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Ophthalmic Technology Assessment

Autologous Serum-Based Eye Drops for Treatment of Ocular Surface Disease

A Report by the American Academy of Ophthalmology

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Purpose: To describe the safety and effectiveness of using autologous serum-based eye drops for the treatment of severe dry eye and persistent corneal epithelial defect.

Methods: Literature searches of the PubMed and Cochrane Library databases were conducted most recently in March 2019. The searches identified 281 citations, which were reviewed in abstract form. Of these, 48 were selected for a full-text review, and 13 met the inclusion criteria and were assigned a quality-of-evidence rating by the panel methodologist. Eight of these studies were rated level II and 5 were rated level III; there were no level I studies.

Results: This analysis included 10 studies of the use of autologous serum-based eye drops for severe dry eye disease and 4 studies of persistent epithelial defect. Several studies showed good effectiveness, with some improvement in symptoms, signs, or both. Eight of the studies reported improved symptoms for severe dry eye disease, and all noted improvement in at least 1 clinical sign. For persistent epithelial defects, all of the studies showed improvement, with 3 of the 4 demonstrating an improvement rate of more than 90%. Adverse events were rare.

Conclusions: Although autologous serum-based tears may be effective in the treatment of severe dry eye and persistent epithelial defect, conclusions are limited owing to the absence of controlled trials. *Ophthalmology 2020;127:128-133*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Cornea and Anterior Segment Disorders Panel was to evaluate the safety and effectiveness of using autologous serum-based eyedrops for the treatment of ocular surface disease.

Background

Blood-derived products have been used for treatment of the ocular surface for decades. The first ophthalmic use reported in the literature was in 1975 for the treatment of ocular burns using an ocular perfusion pump to deliver a variety of solutions, including serum or plasma, to the ocular surface.[1] In 1984, the topical use of serum for the treatment of Sjögren's-related dry eye was reported.[2] In that study, 15 patients were given their own serum, diluted with preservative-free normal saline to 33% concentration, as a tear substitute for a 3-week period. All of the patients noted improved symptoms, and no adverse events were reported. The composition of serum is similar to that of tears produced by the lacrimal gland and includes a variety of components (epithelial growth factor, vitamin A, and others) that may contribute to a beneficial effect of serum tears on the corneal epithelium.[3,4] After further studies showed patient improvement and detailed the stability of some of the biochemical compounds within the serum,[3,5] the use of serum tears for ocular surface disease became more widely accepted. Over the past 20 years, treatment of ocular surface disease using autologous serum tears has expanded. Other topical treatments, including allogeneic serum, umbilical cord serum, platelet-rich plasma, plasma rich in growth factors, and nerve growth factor, have been investigated. Peer-reviewed studies of these topical treatments have been

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carried out for severe dry eye, nonhealing or recurrent epithelial defect, and neurotrophic keratopathy. This assessment focused on autologous serum-based eye drops and their use in severe dry eye and persistent corneal epithelial defect.

Food and Drug Administration Status

Because autologous serum-based eye drops are a blood product and not a pharmaceutical, they are not regulated by the United States Food and Drug Administration. Currently, there is no federal protocol and there are no requirements for the use or preparation of autologous serum-based eyedrops in the United States, although some states do have regulations.

Resource Requirements

There is no universal protocol for the production of autologous serum-based eye drops. In general, serum is obtained by routine blood draw with specialized serum-separating tubes. The blood is allowed to clot, after which the serum and solid components of the blood are separated by centrifugation. The serum then can be removed and diluted with either a balanced salt solution, preservative-free normal saline, or another sterile, preservative-free, eye-compatible solution at an appropriate concentration (the range of serum concentration in the literature is 20%−100%). As soon as they are formulated, these drops must remain frozen until ready for use and be refrigerated while in use.

