Long-term use of autologous serum eye drops for the treatment of dry eye disease

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A tear in the eye is a jewel.

-Arabian proverb

BACKGROUND

Dry eye disease is a common disorder which is caused by either decreased tear production, excessive tear evaporation and/or an abnormality in the production of mucins normally found in the tear film. Dry eye disease impacts nearly 5 million Americans 50 years and older[1] of all races and is more common in women than in men. Conventional treatments for dry eye disease include use of artificial tears and lubricating ointments, topical cyclosporine 0.05%, topical corticosteroids, therapeutic contact lenses and punctal occlusion[2]. However, none of these standard treatments supply growth factors or other essential components present in natural tears.[3] The use of autologous serum eye drops as a substitute for natural tears is based on the fact that most epithelial-promoting growth factors are found in both tears and serum. Human serum has a composition similar to tears and contains immunoglobulins, vitamin A, fibronectin and growth factors which promote epithelial health.[2,4-6] These factors are vital in maintaining the health of the corneal and conjunctival epithelium. Therefore, serum can serve as an excellent surrogate to tears.

Use of autologous serum eye drops was first reported by Fox et al [7] in 1984 for treatment of severe dry eyes, but it was not until the late 1990s that the use of autologous serum gained momentum. Since then, many studies have reported the beneficial effects of autologous tears for the treatment of dry eyes [8-15] and other ocular conditions.[16-21] The purpose of this study is to evaluate the long-term safety and efficacy of autologous serum eye drops in a large cohort of patients.

METHODS

A retrospective chart review was conducted of all patients at the University of Michigan Health System who used autologous serum eye drops from June 2008 to January 2013. This retrospective study was approved by the Institutional Review Board at the University of Michigan Medical School (IRBMED) and the University Human Subjects Review Committee (UHSRC) at the Eastern Michigan University. Records were reviewed for clinical history, systemic risk factors, dry eye etiology, patient symptoms and adverse events. Eye exams included:

Schirmer's testing with anesthesia:

The Schirmer test involves placing small strips of filter paper under the eyelid, closing the eyes and seeing how far down tears reach on the paper within five minutes. The greater the distance, the higher the natural tear production. In order to determine basal tear production, the eye is anaesthetized first. A score of 10 or more suggests normal aqueous tear production. The lower the score, the lower the tear production.

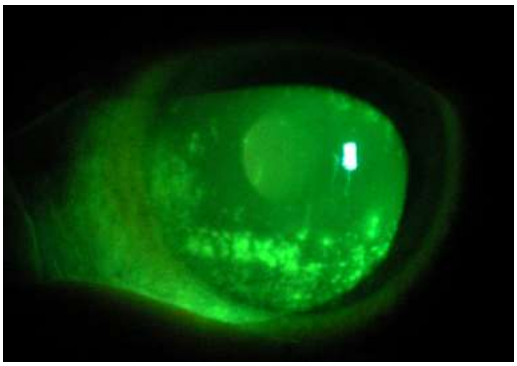
(http://www.dryeyezone.com/encyclopedia/schirmerlacrimationtest.html)

Fluorescein and Lissamine green staining:

(http://avserver.lib.uthsc.edu:8080/Medicine/eye_exam/page35.htm)

(http://www.eag2020.com/dry-eye-syndrome/)

Staining the tear film with fluorescein and/or lissamine green is commonly used for diagnosis of dry eye syndrome. Fluorescein and lissamine green is usually applied from a sterile strip moistened with a drop or two of sterile irrigating solution. The patient is instructed to look upward and the moistened strip gently touched to the lower lid margin. The patient is asked to blink several times to spread the dye. The eye is viewed through the slit lamp camera using a blue filter to illuminate the surface of the eye. Areas where the epithelium is disrupted will take up the dye and stain a bright yellow-green when viewed with a cobalt blue filter.

