 6 times a day, for 2 months), while study group was treated with both SH (the same dosage and use with control group) and cyclosporine eye drop (1 - 2 drops each for both eyes, 4 - 6 times a day, for two months). Tear film stability indices such as schirmer I test (SIT), tear break-up time (BUT) and corneal fluorescein stain (FL) of both groups were analyzed before and after therapy.*
Results: *There was no significant difference in BUT, SIT and FL score between the two groups before treatment. Compared with before treatment, BUT and SIT increased significantly ($p < 0.05$), while FL score dropped significantly in both groups after treatment ($p < 0.05$). After treatment, study group showed significantly higher BUT and SIT levels, and significantly lower FL score than control group ($p < 0.05$).*
Conclusion: *The combination of cyclosporine eye drops with SH eye drops is effective in treating DES. This combination regimen protects tear film stability, effectively alleviates DES symptoms, improves ocular surface and meibomian gland function, and also increases lacrimal river height, without increasing adverse reactions. Further studies will be required, to provide more evidence for clinical application of this combination regimen.*

Keywords: *Cyclosporine eye drop, Sodium hyaluronate eye drop, Dry eye syndrome, Efficacy, Adverse reactions*

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INTRODUCTION

Dry eye syndrome (DES) is a common ocular surface disease, of which the clinical manifestations include dry eyes, fatigue, red eyes, foreign body sensation, photosensitivity, and decreased tear secretion [1]. It is classified into primary DES and secondary DES. Primary DES refers to DES caused by decreased tear secretion, rapid tear evaporation or abnormal tear quality, which isn't associated with other systemic diseases; while secondary DES is triggered by other systemic diseases or pathological conditions [2,3].

Currently, due to the increasing time for people spending on digital equipment and indoor activities, the incidence of DES is growing annually, which is around 17.7 % in China [2]. Dry eye syndrome (DES) is closely associated with abnormal tear quality and dynamics, which reduces stability of tear film and causes uncomfortable eye symptoms [2,3]. Its underlying pathogenesis is related to the inflammatory reaction caused by ocular hypertonic environment. Corneal hypertonic environment induced by decreased tear secretion, rapid tear evaporation and abnormal tear quality activates inflammatory signal pathway, which triggers ocular surface inflammation and eventually causes DES [4].

Dry eye syndrome is primarily treated with drugs such as artificial tears or eye ointment to relief symptoms. Sodium hyaluronate (SH) eye drop, a kind of an artificial tear made by hydrophilic polymer, can relieve eye dryness, tingling, fatigue and blurred vision [5]. It effectively promotes the connection and extension of epithelial cells by effectively combining with fibronectin to effectively promote the healing of corneal epithelial injury [6]. Cyclosporine is a powerful immunosuppressant, which can alleviate the symptoms of dry eye in various ways, such as inhibiting the release of inflammatory mediators and preventing apoptosis of ocular surface epithelial cells [7]. Wirta *et al* [8] had reported that cyclosporine preparation effectively treats DES in clinics. However, there is paucity of information on the efficacy of cyclosporine in combination with SH eye drops in treatment of DES.

Therefore, this study investigated the efficacy and adverse reactions of cyclosporine in combination with SH eye drops on DES with the hope of providing more reliable reference for clinical treatment of DES.

METHODS

Patient data

A total of 148 patients with DES treated in Nanjing Drum Tower Hospital Group Suqian Hospital (Suqian city, Jiangsu Province, China) between January 2022 and February 2023 were retrospectively and randomly assigned to control (70 patients) and study groups (78 patients). Control group was treated with SH eye drop (1 drop each on both eyes, 5 - 6 times a day, for 2 months), while study group was treated with both SH (the same dosage and use with the control group) and cyclosporine eye drop (1 - 2 drops each for both eyes, 4 - 6 times a day, for two months). The study was conducted with permission from the Medical Ethics Committee of Nanjing Drum Tower Hospital Group Suqian Hospital (approval no. 2021016) and met the criteria in the Declaration of Helsinki [9].

Inclusion criteria

Patients meeting the diagnostic criteria of Chinese Expert Consensus of Clinical Diagnosis and Treatment of Dry Eye Syndrome and were diagnosed as primary DES [10], no allergic reaction to the drugs used in this study, and patients with complete clinical records.