Compounding pharmacies with the appropriate facilities can produce autologous serum eye drops, and some provide mail service. In some areas of the United States, eye banks have the facilities to compound autologous serum eye drops. Some ophthalmology offices provide this as a service to their patients, although regulations differ by state, so adherence to local standards of care should be ensured. Costs differ substantially between suppliers, and serum-based eye drops usually cost several hundred dollars for a 2- to 3-month supply. Insurance coverage varies greatly. Accessibility and cost are substantial barriers to the use of this treatment method.

Questions for Assessment

The purpose of this assessment was to address the following 2 questions: (1) Are autologous serum-based eyedrops safe and effective for the treatment of dry eyes? (2) Are autologous serum-based eyedrops safe and effective for the treatment of nonhealing corneal epithelial defect?

Description of Evidence

Literature searches of the PubMed and Cochrane library databases were conducted most recently in March of 2019. They identified 281 citations, which were reviewed in abstract form, and 48 were selected for a full-text review. Of these, 13 met the following inclusion criteria: (1) the study had to have 1 month or more of follow-up, and (2) the study population had to include 20 or more patients treated for severe dry eye disease or 15 or more patients treated for nonhealing epithelial defect. The inclusion criteria for nonhealing epithelial defect studies allowed fewer patients because large collections of patients with this condition are rare.

The panel methodologist (R.M.S.) assigned a level of evidence to each of the 13 articles that met the inclusion criteria based on the rating scale developed by the British Centre for Evidence-Based Medicine and adopted by the American Academy of Ophthalmology.[6] A level I rating was assigned to well-designed and well-conducted randomized clinical trials, a level II rating was assigned to well-designed case-control and cohort studies and lower-quality randomized clinical trials, and a level III rating was assigned to case series, case reports, and lower-quality cohort and case-control studies. Of the 13 studies, 8 were rated level II and 5 were rated level III. There were no level I-rated studies of autologous serum-based eyedrops found in the literature.

Published Results

Basic information about the 13 studies included in this analysis is summarized in Table 1. Table 2 provides more detailed information on outcomes for patients with severe dry eye disease or nonhealing corneal epithelial defect. None of the studies directly addressed the issues of cost or accessibility of the treatment.

Severe Dry Eye Disease

Ten of the studies evaluated the use of autologous serum-based eye drops for the treatment of severe dry eye.[7−16] These studies included patients with moderate to severe dry eye symptoms and signs, some of whom had Sjögren's syndrome or graft-versus-host disease, and all were resistant to conventional dry eye treatment options. All of these studies provided level II or III evidence, and most were case series or case-control studies. There were no randomized controlled studies found in the peer-reviewed literature. The 10 studies included patients with severe dry eyes resulting from multiple causes, used a variety of different serum concentrations, and included variable frequencies of eye drop use (Table 1). Despite these variations, the available evidence supports the effectiveness of topical autologous serum eye drops. Patient symptoms were assessed subjectively using a survey questionnaire symptom score. There was statistically significant improvement in the subjective symptom score in 6 of 10 studies,[7,8,10,13,14,16] and there was improvement that was not statistically significant in 2 studies.[9−11] One study reported no change in symptom scores,[15] and the final study did not report on patient symptoms.[12] At least 1 clinical measure of ocular surface disease (i.e., ocular surface staining, Schirmer testing, tear film breakup time, or cytologic analysis) showed statistically significantly improvement after treatment in 8 studies.[7,8,10,12−16] Only 1 of the studies

