Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

Autologous serum compared to artificial tear drops for dry eye disease

Franco Manzur Yarur[a,b], Gonzalo Ordenes[a,c], Andrea Cruzat[a,c,*]

[a] Proyecto Epistemonikos, Santiago, Chile
[b] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[c] Departamento de Oftalmología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

* **Corresponding author** andreacruzat@gmail.com

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Abstract

Introduction

Dry eye is one of the most common ocular surface disorders. Although artificial tear drops therapy is the most widely used treatment, it has recently been suggested that autologous serum could be a beneficial alternative treatment for this disorder, but its use is controversial.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE/PubMed, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified six systematic reviews, including seven primary studies overall, of which all were randomized trials. We concluded that autologous serum treatment might not lead to adverse effects compared to artificial teardrops, but the certainty of the evidence is low. On the other hand, we are uncertain whether autologous serum therapy improves the quality of life, severity of the pathology, pain or the corneal epitheliopathy grade compared to artificial tear drops as the certainty of the evidence has been assessed as very low.

Problem

Dry eye affects hundreds of millions of people worldwide. It is a chronic multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis. Several factors play an etiological role in this condition. These factors are tear film instability and hyperosmolarity, ocular surface inflammation, damage and neurosensory abnormalities[1]. Common symptoms are irritation or burning sensation, foreign body sensation, visual disturbances, blurred vision, photophobia and pain.

Artificial tears are the most commonly used treatment. However, artificial tears differ in their components from physiological tears. For this reason, other alternatives have been proposed that consider pathophysiology elements in their composition. One alternative is autologous serum.

Autologous serum contains several growth factors involved in the epithelial migration process, necessary for ocular surface repair and maintenance of tear stability. These factors are not present in artificial tears. Some of these factors are epithelial growth factor, nerve growth factor, fibronectin and vitamin A. It has also been shown that the use of autologous serum would inhibit the release

of inflammatory cytokines. This process would generate an environment that enables tear film stabilization, promoting epithelial migration and fibroblastic activation necessary for corneal repair[1]. However, its use is controversial.

Key messages

- The use of autologous serum may have no adverse effects (low certainty of the evidence).
- It is not possible to establish whether the use of autologous serum improves the quality of life, severity of dry eye, pain, or degree of corneal epitheliopathy because the certainty of the existing evidence assessed is very low.

About the body of evidence for this question

What is the evidence. See the evidence matrix in Epistemonikos below.	We found six systematic reviews[2-7], which included seven primary studies reported in eight references[8-15] of which, all are randomized trials.
What type of patients did the studies include? *	All trials included patients with dry eye[8-14]. The patients average age included in the trials was 46 years. Three trials[8,9,14] included patients with severe dry eye defined as Schirmer's test score less than five millimeters and tear film breakup time less than five seconds. Two trials[8,9] included patients with fluorescein staining scores greater than or equal to one on the Oxford scale. Only one trial included patients with dry eye due to Sjögren's syndrome[11]. One trial included only male patients with dry eye following surgery with the laser-assisted in situ keratomileusis technique[12]. Two trials did not define diagnostic criteria for dry eye[10,13]. Regarding exclusion criteria, one trial excluded patients with uncontrolled cerebrovascular or cardiovascular disease, history of refractive surgery, lactating or pregnant women[8]. Two trials excluded patients with any other ocular pathology, severe anemia, previous use of autologous serum or use of drops for other indications[8,9]. In addition, two trials excluded patients with a history of lacrimal occlusion or the use of contact lens[8,14]. The remaining trials reported no exclusion criteria[10-13].
What type of interventions did the studies include? *	All trials compared the use of autologous serum versus artificial tears[8-14]. Regarding differences in autologous serum concentration, five trials used 20% autologous serum[8-10,12,14], one trial used 50% autologous serum[11] and one trial used 40% autologous serum[13]. Regarding the frequency of autologous serum administration, two trials used autologous serum four times daily[8,9]. Two trials used autologous serum five times daily[11,12]. One trial used autologous serum six times daily[10]. The remaining trials did not report the frequency of autologous serum use[13,14].
What type of outcomes did they measure	The trials reported multiple outcomes, which were grouped by the systematic reviews as follows: • Pain, measured through a visual analog scale.