Exclusion criteria

Patients diagnosed as secondary DES, patients with infectious eye diseases such as ocular allergy, cornea and conjunctiva, special diseases affecting lacrimal secretion or diseases with high risk factors for dry eye, such as Sjogren syndrome, Steve-Johnson syndrome, diabetes mellitus, and thyroid disease, history of ophthalmic operations, and had recently received eye drops or other ophthalmic drugs that may affect treatment outcomes.

Therapeutic regimen

In the control group, patients received 0.1 % SH eye drop (Zhejiang Jianfeng Pharmaceutical Co., Ltd.; SFDA approval no. H20063950; 5 mL: 5 mg). The drug was dropped to the conjunctival sac of both eyes (1 drop each time, 5 - 6 times a day for 2 months), and the number of drops was be increased or decreased according to patients' clinical symptoms [5].

In the study group, patients received 0.1 % cyclosporine eye drop (North China Pharmaceutical Co., Ltd., SFDA approval no. H20070106; 3 mL: 30 mg) in addition to SH eye drop. The usage and dosage of SH eye drops were same as those of control group. The drug (0.1 % cyclosporin) was applied to the conjunctival sac of both eyes, 4 - 6 times /day, 1 - 2 drops/time for 2 months, and the number of eye drops was increased or decreased based on the patients' clinical symptoms [8].

Evaluation of parameters/indices

Tear break-up time (BUT)

Rear film rupture time of each patient was recorded by DED-1L ocular surface analyzer (Chongqing Kanghua Ruiming Technology Co., Ltd.) before and after treatment [8].

Schirmer I test (SIT)

A tear test paper was placed in 1/3 part of the conjunctival sac of the patient's both eyes, and the patient was instructed to look straight ahead and then close the eyes. Then, the infiltration length of tears above the test paper was evaluated after 5 mins [11].

Corneal fluorescein stain (FL) score

A fluorescent test paper was placed in the conjunctival sac of the lower eyelid of both eyes, and the corneal staining was evaluated by cobalt blue light. A total of 3 points was assigned if the staining area was equal or over 1/2 of the total area; 2 points, if the staining area was equal or over 1/3 but less than 1/2 of the total; 1 point, if the staining area was less than 1/3 of total; 0 point, if the membrane on the cuticle was not stained [12].

Clinical efficacy

The clinical efficacy was evaluated after 2 months of treatment in both groups according to the following clinical efficacy criteria: *cured* (C), if monocular FL score was 0 points and SIT was greater than 10 mm with complete disappearance of clinical symptoms; *markedly effective* (ME), if monocular FL score was 1 point, and SIT was 5 - 10 mm with obvious alleviation of clinical symptoms; *effective* (E), if monocular FL score was 2 points, and SIT was less than 5 mm with partial alleviation of the clinical symptoms; *ineffective* (I), if the monocular FL score was 3 points, and SIT < 5 mm with clinical symptoms not alleviated but rather worsened. Overall response rate (RR, %) was calculated using Eq 1.

RR (%) = (ME+E+C) /N)100 ……. (1)

Where N is the total number of cases

Ocular surface disease index (OSDI)

The OSDI of each patient before and after 2 months treatment was evaluated and graded from 0 - 100 points. A higher score indicated more severe ocular surface disease [13].

Meibomian gland (MG) function

The MG function of the two groups before and after 2-months treatment was evaluated according to the following criteria: Level 1 (1 point which occurs when the meibomian margin is congested, irregular, thickened, dull and ectropion), level 2 (2 points which occurs when the opening of MG is blocked by yellow viscous secretion), level 3 (3 points which occurs when the compression of glands showed that lipid secretions are discharged), level 4 (4 points which occurs when excessive abnormal lipid is excreted, such as yellow, foamy, granular or toothpaste abnormal lipid).

Severity of dry eye syndrome

Symptoms of DES in every patient were assessed based on the following criteria: 0 points (no burning sensation, foreign body sensation and other symptoms), 1 point (occasional occurrence of the above symptoms), 2 points (intermittent or mild occurrence of the above symptoms), 3 points (continuous or serious occurrence of the above symptoms) [10].

Adverse drug reactions

Adverse reactions such as tingling or burning sensation, eye redness, itching of eyes and increased secretion were recorded in the two groups during treatment.

Lacrimal river height

The lacrimal river height was determined using a comprehensive ocular surface analyzer (Oculus Company, Germany [8].

Tear film lipid layer thickness (LLT)

The average tear film LLT of the two groups before and after 2 months treatment was evaluated using a LipiView II Ocular Surface Interferometer (TearScience, USA).