Table 1. Summary of Included Studies

Authors (Year)	Title	Level of Evidence	Dilution (%)	No. of Participants	Age (yrs; Mean ± Standard Deviation)	Gender (%; Female/Male)	Condition	Follow-up (mos)
Noda-Tsuruya et al[15] (2006)	Autologous serum eye drops for dry eye after LASIK	II	20	27	30±6	0/100	DED	6
Yoon et al[16] (2007)	Comparison of autologous serum and umbilical cord serum eye drops for dry eye syndrome	II	20	48	40±11	52/48	DED	2
Kim et al[17] (2012)	Effect of autologous platelet-rich plasma on persistent corneal epithelial defect after infectious keratitis	II	20	17	67	41/59	PED	1
Cho et al[8] (2013)	Comparison of autologous serum eye drops with different diluents	II	100	85	NR	61/39	DED, PED	3
Celebi et al[7] (2014)	The efficacy of autologous serum eye drops for severe dry eye syndrome: a randomized double-blind crossover study	II	20	20	56±8	190/10	DED	2
Hussain et al[9] (2014)	Long-term use of autologous serum 50% eye drops for the treatment of dry eye disease	II	50	63	61±11	83/17	DED	12
Hwang et al[10] (2014)	Comparison of clinical efficacies of autologous serum eye drops in patients with primary and secondary Sjögren syndrome	II	50	34	56±9	100/0	DED	1
Lopez-Garcia et al[13] (2014)	Autologous serum eye drops diluted with sodium hyaluronate: clinical and experimental comparative study	II	20	52	52±13	92/8	DED	2
Liu et al[12] (2015)	Effectiveness of autologous serum eye drops combined with punctal plugs for the treatment of Sjögren syndrome-related dry eye	III	20	28	56±14	89/11	DED	42
Lee and Chen[11] (2008)	Autologous serum in the management of recalcitrant dry eye syndrome	III	20	23	63±14	83/17	DED	17
Lekhanont et al[18] (2013)	Topical 100% serum eye drops for treating corneal epithelial defect after ocular surgery	III	100	181	62±14	51/49	PED	3
Semeraro et al[19] (2014)	Evaluation of the efficacy of 50% autologous serum eye drops in different ocular surface pathologies	III	50	15	40±17	NR	PED	4
Mahelkova et al[14] (2017)	Using corneal confocal microscopy to track changes in the corneal layers of dry eye patients after autologous serum treatment	III	20	26	51±14	73/27	DED	3

DED = dry eye disease; NR = not reported; PED = persistent epithelial defect.

reported visual acuity results with no changes noted after treatment.[13] Eight of the studies reported side effects or adverse events,[7–9,11–15] and only 1 study reported an adverse event of microbial growth measured in an eye drop bottle with no clinical sequelae.[8] No patient-reported negative symptoms from the treatments were noted. One study compared serum concentrations of 50% versus 100% and found that the 100% concentration was more effective in patients with Sjögren's syndrome yet was not better for other types of severe dry eye.[8] Another study compared the treatment effectiveness in primary versus secondary Sjögren's syndrome and suggested that autologous serum-based eye drops work better for patients with primary Sjögren's syndrome.[10] A different study compared the diluent (normal saline vs. sodium hyaluronate) and showed no statistical difference.[13]

Nonhealing Corneal Epithelial Defect

Four studies evaluated the use of autologous serum-based eye drops for the treatment of persistent corneal epithelial defect, 2 with level II evidence and 2 with level III evidence.[8,17–19] All showed substantial improvement in the epithelial defects, and 3 showed a reduction of more than 90% in the size of the defects.[8,18,19] A study comparing 50% versus 100% serum concentration found faster closure of the epithelial defects in patients using the 100% concentration eye drops.[8] In 1 study, a patient experienced a recurrence of the epithelial defect when the serum-based eye drops were discontinued.[19] In another study, 1 of the bottles of serum eye drops was found to have microbial growth that matched the bacterium (*Serratia marcescens*) cultured from the patient's corneal lesion.[8]