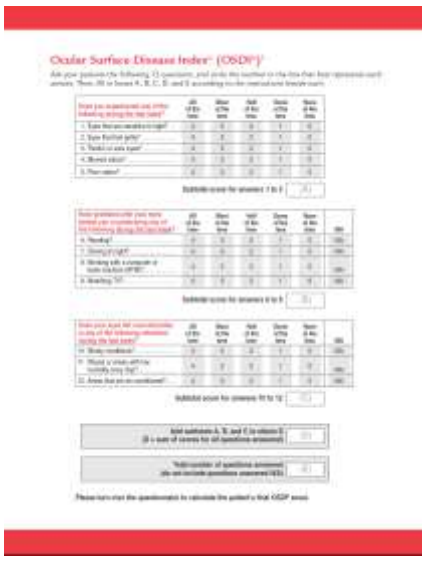


(http://health.allrefer.com/health/glaucoma-slit-lamp-exam.html)

(http://www.theeyepractice.com.au/optometrist-sydney/aer_you_experiencing_dry_eyes)

Ocular Surface Disease Index (OSDI):

The OSDI is a tool of 12 questions for dry eye patients to document their symptoms at different times of the year or under different treatment regimens.



(http://www.dryeyezone.com/encyclopedia/documents/OSDI.pdf)

All data were reviewed at baseline, 1 month and every 3 to 6 months during treatment with autologous serum. Paired t-tests were performed to compare progression of signs and symptoms of ocular surface disease with respect to baseline. P-value <0.05 was considered statistically significant.

Patients

One hundred twenty-three eyes of 63 patients were treated with 50% autologous serum eye drops four times per day for a minimum of 3 months with a mean follow-up of 12±11.4 (range 3 to 48) months. Patients included 11 (18%) men and 52 (82%) women. Mean age of patients was 61±11 years (range 40 to 93 years). Indications for autologous serum use included severe idiopathic dry eye disease in 40 (63%), Graft versus Host Disease (GVHD) in 11 (17.5%), Sjögren's syndrome in 11 (17.5%) and Steven Johnson Syndrome in 1 (2%) patients.

Table 1: Demographics of patients using Autologous Serum eye drops:

Number of patients	63
Age (Mean±SD)	61±11
Gender	
Male	11 (17.5%)
Female	52 (82.5%)
Indication	
Severe idiopathic Dry Eye Disease	40 (63%)
GVHD	11 (17.5%)
Sjögren's syndrome	11 (17.5%)
Steven Johnson Syndrome	1 (2%)
PROSE	21 (33%)
Mean serum tears use (months, range)	11.8 (3-48)

Twenty-one (33%) patients concurrently used the Prosthetic Replacement of Ocular Surface Environment (PROSE) device for management of severe dry eyes.

PROSE is used to treat patients suffering from complex corneal diseases. The prosthetic device rests on the white part of the eye, the sclera, and is composed of material that allows oxygen to reach the cornea. When inserted onto the eye, it is filled with saline that remains in the reservoir while the device is worn. The device creates a smooth surface over the damaged cornea and the saline provides lubrication and a healthy supply of

oxygen to the cornea, allowing the damage to heal with time. When the device is fitted properly, the pain disappears.
(http://www.kellogg.umich.edu/news/newsletter/fall2010/prose-lens.html)

