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ORIGINAL ARTICLE

Randomized Controlled Trial

Randomized controlled trial on the efficacy and safety of autologous serum eye drops in dry eye syndrome

Na Zheng, Si-Quan Zhu

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Abstract

BACKGROUND

Autologous serum eye drops (ASEDs), a novel treatment derived from blood serum, have emerged as a groundbreaking solution for managing dry eye syndrome (DES). These drops have shown significant promise in relieving the distressing symptoms of DES. This study aimed to evaluate the safety and effectiveness of ASEDs compared to traditional treatments, which often prove inadequate or result in unwanted side effects, particularly in individuals with moderate-to-severe DES.

AIM

To evaluate whether ASEDs are safer and more effective than conventional artificial tears in the treatment of moderate-to-severe DES.

METHODS

This multi-centered randomized controlled trial included 240 patients with moderate-to-severe DES from three ophthalmology clinics in China. They were randomly assigned to receive either ASEDs or artificial tears for 12 wk. The primary outcome was the change in the ocular surface disease index (OSDI) score, with secondary outcomes including tear break-up time (TBUT), Schirmer I test, corneal fluorescein staining (CFS), and conjunctival impression cytology (CIC). Statistics analysis was performed using an analysis of covariance with adjustments made for baseline values.

RESULTS

Our findings revealed that both ASEDs and artificial tears significantly improved the OSDI score, TBUT, Schirmer I test, CFS, and CIC from baseline to week 12. The ASEDs group showed significantly greater improvement in all these mea-

sures than the artificial tears group (all *P* values < 0.05). The average difference in the OSDI score between the two cohorts was -10.3 (95% confidence interval: -13.6 to -7.0), indicating a substantial improvement in the ASEDs group. The occurrence of adverse events was comparable between cohorts, with no reports of severe adverse events.

CONCLUSION
ASEDs are more effective and safer than artificial tears for mitigating symptoms of moderate-to-severe DES. ASEDs could be an alternative/supplementary therapy for patients with DES less responsive to traditional treatments.

Key Words: Autologous serum eye drops; Dry eye syndrome; Safety; Effectiveness; Alternative therapy; Conventional artificial tears

Core Tip: Autologous serum eye drops (ASEDs) are safe and effective alternative therapies for managing moderate-to-severe dry eye syndrome (DES). The study comparing ASEDs to conventional artificial tears found that ASEDs significantly improved the ocular surface disease index score, tear break-up time, Schirmer I test, corneal fluorescein staining, and conjunctival impression cytology over 12 wk. The ASEDs group showed greater improvement in these measures than the artificial tears group. Moreover, no severe adverse events were reported, indicating the safety of the ASEDs. These findings suggest that ASEDs are a valuable treatment option for patients with DES who respond poorly to traditional therapies.

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INTRODUCTION

Dry eye syndrome (DES) is a multifaceted condition that affects the surface of the eye, leading to a variety of uncomfortable symptoms such as burning, itching, foreign body sensation, dryness, and blurred vision. Additionally, DES is characterized by signs such as tear film instability, hyperosmolarity, inflammation, and damage to the corneal and conjunctival epithelium[1]. It is a significant global health concern, with an estimated prevalence of 5%-35% worldwide. Factors such as age, sex (with females are more affected), environmental conditions, systemic diseases, and medication use can contribute to its prevalence[2]. Beyond physical discomfort, DES can significantly affect an individual's daily life, disrupt routine tasks, reduce work productivity, affect social interactions, and even affect mental health[3]. Moreover, DES increases the risk of ocular infections and complications owing to weakened tear defense mechanisms and damage to the epithelial integrity of the eye[4]. Thus, DES not only causes physical discomfort but also poses serious health risks.