Table 2. Autologous Serum Results

Authors (Year)	Level of Evidence	Dilution (%)*	Condition	Follow-up (mos)	Visual Acuity	Surface Stain	Schirmer's Test Results	Tear Film Breakup Time	Cytologic Analysis Results	Persistent Epithelial Defect Healed (%)	Symptoms	Side Effects
Noda-Tsuruya et al[15] (2006)	II	20	DED	6	NR	Improved but not SSI	Unchanged	SSI	NR	NA	Unchanged	None
Yoon et al[16] (2007)	II	20	DED	2	NR	SSI	Unchanged	SSI	SSI	NA	SSI	NR
Cho et al[8] (2013)	II	50/100	DED	3	NR	SSI	SSI	SSI	NR	NA	SSI	MGB†
Celebi et al[7] (2014)	II	20	DED	2	NR	SSI	NR	SSI	NR	NA	SSI	None
Hussain et al[9] (2014)	II	50	DED	12	NR	Improved but not SSI	Improved but not SSI	NR	NR	NA	Improved but not SSI	None
Hwang et al[10] (2014)	II	50	DED (1° SS)	1	NR	SSI	NR	SSI	NR	NA	SSI	NR
		50	DED (2° SS)	1	NR	Improved but not SSI	NR	Improved but not SSI	NR	NA	Improved but not SSI	NR
Lopez-Garcia et al[13] (2014)	II	20/saline	DED	2	Unchanged	SSI	Improved but not SSI	SSI	SSI	NA	SSI	None
		20/hyaluronidase	DED	2	Unchanged	SSI	Improved but not SSI	SSI	SSI	NA	SSI	None
Liu et al[12] (2015)	II	20	DED	42	NR	SSI	Unchanged	SSI	NR	NA	NR	None
Lee and Chen[11] (2008)	III	20	DED	17	NR	Improved but not SSI	NR	NR	NR	NA	Improved but not SSI	None
Mahelkova et al[14] (2017)	III	20	DED	3	NR	SSI	NR	NR	NR	NA	SSI	None
Kim et al[17] (2012)	II	20	PED	1	NR	NR	NR	NR	NR	71	NR	NR
Cho et al[8] (2013)	II	50/100	PED	3	NR	SSI	SSI	Unchanged	NR	100	SSI	MGB‡
Lekhanont et al[18] (2013)	III	100	PED	3	NR	NR	NR	NR	NR	94	NR	None
Semeraro et al[19] (2014)	III	50	PED	4	SSI	NR	NR	NR	NR	100	SSI	None

DED = dry eye disease; MGB = microbial growth in bottle; NA = not applicable; NR = not reported; PED = persistent epithelial defect; SS = Sjögren's syndrome; SSI = statistically significantly improved.
*Percent autologous serum used.
†No clinical infection.
‡Correlated with microbe in corneal lesion.

Conclusions

Conclusive evidence on the safety and effectiveness of autologous serum-based tears is limited by the lack of controlled studies and by the variability in components of the study protocols. The limited accessibility and substantial cost of autologous serum-based eye drops create challenges for implementation, and therefore result in reserving their use either for more severe cases or for cases that have not improved using more readily available and less costly therapies. The results of the studies in the peer-reviewed literature suggest that this treatment is a reasonable option in refractory cases of dry eyes or nonhealing epithelial defects.

The primary safety consideration for autologous serum-based eye drops is the risk of microbial growth during storage, because serum-based solutions essentially are growth media. Care must be taken in the preparation of these eye drops to ensure that they are prepared in a sterile manner, and proper care and use instructions must be followed by patients to minimize contamination. Compounding pharmacies and eye banks have the equipment necessary to reduce the risk of contamination during preparation. Microbial contamination remains a considerable risk in patients who have a compromised ocular surface. Although no patients in the dry eye studies included in this assessment experienced any reported clinical adverse events, bacterial growth was reported in the eye drops of 2 patients with no adverse clinical consequence. A patient in 1 of the nonhealing epithelial defect studies demonstrated microbial infection of the corneal lesion, and the bacterium identified in the eye drop solution was the same as the bacterium identified from the corneal culture.[8]

Future Research

The existing peer-reviewed studies on the use of autologous serum-based eye drops are limited to observational designs and are mostly case series. A randomized controlled study would make it possible to evaluate the effectiveness of the treatment and to assess the optimal concentration and frequency of use of the drops for various ocular surface conditions. However, the low prevalence of persistent epithelial defects makes it unlikely that such a study will be conducted. It is also possible that further research may help to improve accessibility of serum-based eye drops. Further research also is warranted to develop greater understanding of the mechanism of action of serum-based eye drops and to target the specific components of serum that are most helpful to the ocular surface.

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Footnotes and Financial Disclosures

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