Statistical analysis

Statistical Packages for Social Sciences (SPSS version 22 software) and GraphPad Prism (version 8) was used for statistical analysis. Categorical data were presented in percentages, and differences compared using chi-square test. Measurement data were presented as mean ± standard deviation (SD) and comparison was conducted using student *t*-test. Differences within a group before and after treatment was compared using paired t-test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data of patients

There was no significant difference in sex, age, course of disease, body mass index (BMI), severity of DES, causes of DES and place of

residence between control and study groups indicating that the data are comparable ($p > 0.05$) (Table 1).

Tear film stability indices

There was no significant difference in BUT, SIT and FL between the two groups ($p > 0.05$) before treatment. After treatment, BUT and SIT levels increased significantly ($p < 0.05$), while FL score dropped significantly ($p < 0.0001$) in both groups when compared with before treatment. After treatment, study group showed significantly higher BUT and SIT levels ($p < 0.05$) and a significantly lower FL score ($p < 0.05$) compared to control group (Figure 1).

Table 1: Baseline data of the two groups

Factor		Study group	Control group	χ^2	*P*-value
Cases		**78**	**70**		
Age					
	< 55 years old	42	38	0.003	0.957
	≥ 55 years old	36	32		
Gender					
	Male	31	29	0.0435	0.835
	Female	47	41		
BMI					
	≥23 kg/m^2	29	30	0.496	0.481
	<23 kg/m^2	49	40		
Course of disease					
	1-4 weeks	51	41	0.728	0.394
	4-8 weeks	27	29		
Severity of dry eye syndrome					
	Light	43	36	0.203	0.652
	Heavy	35	34		
Causes of dry eye syndrome					
	Autoimmune diseases	52	40	1.423	0.233
	Injury	26	30		
Place of residence					
	Urban area	21	29	3.470	0.063
	Rural area	57	41		

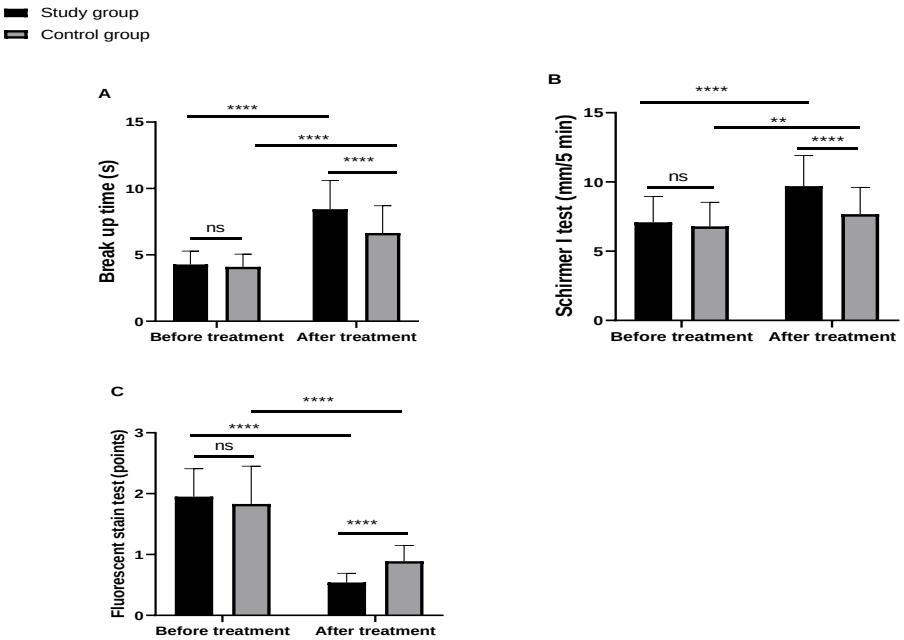

Figure 1: Comparison of tear film stability indices. (A) Between the two groups before and after treatment. (B) Schirmer I test level between the two groups before and after treatment, (C) Corneal fluorescein stain score between the two groups before and after treatment. $P > 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$. ns means not significant

Dry eye symptom score, OSDI, and MG function

There was no significant difference in dry eye symptom, OSDI and MG function scores between the two groups ($p > 0.05$). After treatment, dry eye symptom, OSDI, and MG function scores of both groups significantly reduced compared to before treatment ($p < 0.05$). Also, after treatment, study group showed significantly lower levels of dry eye symptom, OSDI and MG function scores compared to control group ($p < 0.05$) (Figure 2).