Methods

We searched Epistemonikos, the largest database of systematic reviews in health, which is maintained by multiple sources of information. These sources include MEDLINE/PubMed, EMBASE, and Cochrane, among others. We extracted and analyzed data from the identified reviews and primary studies. We generated a structured summary called FRISBEE (Friendly Summaries of the Body of Evidence using Epistemonikos), following a pre-established format with this information. This format includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analyses of all studies when possible, a summary table of results using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) method, and a section on other decision-making considerations.

	• Corneal epitheliopathy, measured through fluorescein staining. • Quality of life, measured using the ocular surface disease index questionnaire. • The severity of the pathology, measured through Schirmer's test and tear film breakup time test. • Adverse reactions. The average follow-up of the trials was three months, with a range between two weeks and 12 months.

*Information on primary studies is extracted from the identified systematic reviews, not directly from the studies unless otherwise specified.

Summary of results

Information on the effects of using autologous serum compared with artificial tears for dry eye is based on seven randomized trials[8-14] involving 271 patients.

Four trials measured quality-of-life (160 eyes)[8,9,11,13]. All trials measured dry eye severity by tear film breakup time test (481 eyes)[8-14]. Six trials assessed dry eye severity using the Schirmer test (456 eyes)[8-14]. Four trials measured corneal epitheliopathy (360 eyes)[8,10,12,14], and only one trial assessed pain (20 eyes)[14].

All trials evaluated adverse effects associated with the use of autologous serum[8-14]. However, no review allowed the extraction of data in a way that could be incorporated into a meta-analysis. Thus, the information on this outcome is presented as a narrative synthesis.

The summary of the results is as follows:

- It is not possible to establish whether autologous serum improves the quality of life because the certainty of the existing evidence has been assessed as very low.
- It is not possible to establish whether autologous serum decreases the severity of the condition because the certainty of the existing evidence has been assessed as very low.
- It is not possible to establish whether the use of autologous serum decreases pain because the certainty of the existing evidence has been assessed as very low.
- It is not possible to establish whether autologous serum improves the degree of corneal epitheliopathy because the certainty of the existing evidence has been assessed as very low.

The use of autologous serum may have no adverse effects associated with its use (low certainty in evidence).

Autologous serum compared to artificial tears for dry eyes

Patients Patients with dry eye
Intervention Autologous serum
Comparison Artificial tears

Outcomes	Absolute effect size*		Relative risk (95% CI)	Certainty in evidence (GRADE)
	WITH artificial tears	**WITH autologous serum**		
Quality of life**	32.9 points	22 points	--	⊕◯◯◯[1,2,4] Very low
	MD: -10.8 (Margin of error: 4.5 to -17.1)			
Severity***	Six trials (456 eyes)[8,10-14] reported that the use of autologous serum reduces the severity of pathology compared with artificial tears, based on the results obtained in the Schirmer test (MD: 1.1 millimeters; 95% confidence interval: 0.1 to 2.3). Seven randomized trials (481 eyes)[8-14] reported that the use of autologous serum compared with artificial tears reduces the severity of the pathology, as measured by tear film breakup time (MD: 2.5 s; 95% confidence interval: 1 to 4).		--	⊕◯◯◯[1,2,3,4] Very low
Pain****	-7.2 points	-19.2 points	--	⊕◯◯◯[1,3,5] Very low
	MD: -12 (Margin of error: 3.8 to -20.2)			
Epitheliopathy*****	3.5 points	2.7 points	--	⊕◯◯◯[1,2,3,4] Very low
	MD: -0.76 (Margin of error: -1.8 to plus 0.3)			
Adverse effects	Five systematic reviews[2,3,5-7] concluded that no adverse effects resulted from autologous serum use. None of the systematic reviews reported adverse events related to artificial tears use.			⊕⊕◯◯[1,3] Low

Margin of error: 95% confidence Interval (95% CI).
MD: Mean difference.
GRADE: Levels of evidence from GRADE *Working Group* (see below).

*The mean **WITH artificial tears** is based on the average of the control group in the studies. The mean **WITH autologous serum** (and its margin of error) is calculated from the mean difference (and its margin of error).