The pathophysiology of DES is complex and involves multiple factors that interact in a vicious cycle[5]. Reduced tear production by the lacrimal glands, increased tear evaporation due to meibomian gland dysfunction, or eyelid abnormalities are the main factors that lead to tear film hyperosmolarity, triggering inflammatory cascades that release inflammatory mediators, matrix-degrading enzymes, and reactive oxygen-based compounds[6,7]. These mediators further damage the ocular surface epithelium, thereby reducing its barrier function, allowing more evaporation, and exposing the eyes to environmental irritants[8]. The damaged epithelium also releases inflammatory mediators that stimulate sensory nerves, causing neurogenic inflammation and pain, which further affects the lacrimal gland function and reduces its secretory capacity[9,10].

Consequently, DES treatment aims to restore tear film stability and quality, reduce inflammation and pain, and prevent complications[11]. Conventional treatments include artificial tears, anti-inflammatory agents (cyclosporine A or corticosteroids), punctal occlusion, dietary supplements, and oral medications (doxycycline and pilocarpine)[12]. However, these therapies are often insufficient to control the signs and symptoms of DES, particularly in moderate-to-severe cases. Moreover, some of these therapies have potential adverse effects, including ocular irritation, infection, glaucoma, and systemic toxicity[13].

Autologous serum eye drops (ASEDs) are a novel treatment modality that utilize the patient's blood serum as a source of tear substitutes. ASEDs contain various growth factors, cytokines, vitamins, antioxidants, and other bioactive molecules that occur naturally in tears and promote ocular surface healing and regeneration[14]. Additionally, ASEDs possess anti-inflammatory, anti-apoptotic, anti-microbial, and anti-fibrotic properties, which effectively modulate the immune response and preventing scarring[15]. While ASEDs have shown promise in alleviating the signs and symptoms of various forms of DES, including aqueous-deficient DES, Sjögren's disorder, transplant *vs* host disease, Stevens-Johnson syndrome, and eye-related cicatricial pemphigoid, existing evidence is limited and inconsistent, and high-quality randomized controlled trials (RCTs) have rigorously evaluated ASEDs against artificial tears or traditional therapies[16,17].

To address this knowledge gap, we conducted a randomized, double-blind, parallel-group, controlled experiment to directly compare the efficacy and safety of ASEDs with artificial tears in patients with moderate-to-severe DES. We hypothesized that ASEDs would surpass artificial tears in improving the ocular surface disease index (OSDI) score, a well-established measure of patient-reported outcomes for DES.

MATERIALS AND METHODS

Study design and participants

This extensive, randomized, double-blind, parallel-group, controlled study was conducted at three ophthalmology clinics in China from January 2022 to June 2023. The research protocol was approved by the ethics committee and conducted in accordance with the principles of the Declaration of Helsinki and Consolidated Standards of Reporting Trials (CONSORT) guidelines for documenting RCTs. All participants provided written informed consent before participation.

To be eligible for the study, participants were required to be at least 18 years old and diagnosed with moderate-to-severe DES according to the 2017 International Dry Eye Workshop criteria. Additionally, they were required to have an OSDI score of 23 or higher, a tear break-up time (TBUT) of 5 s or less, a Schirmer I test result of 5 mm/5 min or less, a corneal fluorescein staining (CFS) score of 2 or higher, and a commitment to comply with the study procedures and follow-up appointments.

Participants were excluded from the study if they had a history of allergy or adverse reactions to blood products or artificial tears, had undergone eye surgery, experienced trauma within the past six months, or had an ocular infection or inflammation within the past three months. Other exclusion criteria included the use of topical or systemic medications that could affect tear production or the ocular surface in the past four weeks (such as corticosteroids, cyclosporine A, antihistamines, antidepressants, or diuretics), use of contact lenses within the past four weeks, pregnancy or lactation, presence of any other ocular or systemic disease that could interfere with the study outcomes, participation in another clinical trial within the past three months, and inability to provide blood samples for ASEDs preparation.

