Serum eye drops for the treatment of ocular surface diseases: a systematic review and meta-analysis

Massimo Franchini[1,2], Mario Cruciani[1,3], Carlo Mengoli[1,4], Giuseppe Marano[1], Enrico Capuzzo[2], Ilaria Pati[1], Francesca Masiello[1], Eva Veropalumbo[1], Simonetta Pupella[1], Stefania Vaglio[1,5], Giancarlo M. Liumbruno[1]

[1]Italian National Blood Centre, National Institute of Health, Rome; [2]Department of Haematology and Transfusion Medicine, "Carlo Poma" Hospital, Mantua; [3]Infection Control Committee and Antibiotic Stewardship Programme, AULSS9 "Scaligera", Verona; [4]"Fondazione per la Ricerca sulle Anemie ed Emoglobinopatie in Italia", Genoa; [5]Department of Clinical and Molecular Medicine, "Sapienza" University of Rome, Rome, Italy

Background. The use of blood-derived eye drops for topical treatment of ocular surface diseases has progressively increased in recent years.

Materials and methods. To evaluate the use of serum eye drops in ocular surface disorders, we performed a systematic search of the literature.

Results. In this systematic review, we included 19 randomised controlled trials (RCTs) investigating the use of serum eye drops in 729 patients compared to controls. For the quantitative synthesis, we included only 10 RCTs conducted in patients with dry eye syndrome comparing autologous serum to artificial tears. At 2-6 weeks, no clear between-group differences in Schirmer test (MD 1.05; 95% CI: −0.17-2.26) and in fluorescein staining (MD −0.61; 95% CI: −1.50-0.28) were found (very low-quality evidence, down-graded for inconsistency, serious risk of biases, and serious imprecision). Slightly higher increase in tear film break-up time (TBUT) scores in autologous serum compared to control (MD 2.68; 95% CI: 1.33-4.03), and greater decrease in ocular surface disease index (OSDI) in autologous serum compared to control (MD −11.17; 95% CI: −16.58 - −5.77) were found (low quality evidence, down-graded for serious risk of bias, and for inconsistency). For the Schirmer test, fluorescein staining and TBUT, data were also available at additional follow-up timing (2-12 months): no clear between-group differences were found, and the quality of the evidence was graded as low/very-low.

Conclusions. In patients with dry eye syndrome, it is unclear whether or not the use of autologous serum compared to artificial tears increases Schirmer test and fluorescein staining scores at short-term and medium-/long-term follow up. Some benefit at short-term follow up for the outcome of TBUT and OSDI was observed, but the quality of the evidence was low.

Keywords: ocular surface disease, dry eye syndrome, serum eye drops, autologous allogeneic umbilical cord blood.

Introduction

The idea of using blood-derived topical therapy in treating ocular surface diseases was first presented over 40 years ago by Ralph *et al.*[1]. They developed a mobile ocular perfusion pump to deliver autologous serum to the injured ocular surface of patients with chemical burns. Since then, many other authors have experimented the use of serum eye tears in a wide range of surface ocular diseases, mainly in the field of Sjögren syndrome-related dry eye, and have documented their direct effect, not only in alleviating symptoms, but also in promoting the re-epithelisation process[2-12].

Blood-derived eye drops may be autologous, i.e. prepared from patients' own peripheral blood (such as autologous serum, platelet-rich plasma and platelet lysate) or homologous, i.e. prepared from donors (such as allogeneic peripheral blood serum and umbilical cord blood serum)[3]. The biochemical properties of autologous serum eye drops resemble those of human tears. In particular, they contain several growth factors, including epidermal growth factor, transforming growth factor-β and platelet-derived growth factors, nutrients and proteins that allow tissue repair and regeneration to take place[13,14]. These characteristics form the basis of the increasing clinical use of autologous and homologous serum eye drops in ophthalmology seen over the last 20 years.

The purpose of this systematic review and meta-analysis is to summarise the existing literature on the use of serum eye drops in ocular surface alterations in order to assess their potential clinical benefit[15-33].

Material and methods

Search strategy

A computer-assisted literature search of the MEDLINE (through PUBMED), EMBASE, SCOPUS, OVID and Cochrane Library electronic databases was performed (last accessed March 30, 2019) to identify studies on the use of serum eye drops in ocular surface diseases. A combination of the following text words was used to maximise search specificity and sensitivity: "serum eye drops", "blood-derived" AND "autologous" AND "homologous" AND "allogeneic" AND "cord blood" AND "platelet-rich plasma" AND "ophthalmology" AND "dry eye" AND "Sjögren syndrome" AND "ocular surface alterations" AND "corneal" AND "superficial ocular disease" AND "randomised controlled trial". In addition, we checked the reference lists of the most relevant items (original studies and reviews) in order to identify potentially eligible studies not captured by the initial literature search.