Lacrimal river height and tear film LLT

There was no significant difference in lacrimal river height and tear film LLT ($p > 0.05$) before treatment. However, after treatment, lacrimal river height and tear film LLT of both groups significantly increased compared to before treatment ($p < 0.05$). After treatment, study group showed significantly higher lacrimal river height compared to control group ($p < 0.05$). Tear film LLT was not significantly different between the two groups ($p > 0.05$) (Figure 3).

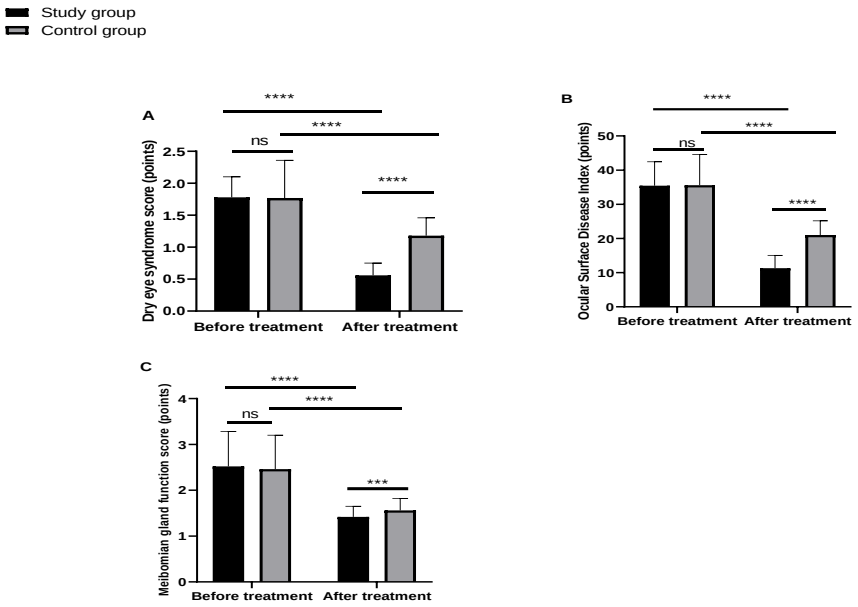

Figure 2: Dry eye symptom score, ocular surface disease index score and meibomian gland function score. (A) Dry eye symptom score between the two groups before and after treatment. (B) Ocular surface disease index score between the two groups before and after treatment. (C) Meibomian gland function score between the two groups before and after treatment. $P > 0.05$, ***$p < 0.001$, ****$p < 0.0001$. ns=not significant

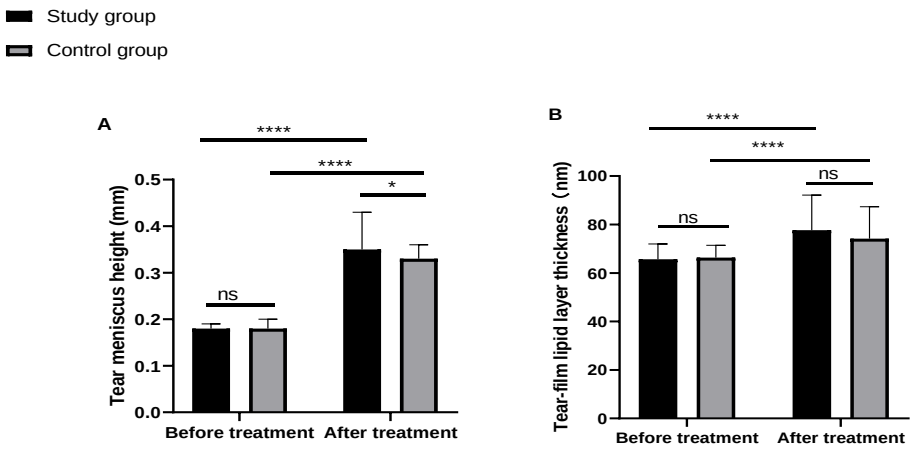

Figure 3: Comparison of lacrimal river height and tear film LLT. (A) Lacrimal river height between the two groups before and after treatment. (B) Tear film LLT between two groups before and after treatment. $P > 0.05$, *$p < 0.05$, ****$p < 0.0001$, ns=not significant

Table 2: Efficacy of the two groups N (%)