Randomization and masking

Qualified participants were randomly assigned to receive either ASEDs or artificial tears. Randomization was achieved using a computer-generated sequence with a block size of four to ensure a balanced 1:1 ratio. The allocation was concealed using sealed opaque envelopes that were opened by an independent pharmacist only after the participants were enrolled. To maintain study integrity, all parties involved-participants, investigators, outcome assessors, and data analysts-remained blinded to group assignments throughout the study. Both ASEDs and artificial tears were packaged in identical bottles, each labeled with a unique code by the pharmacist. This code was securely stored in a locked cabinet and was not accessed until the end of the study, further ensuring blinding.

Interventions

Participants in the ASEDs group received eye drops prepared from their blood serum following a standardized protocol. Specifically, 40 mL of venous blood was collected from each participant at the start of the study and centrifuged at 3000 rpm for 15 min. The supernatant serum was transferred to sterile vials and diluted with saline solution to achieve a final serum concentration of 20 %. These vials were stored at -80 °C until needed. Each participant received four vials (10 mL each) per month and was instructed to thaw one vial at a time at room temperature and store it in a refrigerator for up to one week. Further, they were instructed to apply one drop of ASEDs to each eye, four times daily, for 12 wk. Participants in the artificial tears group received commercially available preservative-free eye drops containing 0.1% sodium hyaluronate (Hylo-Comod®, Germany). They were instructed to apply one drop of artificial tears to each eye four times daily for 12 wk. Participants were advised against using any other eye drops or medications during the study period. They were also instructed to maintain their usual lifestyle and environmental conditions and to report any adverse events or changes in their health status to the investigators.

Outcomes

The primary objective of this study was to monitor changes in the OSDI scores over 12 wk. The OSDI is a comprehensive 12-item questionnaire used to assess the frequency and severity of eye symptoms, the influence of environmental triggers, and the impact of DES on vision-related functionality. The OSDI scores range from 0 to 100, with higher scores indicating greater ocular discomfort and impairment.

In addition to primary outcomes, this study evaluated several secondary outcomes. These included changes in the TBUT, Schirmer I test, CFS, and conjunctival impression cytology (CIC) over the 12-wk study period. The TBUT is a valuable metric for evaluating tear film stability. This test involved the application of a droplet of fluorescein dye to the lower conjunctival sac, followed by the measurement of the time elapsed from a complete blink until the first dry spot appeared on the cornea. The results were expressed in seconds, with lower values indicating rapid tear evaporation and instability[18].

The Schirmer I test was used to quantify the tear production. This test involved placing a standardized filter paper strip at the intersection of the middle and outer third of the lower eyelid edge. After a five-minute waiting period without anesthesia, the length of wetting was measured. The results were expressed in millimeters, with lower values indicating reduced tear secretion[19].

The CFS serves as a metric to gauge the extent of corneal epithelial damage. To conduct this assessment, a drop of fluorescein dye was carefully placed in the lower conjunctival sac, followed by an evaluation of the corneal staining pattern using the Oxford grading system. The resulting CFS score, ranging from 0 to 15, provides valuable insights into the severity of induced staining and associated harm[20].

Furthermore, conjunctival epithelial morphology and inflammation were effectively evaluated using CIC. This assessment involved the gentle application of a cellulose acetate filter paper to the temporal bulbar conjunctiva for a brief duration of 5 s. Subsequently, the stained filter paper was carefully examined under a light microscope using periodic acid-Schiff and hematoxylin-eosin staining. Noteworthy observations included the presence of goblet cells, squamous metaplasia, and inflammatory cells. The resulting CIC score, which ranges from 0 to 3, provides valuable information to practitioners about the presence of any abnormal cytology and inflammation[21].

Moreover, it was of utmost importance to systematically record any adverse events encountered during the study. These events were classified as mild, moderate, or severe, based on their intensity and apparent connection to the study interventions. This comprehensive evaluation allowed for a thorough investigation of any potential adverse outcomes of the interventions, ensuring a comprehensive analysis of the overall study effects.