Study selection and inclusion criteria

Study selection was performed independently by two reviewers (MF and MC), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (CM). Eligibility assessment was based on the title or abstract and on the full text if required. Articles were eligible for this systematic review and meta-analysis if they reported the use or serum eye drops in surface ocular disease either in the title or in the abstract. The other inclusion criteria required that the article should be: i) original; ii) report a randomised control trial (RCT); iii) published in full in English between 1999-2019. For studies using a cross-over design, we summarised data according to Curtin *et al.*[34], using parallel data from the first cross-over period and paired data from both cross-over periods. In the qualitative analysis (bias assessment, see *Online Supplementary Content, Table SI*) of this systematic review, we included studies investigating autologous serum compared to controls in ocular surface disease. However, for the quantitative synthesis, we only included studies that compared autologous serum to artificial tears in dry eye syndrome and reported usable outcomes data. Studies enrolling less than ten patients were excluded.

Data collection and analysis

For each RCT included in the systematic review, the following data were extracted by two reviewers (MF and MC) independently: first author, year of publication, type of ocular surface disease, details of intervention in study and control group, sample size, mean age and male/female ratio, outcome measurements, follow up period and main results. Measures of treatment effect were mean differences (MD) together with 95% confidence intervals (CI). For this measure, the score had to be reported as mean and standard deviation (SD); when studies reported other dispersion measures such as standard error (SE) of the mean or 95% CI of the mean, we calculated the SD in order to perform the relevant meta-analytical pooling[35]. We used final scores in preference to change in scores or cumulative incidence. Primary outcomes included Schirmer test, tear film break-up time (TBUT), fluorescein staining and ocular surface disease index (OSDI). The unit of analysis was the eye. The study weight was calculated using the Mantel-Haenszel method. We assessed statistical heterogeneity using t^2, Cochran's Q and I^2 statistics. The I^2 statistic describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error. In the case of no heterogeneity (I^2=0), studies were pooled using a fixed-effects model. Where values of I^2 were >0, a random-effects analysis was undertaken[36]. All calculations were made using Stata 15.1, R v.3.4.3 (StataCorp LLC, College Station, TX, USA), and REVMAN 5[37]. Disagreement was resolved by consensus and by the opinion of a third reviewer (CM), when necessary.

Assessment of risk of bias in included studies

Two review Authors (MF, MC) independently assessed the risk of bias of each included study following the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions[37]. They discussed any discrepancies and achieved consensus on the final assessment. The Cochrane "Risk of bias" tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other issues relating to bias. We have presented our assessment of risk of bias using two "Risk of bias" summary figures: 1) a summary of bias for each item across all studies; and 2) a crosstabulation of each trial by all of the "Risk of bias" items.

"Summary of findings" tables

We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes, and constructed a "Summary of findings" table using REVMAN 5. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of available data for the main outcomes[38]. The "Summary of findings" tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The certainty of a body of evidence involves consideration of within-trial risk of

bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias[39]. When evaluating the "Risk of bias" domain, we down-graded the GRADE assessment when we classified a study as being at high risk of bias for one or more of the following domains: selection, attrition, performance, detection, reporting, and other bias; or when the "Risk of bias" assessment for selection bias was unclear (this was classified as unclear for either the generation of the randomisation sequence or the allocation concealment domain). We have presented the following outcomes in the "Summary of findings" table: Schirmer test, TBUT, fluorescein test and OSDI.

Results

In this systematic review, we included 19 RCTs investigating autologous serum compared to controls[15-33]. A total of 729 patients were evaluated. The main characteristics of the included studies are summarised in Table I. The study flow chart is summarised in Figure 1. For the quantitative synthesis, we included only ten studies conducted in 353 patients with dry eye syndrome comparing autologous serum to artificial tears and reporting usable outcomes data[15,17,18,20,22,26-28,30,31].

Risk of bias in included studies

Ten studies (50%) were at high risk of bias for one or more domains, and 16 studies (80%) were at unclear risk of bias for one or more domains; three studies[22,23,26] were judged at low risk of bias in all the domains (Figures 2 and 3).

Sequence generation and allocation concealment

Randomisation depends on two important aspects: adequate generation of the allocation sequence and concealment of the allocation sequence until assignment occurs. We assessed three studies as being at high risk of selection bias, as the random sequence generation was by odd or even numbers, or based on date of admission, so the intervention allocations could have been foreseen in advance[15,31,32]. For the random sequence generation, the reports of another nine studies were at unclear risk of bias, while seven studies were judged at low risk[16,21-23,26,27,29]. For allocation concealment, 13 studies were judged at unclear risk of bias, and four studies[22,23,25,26] at low risk of bias.