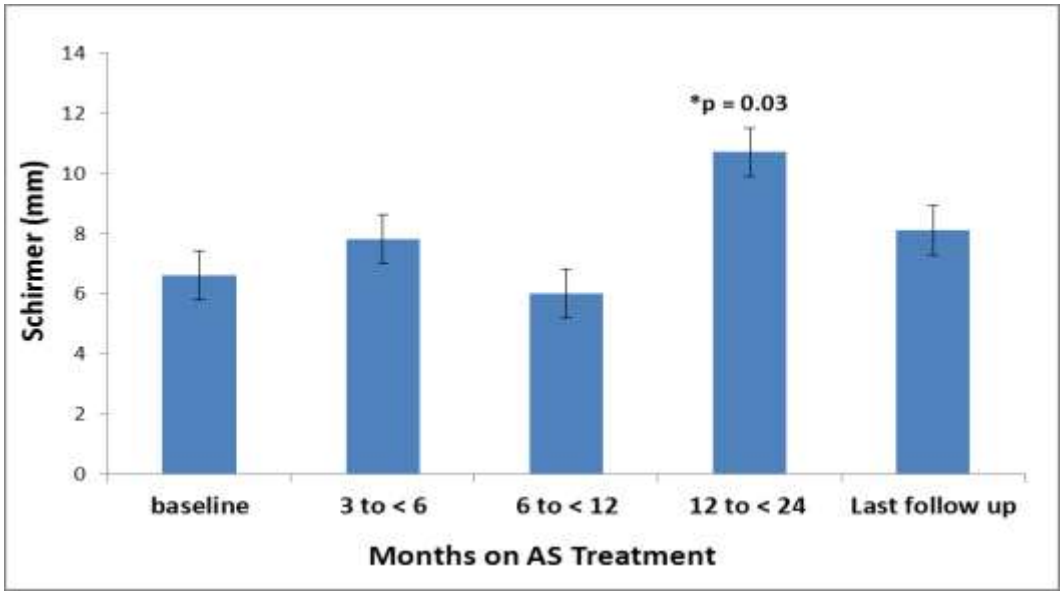
All patients were refractory to conventional treatments for dry eyes including maximal lubrication, topical corticosteroid, topical cyclosporine and/or punctal occlusion. Five (8%) patients discontinued serum tears use after a mean of 3 months due to transient or no improvement of symptoms. Four (6%) patients discontinued use of autologous serum eye drops due to its high cost after using it for an average of 8 (range 3 to 20) months.

Preparation of autologous serum eye drops

Autologous serum eye drops were prepared as follows: a total of 60 mL of blood was collected by venipuncture using 5 mL BD Vacutainer SST (Serum Separator Tubes) (Becton Dickinson, NJ, USA). The blood was allowed to clot for 15 minutes at room temperature after which it was spun at 14000 rpm for 15 minutes. The spun serum tubes were carried on ice by the patients to a local pharmacy which compounded the eye drops in an International Standards Organization (ISO) class 5 environment using proper aseptic techniques. The serum was diluted to 50% solution using sterile 0.9% sodium chloride. The solution was filtered using PaII filter and aliquoted in sterile 3 mL dropper vials. Patients were instructed to store unopened vials in the freezer (-20ºC) for up to 3 months and opened vials in the refrigerator (4ºC) for no longer than a week.

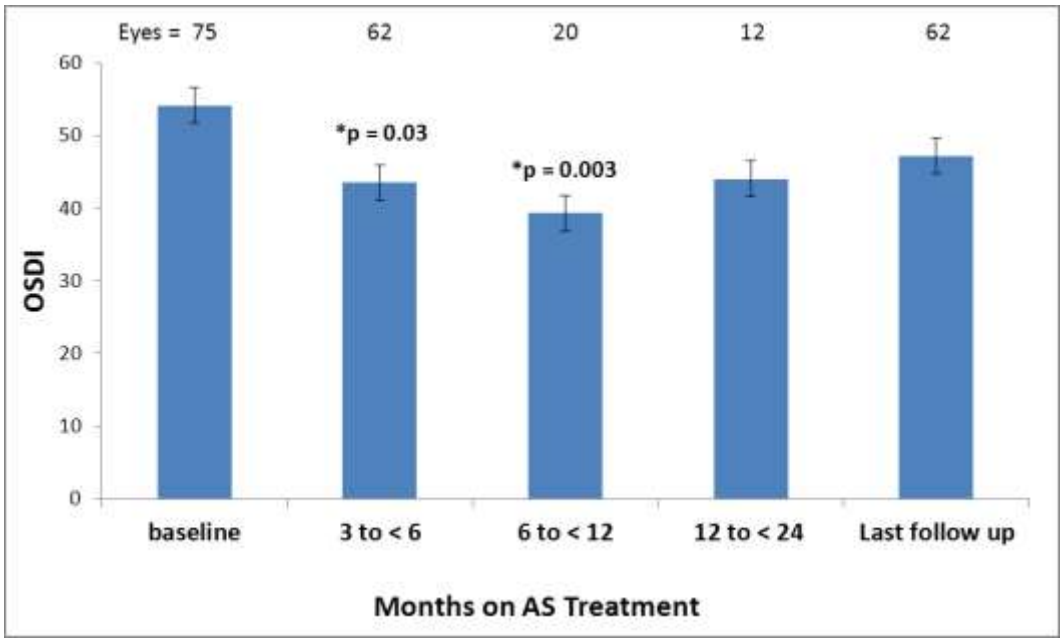
RESULTS

Figure 1a: Tear production by Schirmer with anesthesia:



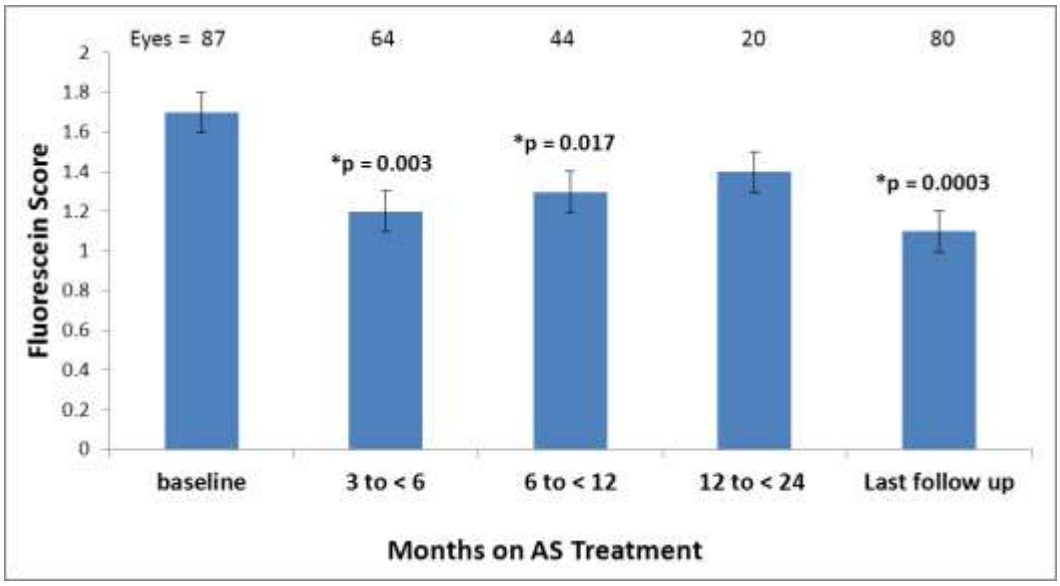
After treatment with autologous serum tears, the mean Schirmer score improved from 6.6 ± 6.5 mm to 10.7 ± 11.4 at the 12 to <24 month follow up visit (p=0.03). There was no difference in Schirmer scores from baseline at any of the other time point.

Figure 1b: Ocular Surface Disease Index Score:



OSDI scores improved at the 3 to <6 (mean= 43.5 ± 8.2, p=0.03) and 6 to <12 months follow up (mean= 39.3 ± 21.4, p=0.003) compared to baseline (mean= 54.1 ± 22.3). OSDI scores did not differ from baseline at the last follow up

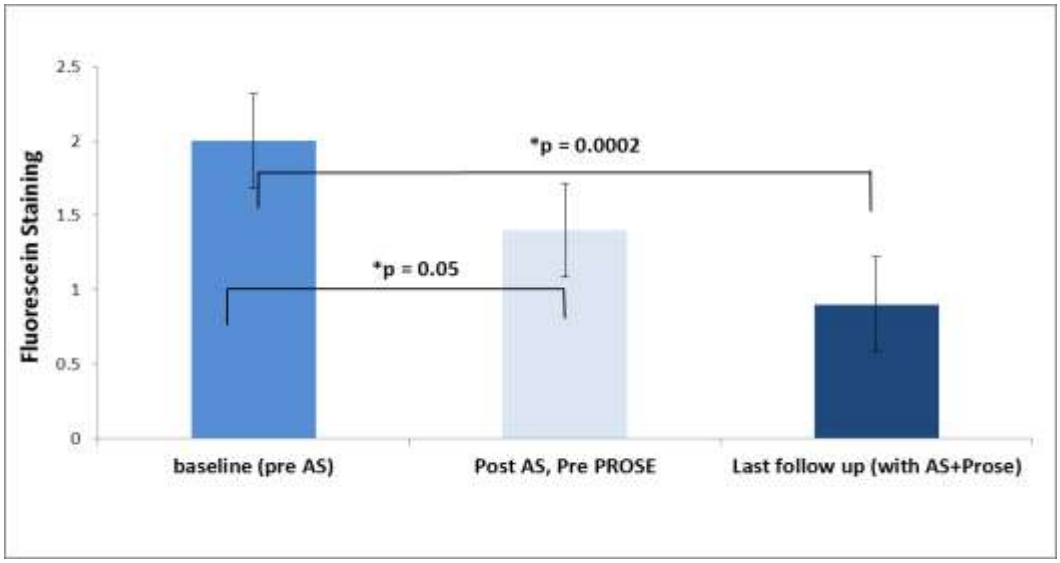
Figure 1c: Corneal Fluorescein Staining Score:



There was improvement in fluorescein staining from baseline (mean=1.7 ± 1.0) compared to the last follow up visit (mean=1.1, SD=1.1; p=0.0003). Fluorescein staining was also significantly improved at the 3 to <6 month (mean=1.2 ± 1.0, p=0.003) and 6 to 12 month (mean=1.3 ± 1.0, p=0.0017) follow-up compared to baseline.

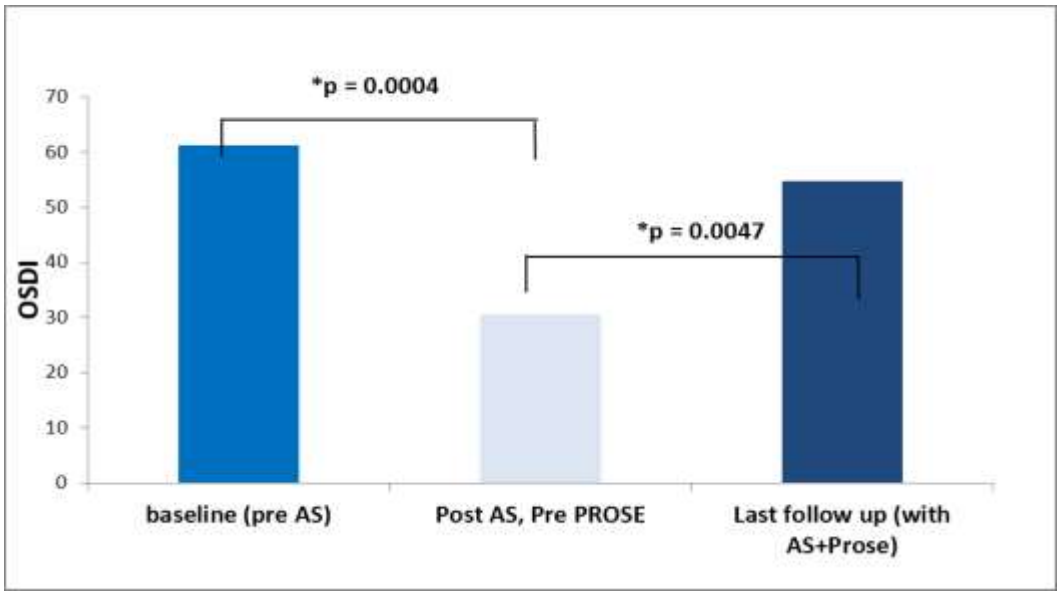
Twenty-one (33%) patients concurrently used PROSE for management of their dry eye symptoms with a mean of 8 (range 0-30) months after starting serum eye drops.