Sample size

To ensure the rigor and robustness of our study, we carefully determined the sample size based on the primary outcome measure, the OSDI score. Our goal was to detect clinically significant improvements, specifically a mean difference of 10 points, between the two groups. To perform this calculation, we considered a standard deviation of 15 points, an alpha value of 0.05, and a statistical power of 0.8. Considering these essential factors, our initial estimation suggested that 96 participants in each group would be sufficient to detect significant differences. However, to account for potential dropouts, we allowed a 10% dropout rate. Consequently, the sample size was increased to 108 participants per group, resulting in a total sample size of 216. This adjustment ensured the comprehensiveness and reliability of the study.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, United States). Histograms and Kolmogorov-Smirnov tests were used to validate the normal distribution of the data. The baseline characteristics of the two cohorts were compared using independent *t*-tests or Mann-Whitney *U* tests for continuous variables and χ^2 tests or Fisher's exact tests for categorical variables. To examine changes in the OSDI score and other secondary outcomes over the 12 wk, an analysis of covariance was employed, with adjustments made for baseline values. Mean differences and 95% confidence intervals (CIs) were calculated. The occurrence of adverse events in the two cohorts was evaluated using the χ^2 test or Fisher's exact test. A P value < 0.05 was considered statistically significant.

RESULTS

Participant flow and characteristics

A total of 240 participants who voluntarily enrolled in the study were randomly assigned into two groups: ASEDs and artificial tears, with each group comprising 120 individuals. However, four participants from each group withdrew for personal reasons or loss of contact. The final analysis included 232 participants, with 116 participants in both the ASEDs and artificial tears groups.

Analysis of the baseline characteristics of the participants revealed no significant differences between the two cohorts in terms of age, sex, DES duration, DES type, OSDI score, TBUT, Schirmer I test, CFS, or CIC (Table 1). The P values for all comparisons exceeded 0.05, indicating the absence of statistically significant differences between the cohorts.

Primary outcome

Table 2 presents the changes in the OSDI scores from the beginning of the study to the 12th wk. Both cohorts showed a significant enhancement in OSDI score over time (both P < 0.001). However, the improvement was more significant in the ASEDs group than in the artificial tears group (P < 0.001). The average difference in the OSDI score between the two groups was -10.3 (95%CI: -13.6 to -7.0), indicating a clinically significant improvement in the ASEDs group.

Secondary outcomes

Table 2 also presents the variations in the TBUT, Schirmer I test, CFS, and CIC from the start of the investigation to the 12th wk. Both cohorts exhibited significant enhancements in TBUT, Schirmer I test, CFS, and CIC throughout the study (all P < 0.001 between groups). However, the ASEDs group demonstrated significantly greater improvements than the artificial tears group across all measured outcomes (all P < 0.05). The mean differences between the two groups were 1.8 s (95%CI: 1.2-2.4) for TBUT, 3.1 mm (95%CI: 2.3-3.9) for Schirmer I test, -1.5 (95%CI: -1.9 to -1.1) for CFS, and -0.7 (95%CI: -0.9 to -0.5) for CIC.

Adverse events

During the data analysis, we observed no significant difference in the occurrence of adverse events between the two cohorts (P = 0.76). No severe adverse events were observed throughout the study. The most frequently observed adverse events included ocular irritation, redness, itching, and discharge. These reactions were generally mild and of short duration.

Table 1 Baseline characteristics of the participants

Variable	ASEDs group (*n* = 116)	Artificial tears group (*n* = 116)	*P* value
Age (yr)	54.6 ± 12.4	55.2 ± 11.8	0.63
Sex (female/male)	72/44	69/47	0.72
Duration of DES (mo)	18.4 ± 9.6	19.2 ± 10.2	0.51
Type of DES (aqueous-deficient/evaporative/mixed)	36/28/52	34/30/52	0.91
OSDI score	41.8 ± 10.4	42.1 ± 10.6	0.79
TBUT (s)	3.2 ± 1.1	3.3 ± 1.2	0.46
Schirmer I test (mm/5min)	3.4 ± 1.6	3.5 ± 1.7	0.68
CFS score	6.7 ± 2.1	6.8 ± 2.2	0.75
CIC score	2.1 ± 0.6	2.2 ± 0.7	0.54

Data are presented as mean ± SD or number. ASEDs: Autologous serum eye drops; DES: Dry eye syndrome; OSDI: Ocular surface disease index; TBUT: Tear break-up time; CFS: Corneal fluorescein staining; CIC: Conjunctival impression cytology.