** Quality of life was measured using the ocular surface disease index scale. This scale consists of a self-administered questionnaire and gives scores ranging from 0 to 100 points according to the level of functionality, ocular discomfort and environmental factors. According to this score: from 0 to 12 is considered normal, from 13 to 22 is classified as mild dry eye, from 23 to 32 as moderate dry eye and over 32 is considered severe dry eye. The minimally important difference according to one study[16] for patients with severe symptoms would range from 7.3 to 13.4 points.

*** Severity outcome was measured using the Schirmer test and tear film breakup time. The former evaluates the amount of tear production in five minutes, after administration of topical anesthetic, through tear impregnation on a millimeter paper. It is considered pathological if the impregnation is less than five millimeters. The second test evaluates the quality and stability of the tear film by measuring the time it takes for the film to break. A value greater than 10 seconds is considered normal. If it is less than five seconds, it is considered frankly pathological.

**** Pain outcome was measured using a self-administered visual analog scale for pain ranging from 0 to 100 points. The lower limit of this scale represents no pain, and severe or unbearable pain is assigned 100 points. The results evaluated correspond to the difference in pain from baseline, according to the intervention used.

***** Epitheliopathy was measured using the fluorescein staining test, which evaluates the degree of damage and disruption of the corneal epithelium by dry eye. A score between 0 and 9 is given by visualizing the staining, with the higher the score corresponding to the more severe damage to the corneal epithelium.
[1] One level of certainty in evidence was lowered by considering the evidence as indirect, given the variability of autologous serum schedules used in the included trials.
[2] One level of certainty in evidence was lowered by inconsistency, given the variability in the results of the studies.
[3] One level of certainty in evidence was decreased due to the risk of bias, considering that selective reporting, randomization, blinding in outcome assessment, and blinding of patients and treating physicians were unclear among the included trials.
[4] One level of certainty in evidence was decreased for imprecision, since if we consider upper or lower boundaries of the confidence interval as true, this would lead to different decisions.
[5] One level of certainty in evidence was decreased for imprecision, since the number of patients included in this outcome was small.

Follow the link to access the interactive version of this table (Interactive Summary of Findings - iSoF)

About the levels of evidence (GRADE)*

⊕⊕⊕⊕
High: the research provides a very good indication of the likely effect. The probability that the effect is substantially different† is low.

⊕⊕⊕◯
Moderate: the research provides a good indication of the likely effect. The probability that the effect is substantially different† is moderate.

⊕⊕◯◯
Low: research provides some indication of the likely effect. However, the probability that the effect will be substantially different† is high.

⊕◯◯◯
Very low: research does not provide a reliable estimate of the likely effect. The probability that the effect is substantially different† is very high.

*This is also called 'quality of evidence' or 'confidence in the effect estimate'.

†Substantially different = a difference large enough to affect a decision.

Other considerations for decision-making

To whom this evidence applies and to whom it does not apply.

The evidence presented in this summary applies to adult patients with dry eye and patients with a fluorescein staining result greater than or equal to one.

The patients included in these trials are adults, so the results should be extrapolated with caution to the pediatric population in the absence of direct evidence.

The presented evidence does not apply to patients with a history of severe anemia, previous use of autologous serum or patients with previous ocular or eyelid pathology other than dry eye that required topical use of medications.

About the outcomes included in this summary

The authors of this summary consider that the outcomes selected are critical for decision-making. They are also in line with the outcomes reported by the identified systematic reviews.

Corneal epitheliopathy, quality of life and severity of dry eye outcomes are necessary for visual prognosis and associated long-term repercussions.

Pain and adverse effects are necessary to know the symptomatology, intervention efficacy and complications during treatment.

Harm/benefit balance and certainty in evidence

The use of autologous serum for dry eye may be safe compared to artificial tears, as the evidence shows little or no adverse effects.

Additionally, there is uncertainty on the benefits autologous serum could have on the quality of life, disease severity, pain or development of epitheliopathy, given the existing evidence.

Because of this, it is not possible to make an adequate balance between harms and benefits and other aspects such as costs. For this reason, patient and treating physician preference should be considered in decision-making.

Costs

Three systematic reviews have indicated that the cost associated with the monthly use of autologous serum for dry eye can reach hundreds of dollars[3,5,6].

However, it is not appropriate to perform a cost-effectiveness analysis until there is a proven benefit of the intervention.