Group	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Study (n=78)	32 (41.03)	24 (30.77)	15 (19.23)	7 (8.97)	71 (91.3)
Control (n=70)	21 (30.00)	18 (25.71)	14 (20.00)	17 (24.29)	53 (75.71)
χ^2 value					6.366
P-value					0.012

Table 3: Incidence of adverse reactions in the two groups N (%)

Group	Tingling burning sensation	Eye redness and itching	Increased secretion	Adverse reactions
Study group (n=78)	1(1.28）	0(0.00）	1(1.28）	2(2.56）
Control group (n=70)	1(1.43）	1(1.43）	2(2.86）	4(5.72）
χ^2 value				1.015
P-value				0.314

Efficacy

Study group showed significantly higher overall response rate than control group ($p < 0.05$) (Table 2).

Adverse reactions

There was no significant difference in incidence of adverse reactions between the two groups ($p > 0.05$) (Table 3).

DISCUSSION

Dry eye syndrome (DES) is a multifactorial disease, which often triggers eye discomfort or visual impairment, along with different degrees of ocular surface epithelial lesions, inflammation and nerve sensory abnormalities. Due to inadequate knowledge and awareness of the severity of DES, few patients receive timely treatment in the early stage. It is already serious in most patients at the point of meeting a doctor, which seriously affects their quality of life [14]. Nowadays, widespread application of modern electronic products, wearing of contact lenses and abuse of eye drops also contribute to the high incidence of DES [15].

Dry eye syndrome (DES) is mainly treated by artificial tears, anti-inflammatory drugs, sex hormone drugs, traditional Chinese medicine extracts, autologous serum, wearing of bandages, contact lenses, wet room lenses, and surgery [16]. With features of non-Newtonian liquid, excellent biocompatibility, high viscosity and excellent lubricating and moisturizing effects, SH eye drops greatly improves patients' visual function, reduces photophobia, and restores integrity of corneal epithelium in a short time, thus effectively prolonging BUT [17].

As an immunosuppressant, cyclosporine plays a crucial part in inhibiting the release of inflammatory factors. Development and progression of inflammation runs through the whole process of DES, so cyclosporine is helpful in alleviating patient's symptoms [7,8]. However, the pathogenesis of DES is complicated, so a single treatment regimen is not sufficient and the combination of drugs may have a better therapeutic effect [18]. Therefore, this study investigated the efficacy and adverse reactions of cyclosporine eye drop combined with SH eye drop on DES.

Tear film stability indices are commonly adopted to evaluate severity of DES [19]. Tear film plays a crucial role in maintaining eye surface lubrication and nutrition, so its stability is highly essential for eye health. This study analyzed and compared the tear film stability indices of control and study groups before and after treatment. The results revealed that cyclosporine eye drop combined with SH eye drop can protect tear film stability in the treatment of DES and show better effect than SH eye drop alone. Also, the dry eye symptom, OSDI and MG function scores before and after therapy were also evaluated and the results indicated that cyclosporine eye drop combined with SH eye drop alleviates dry eye symptoms and improve ocular surface and MG function. In addition, using SH eye drop alone improved lacrimal river height and lipid layer, but the combination of cyclosporine and SH eye drop had a more significant effect. Furthermore, overall response rate revealed that combined use of cyclosporine and SH eye drops was more effective than single treatment with SH eye drops in treating DES.

Sall *et al* [20] revealed that spore-based dry eye therapy combined with artificial tears effectively alleviated symptoms of DES, which is in agreement with results of this study. Additionally,

there was no significant difference in incidence of adverse reactions between the patients who received cyclosporine in addition to SH eye drops and those who received SH eye drop alone. This finding indicated the combined treatment does not increase adverse reactions. This study has verified the great efficacy of combined application of cyclosporine and SH eye drops on DES without increasing adverse reactions.

Limitations of study

Small sample size used may not be adequate to generalize conclusions of the study. In addition, the study did not take into account the effect of different doses of the combined drugs in DES.

CONCLUSION

Combined application of cyclosporine and SH eye drops is effective in treating DES, protects the tear film stability, and alleviates DES symptoms. It also improves ocular surface and MG function, and elevates lacrimal river height, without worsening adverse reactions. Further studies on the combined application of cyclosporine eye drop and SH eye drop in DES are required, to provide more evidence for its in clinical practice.

DECLARATIONS

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Ethical approval

None provided.

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. Lei Shen and Nana Zhao conceived and designed the study, and drafted the manuscript. Xue Wang and Shuyan Qing collected, analyzed and interpreted the experimental data. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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