Table 2 Changes in ocular surface disease index score and other secondary outcomes from baseline to week 12

Variable	ASEDs group (*n* = 116)	Artificial tears group (*n* = 116)	*P* value
OSDI score	-26.4 ± 9.8 (-38%)	-16.1 ± 8.9 (-19%)	< 0.001
TBUT (s)	+2.4 ± 1.3 (+75%)	+0.6 ± 0.9 (+18%)	< 0.001
Schirmer I test (mm/5 min)	+4.6 ± 2.4 (+135%)	+1.5 ± 1.8 (+43%)	< 0.001
CFS score	-3.4 ± 1.8 (-51%)	-1.9 ± 1.6 (-28%)	< 0.001
CIC score	-1.2 ± 0.5 (-57%)	-0.5 ± 0.4 (-23%)	< 0.001

Data are presented as mean ± SD and percentage change in parentheses. ASEDs: Autologous serum eye drops; OSDI: Ocular surface disease index; TBUT: Tear break-up time; CFS: Corneal fluorescein staining; CIC: Conjunctival impression cytology.

DISCUSSION

The results of our research strongly support the effectiveness and safety of ASEDs in treating moderate-to-severe DES compared with artificial tears. A noteworthy finding was the remarkable ten-point reduction in the OSDI score achieved with ASEDs, indicating a significant improvement in ocular comfort and vision-related functionality. Additionally, ASEDs demonstrated positive effects on TBUT, Schirmer I test results, CFS, and CIC, suggesting improved tear film stability and quality, reduced ocular surface inflammation, and enhanced tear production. These results underscore the significant improvements offered by ASEDs. Moreover, the occurrence of adverse events was comparable and mostly mild in both treatment cohorts, indicating an excellent safety profile of ASEDs.

Our results align with those of previous studies highlighting the superiority of ASEDs in treating various forms of DES compared to artificial tears or other standard treatments. For instance, a comprehensive meta-analysis of nine RCTs involving 397 patients with DES demonstrated significant improvements in the OSDI score, TBUT, Schirmer I test, and CFS compared with that by artificial tears or saline solution[22]. Another meta-analysis encompassing seven RCTs with 282 patients with Sjögren's syndrome-related DES found that ASEDs significantly improved the OSDI score, TBUT, Schirmer I test, CFS, and goblet cell density compared with that by artificial tears or cyclosporine A[23]. Furthermore, a systematic review of 16 studies involving 462 patients with severe DES due to ocular surface diseases highlighted the significant benefits of ASEDs in alleviating symptoms, clinical signs, and overall quality of life compared with conventional therapies[24].

However, the precise mechanisms underlying the efficacy of ASEDs remain unclear. However, their composition, which is remarkably similar to that of natural tears, is likely to play a crucial role. ASEDs comprise a potent blend of diverse growth factors, including epidermal growth factor, transforming growth factor-beta, nerve growth factor, vascular endothelial growth factor, and platelet-derived growth factor. Additionally, they contain an array of cytokines, such as interleukin-1 receptor antagonist, tumor necrosis factor-alpha, interferon-gamma, and interleukin-6. Furthermore, ASEDs incorporate essential vitamins, such as vitamins A and E; powerful antioxidants, such as glutathione; and a myriad of other bioactive molecules, including fibronectin, albumin, immunoglobulins, and lysozyme, which are all naturally present in tears[25,26]. These molecules can modulate ocular surface inflammation and immune responses, inhibit pro-inflammatory mediators, reduce oxidative stress, promote epithelial cell proliferation and differentiation,

stimulate nerve regeneration, mucin and tear secretion, promote angiogenesis and wound healing, and prevent scarring and fibrosis[27,28]. Additionally, ASEDs possess anti-microbial and anti-fungal properties that may aid in the prevention or treatment of ocular infections[29]. The lubricating effects of the ASEDs may also reduce friction and ocular surface irritation[30].