Figure 4a: Fluorescein stain in patients with concurrent PROSE use:



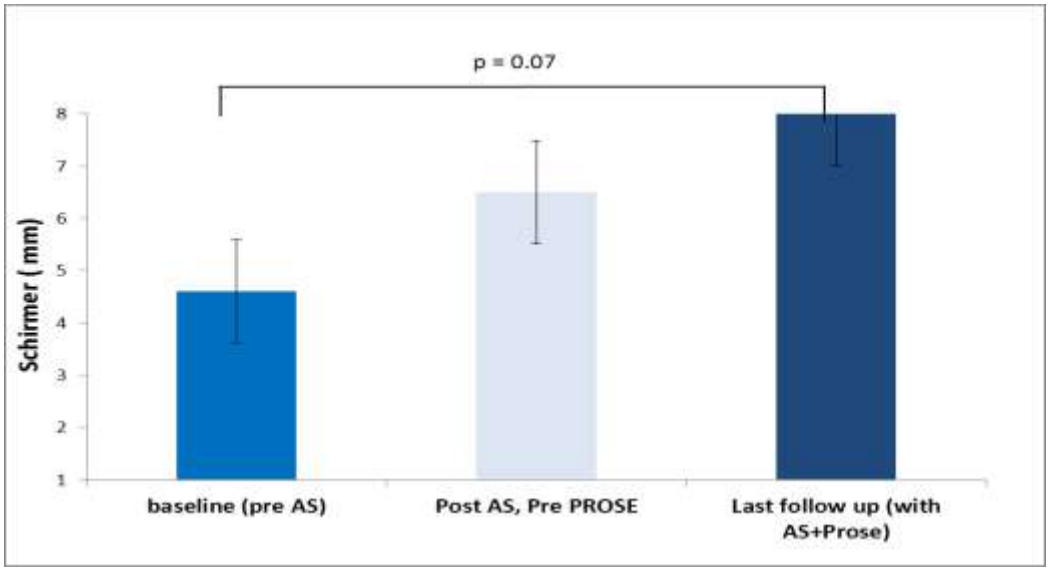
Fluorescein staining improved in patients using autologous serum prior to PROSE placement and at last follow-up after concurrent use of PROSE when compared to baseline (p=0.05 and p=0.0004, respectively).

Figure 4b: OSDI in patients with concurrent PROSE use:



OSDI scores improved in patients after starting serum drops and prior to PROSE placement (p=0.0004). However, OSDI scores went up significantly (p=0.005) at last follow-up after concurrent use of PROSE.

Figure 4c: Schirmer in patients with concurrent PROSE



Schirmer scores improved after start of serum eye drops and after concurrent use of PROSE although it was not statistically significant (Figure 4c). There was a trend towards improved schirmer scores in patients after concurrent use of PROSE when compared to baseline (p=0.07).

No adverse events associated with serum tear drops were noted in this study.

DISCUSSION

In this study, we investigated the safety and efficacy of long-term use of autologous serum eye drops in a large cohort of patients with dry eye disease who were refractory to conventional treatments. Schirmer scores and fluorescein staining improved in our population of patients, especially during the first year, and all patients reported subjective improvement after autologous serum use.

Previous studies have shown variable effectiveness of autologous serum for the treatment of dry eyes. A prospective, placebo-controlled study conducted by Tananuvat et al[10] treated 12 severe dry eye patients with 20% autologous serum drops in one eye and artificial tears in the fellow eye for 2 months. Although the authors noticed a trend toward improvement in cytologic changes in the autologous serum group, there was no statistical difference between the two treatments. Nobel et al[13] compared efficacy of 50% autologous serum tears and conventional treatment after 3 months in 16 patients in a prospective, randomized, controlled cross-over study. They reported improved impression cytology with the autologous serum treatment. When the treatment was reversed to conventional therapy, the cytological improvements were reversed. A retrospective chart review of 23 patients conducted by Lee[15] reported improved fluorescein staining in 74% and subjective improvement in 76% patients using 20% autologous serum for treatment of recalcitrant dry eye syndrome. A recent randomized crossover study[22] comparing 2 weeks treatment with 20% autologous serum compared to conventional artificial tears in 12 patients with severe dry eye syndrome found that patients treated with autologous serum showed significant improvement in OSDI scores compared to those treated with artificial tears. There were no significant changes in Oxford staining scores and tear break-up time between the two groups.