What do patients and their caregivers think

In the face of the existing evidence, both patients and physicians should lean against the use of autologous serum as a first-line treatment for dry eye.

However, autologous serum could be a therapeutic alternative when initial treatment with environmental measures, artificial tears and pharmacological treatment has not worked.

The use of autologous serum could be reserved for a third stage in the stepwise treatment of dry eye.

Differences between this summary and other sources

This summary's conclusions are consistent with the identified systematic reviews[2-7]. While the intervention may have a role in dry eye treatment, the uncertainty of the existing evidence does not allow a clear conclusion of its benefits.

Although no clinical practice guidelines were found that make a direct comparison between the use of autologous saline and artificial tears, *Tear film and Ocular surface Society* and the American Academy of Ophthalmology guidelines[1,17] mention the use of autologous serum in situations of conventional treatment failure or severe symptoms. Thus, it is not a first-line alternative for dry eye treatment. Guidelines indicate first-line treatment should be education, non-pharmacological treatment and use of ocular lubricants if deemed necessary. In addition, guidelines mention that both the high cost required for autologous serum production and the lack of international standards for its production are barriers to widespread use. These factors generate variations in doses and schedules administered to patients.

Could this information change in the future?

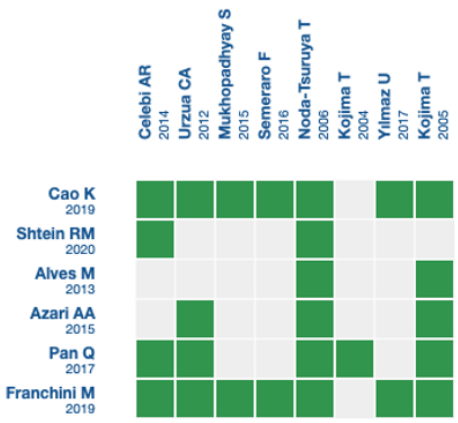
Given the uncertainty of existing evidence, it is likely that this summary's findings will change.

No systematic reviews were identified in the international systematic review registry platform, PROSPERO (International prospective register of systematic reviews), which evaluated the use of autologous serum versus artificial tears for dry eye treatment.

One randomized trial was found in the International Clinical Trials Platform of the World Health Organization. However, this trial was terminated prematurely without reporting results or conclusions[18].

How we conducted this summary

We collected all the relevant evidence for this question and presented it in an evidence matrix using automated and collaborative methods.



An evidence matrix is a table that compares systematic reviews that answer the same question.
The rows represent the systematic reviews, and the columns show the primary studies.
The green boxes correspond to studies included in the respective reviews.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they effectively answer the same question.

Follow the link to access the **interactive version**: Autologous serum compared to artificial tears for dry eye.

Authorship contributions
FMY: methodology, validation, formal analysis, research, resources, data processing, writing, visualization and fund acquisition. GO: conceptualization, methodology, validation, formal analysis, research, resources, data processing and writing. CA: conceptualization, research, resourcing, writing, oversight, administration and fund adquisition.

Competing interest
The authors declare no competing interest.

Ethics
This study did not have an ethics committee evaluation, given the use of secondary data sources.

Funding
There were no external sources of funding for this study.

Language of submission
Spanish.

Notes

If new systematic reviews on this topic are published after the publication of this abstract, a "new evidence" notification will be displayed at the top of the matrix. While the project provides regular updates of these abstracts, users are invited to comment on the Medwave website or contact the authors by e-mail if they believe evidence warrants an earlier update.

After creating an Epistemonikos account, by saving the matrices, you will receive automatic notifications whenever there is new evidence that potentially answers this question.

This article is part of the Epistemonikos evidence synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and an internal peer review process. Each of these articles corresponds to a summary, called FRISBEE (*Friendly Summary of Body of Evidence using Epistemonikos*), whose main objective is to synthesize the body of evidence of a specific question, in a friendly manner for physicians. The main resources are based on the Epistemonikos evidence matrix and the analysis of the result is based on the GRADE methodology. Further details of this FRISBEE elaboration method are described here.

The Epistemonikos Foundation is an organization that seeks to bring information closer to health decision-makers through the use of technologies. Its main source is the Epistemonikos database (www.epistemonikos.org).

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Postal address
Diagonal Paraguay 476
Santiago, Chile