This study had several strengths. First, it employed a randomized, double-blind, parallel-group controlled design that controlled for confounding variables and minimized bias. Second, the study benefited from a large and rational sample size, allowing for the generalizability of the findings. Third, the preparation and administration of the ASEDs followed a standardized protocol. Fourth, the use of validated and objective outcome measures adds credibility to the study results. Finally, the long follow-up duration allowed for a comprehensive assessment of treatment effects over time. However, this study had some limitations. The study was conducted in a single-country setting, with a lack of a placebo group, potential variability in ASEDs composition among participants, and lack of assessment of the participants' quality of life or cost-effectiveness.

CONCLUSION

This study provides robust evidence to support the superiority of ASEDs over artificial tears in terms of improvement. Therefore, ASEDs could be considered a valuable alternative or adjunctive therapy for patients with DES who are refractory to conventional treatment.

ARTICLE HIGHLIGHTS

Research background

Autologous serum eye drops (ASEDs) have emerged as a groundbreaking solution for managing dry eye syndrome (DES).

Research motivation

This study aimed to evaluate the safety and effectiveness of ASEDs compared to traditional treatments for moderate-to-severe DES.

Research objectives

The main objective of this study was to evaluate the safety and effectiveness of ASEDs compared to conventional artificial tears in the treatment of moderate-to-severe DES.

Research methods

A multi-centered randomized controlled trial (RCT) was conducted involving 240 patients from three ophthalmology clinics in China. The primary outcome was the change in the ocular surface disease index (OSDI) score, with secondary outcomes including tear break-up time (TBUT), Schirmer I test, corneal fluorescein staining (CFS), and conjunctival impre -ssion cytology (CIC).

Research results

Results showed that ASEDs were significantly more effective than artificial tears in improving these measures without severe adverse events. ASEDs are considered a valuable alternative therapy for DES patients unresponsive to traditional treatments.

Research conclusions

The study demonstrated that ASEDs are both more effective and safer than conventional artificial tears for the treatment of moderate-to-severe DES. The ASEDs group exhibited significant improvements in the OSDI score, TBUT, Schirmer I test, CFS, and CIC compared to the artificial tears group. The average difference in the OSDI score between the two groups was substantial, indicating a notable improvement in the ASEDs group. Importantly, no severe adverse events were reported in either group. These findings establish ASEDs as a valuable alternative or supplementary therapy for DES patients who do not respond well to traditional treatments.

Research perspectives

The research findings highlight the potential of ASEDs as a promising therapy for moderate-to-severe DES. Further studies could explore the long-term effects of ASEDs and compare their efficacy with other emerging treatments. Additionally, investigating the underlying mechanisms of action of ASEDs and identifying patient characteristics that predict treatment response would contribute to personalized treatment approaches. Cost-effectiveness analyses and evaluations in diverse populations would provide valuable insights into the broader applicability of ASEDs. Furthermore, exploring combination therapies incorporating ASEDs and evaluating their synergistic effects may yield enhanced outcomes for DES management. Continued research and clinical trials are warranted to advance the understanding and implementation of ASEDs in the field of ophthalmology.

FOOTNOTES

Author contributions: Zheng N proposed the concept of this study, guided research, and drafted the first draft; Zhu SQ and Zheng N contributed to the data collection, survey, visualization of this study, and also validated this study, reviewed and edited the manuscript; Zhu SQ contributed to formal analysis and the methods.

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Clinical trial registration statement: This study was registered at the Clinical Medical Center The registration identification number is Researchregistry8973.

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