The variable effectiveness of autologous serum in published studies may be due to the variation in duration of treatment as well as concentration of serum eye drops applied ranging from 20% to 100%. Due to prior limited efficacy observed with 20% autologous serum at our institution (unpublished results), the standard practice has been to use50% serum drops which was well tolerated by the patients in this study. Although there have

been a few complications reported in the literature such as immunoglobulin deposits [23,24], presence of corneal infiltrates [17], conjunctivitis [9,10] and decreased corneal sensitivity [11] in patients using serum tears, the ratio of complications reported in the literature to the usage of serum eye drops is small. Further, there were no complications in our study population.

In the current study, 5 (8%) patients discontinued serum tears use after a mean of 3 months due to transient or no improvement of symptoms. Most studies in the literature report shorter length of follow-up of autologous serum drops ranging from 2 weeks to 6 months. Patients in the current study were followed for more than 48 months after starting autologous serum drops with no serious adverse events. Recently, Lee[15] and Botella[25] have reported follow-up periods of 55 and 42 months, respectively, with no complications.

In the current study, 21 (33%) patients used autologous serum drops in conjunction with using PROSE. These patients demonstrated a trend of improved fluorescein and schirmer scores after use of PROSE along with the serum eye drops, although it was not statistically significant. OSDI scores in this group of patients went up significantly after concurrent use of PROSE. This may be due to the fact these patients have very severe dry eyes to begin with and adjusting to the PROSE lenses may be an added challenge. To our knowledge, there are no previous reports of concurrent use of PROSE and autologous serum in the literature.

Despite the benefits, there are potential barriers to widespread use of autologous serum eye drops:

Risk of Infection: Since the serum eye drops are made preservative-free to avoid toxicity, the treatment includes potential risk of infection. There is a difference of opinion among compounding pharmacists about whether autologous serum should be filtered with a 0.22 micron or other filter. Some argue that subjecting the serum eye drops to filtration removes valuable blood components such as serum proteins during the process. Others consider filtration an important step to prevent bacterial infections. The serum eye drops used in this study were filtered through PaII filters as the high viscosity of the drops clogged the 0.22 micron filters.

Storage and stability: There have also been discrepancies regarding storage and stability of autologous serum eye drops. Some providers recommended storing the autologous serum in the freezer for a month while most others recommend storage no more than 3 months. A recent study has shown that the epitheliotrophic properties of autologous serum remain fairly stable after a prolonged storage of 6 months at -20ºC [26] . The serum eye drops in our study were utilized within 3 months, but in some cases, patients stored the serum eye drops at -20ºC for up to 6 months. There were no adverse events related to the storage or stability of serum eye drops in this study.

Blood draw: Frequent blood extractions are an inconvenience and yet another drawback of serum eye drops especially in patients requiring prolonged treatment. Chiang et al[27] have shown that in patients who need serum treatment but whose autologous serum is unavailable or unsuitable for use, allogeneic serum can offer an alternative. Allogeneic serum was not used in this study.

Cost: Autologous serum eye drops can be expensive. Most insurance carriers in the United States do not cover this treatment, thus patients generally have to pay out-of-

pocket for the serum eye drops. The local compounding pharmacy that majority of patients in this study utilized charged $175 to $250 for 2 months' supply of autologous serum eye drops. Four (6%) patients in the present study discontinued use of autologous serum eye drops due to its high cost after using it for an average of 8 (range 3 to 20) months. As such, there is a need for autologous serum eye drops to become a covered benefit for patients. A well-designed prospective study to test the safety, efficacy and cost of autologous serum eye drops at varying concentrations would help guide the development of appropriate therapeutic guidelines and allow for an evidence-based method of creating a standardized and cost-effective protocol for autologous serum production.

The present study is one of the first to evaluate efficacy of autologous serum tears in a large population of patients with a long duration of follow-up. Since the present study is a retrospective analysis, data for ocular evaluation was not available at specified time points for all patients. Also, it was not possible to assess the effect of solitary autologous serum drops due to the wide variety of previous or current treatments that the patients were on at the time of starting serum eye drops.

In summary, we conclude that autologous serum eye drops are safe and effective for long-term treatment of dry eye disease. It is a valuable option in patients with severe dry disease who have exhausted all other conventional forms of treatment.

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