Blinding

Nine studies (45%) were reported as open label, and they were graded as high-risk of performance bias (blinding of participants and personnel). Four studies were graded as unclear risk of performance bias due to the fact that they did not provide information to allow judgement to be made about high or low risk of bias related to the blinding of participants and personnel[19,20,24,33]. Seven studies were judged at low risk of performance bias since both patients and investigators were masked to group of intervention

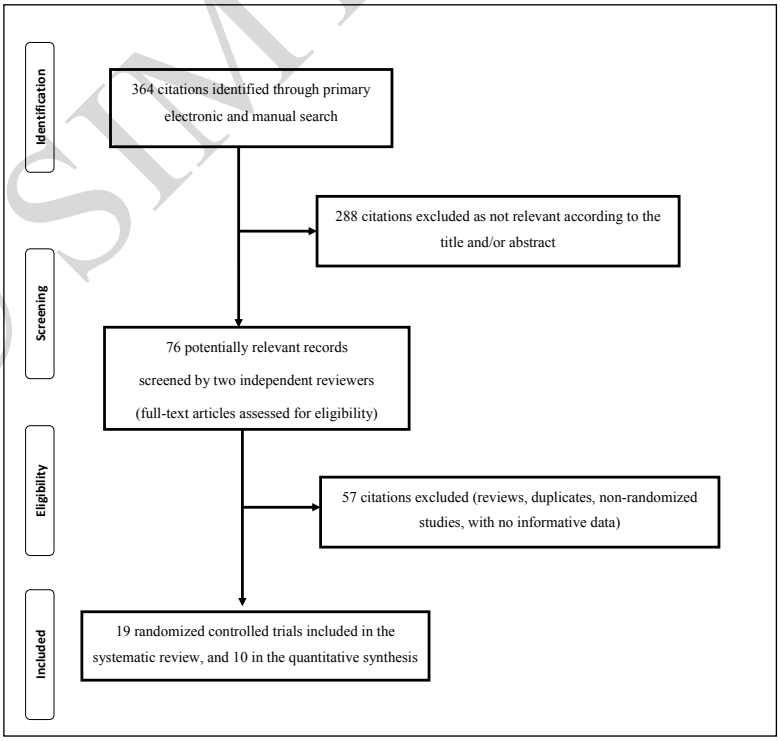

Figure 1 - Flow chart of the selection of the studies.

Table I - Characteristics and main results of the included randomised controlled trials (RCTs) on the use of serum eye drops in ocular surface diseases.

Study (year)[ref]	Patients (n)	Median age, years (range)	Condition	Product	Concentration (frequency)	Control arm	Duration of treatment/ follow up	Concomitant topical therapy	Main results
Tananuvat (2001)[15]	12	59.5 (33-80)	SS, NHL, GvHD, SJS, RA	AS	20% (6 times/day)	NSS	2 months	None	AS group had no statistically significant improvement in symptoms and objective signs (IC, FS, RBS, ST, TBUT) of dry eye
Vajpayee (2003)[16]	59	47.8 (19.8)[1]	CED	CBS	20% (6 times/day)	AS	3 weeks	None	Higher % of re-epithelisation in the CBS group
Noble (2004)[17]	16	54 (30-71)	GvHD, SS, OCP,	AS	50% (NA)	CT	3 months	None	Significant improvement in symptoms and IC
Kojima (2005)[18]	37	NA	SS, non-SS	AS	20% (6 times/day)	AT	2 weeks	None	Significant improvement in symptoms and TBUT, RBS, FS
Schulze (2006)[19]	23	64.8 (9.6)[1]	DCL	AS	100% (hourly)	Hyaluronic acid drops	Variable (until healing)	Isoptomax, atropine, neosynephrine	AS led to a significantly quicker closure of corneal epithelial wounds
Noda-Tsuruya (2006)[20]	27	30.1 (5.8)[1]	Post-LASIK dry eye	AS	20% (5 times/day)	AT	6 months	None	Significant improvement in TBUT, FS and RBS. No change of symptoms
Sharma (2011)[21]	32	NA	OCI	CBS	20% (10 times/day)	AS, AT	3 months	Ofloxacin, prednisolone, homatropine hydrobromide, sodium citrate	Significantly higher % of corneal transparency in CBS group
Urzua (2012)[22]	12	52 (6.3)[1]	DES	AS	20% (4 times/day)	AT	2 weeks	None	Significant improvement in subjective (OSDI), but not objective (FS and TBUT) scores
Panda (2012)[23]	20	NA	OCI	PRP	- (10 times/day)	CT	3 months	None	Significantly faster epithelial healing and improvement in cornea transparency in PRP group
Cho (2013)[24]	85	NA	SS, non-SS, PED	AS	100% (6 times/day)	AS (NSS, hyaluronic acid, ceftazidime)	3 months	None	In SS patients, undiluted AS was the most effective in decreasing symptoms, corneal epitheliopathy and promoting fast closure of wound
Lopez-Garcia (2014)[25]	26	52 (13.4)[1]	SS	AS (sodium hyaluronate)	20% (3 times/day)	AS (NSS)	2 months	None	Significant improvement in subjective symptoms and objective parameters (FS, RBS, TBUT, ST) in group with AS diluted with sodium hyaluronate
Celebi (2014)[26]	20	56 (8.0)[1]	DES	AS	20% (4 times/day)	AT	1 month	None	Significant improvement in OSDI and TBUT scores in AS group
Mukhopadhyay (2015)[27]	144	NA	HD	CBS/AS	20% (6 times/day)	AT	6 weeks	None	CBS/AS therapy improved clinical parameters and tear protein profile in comparison with AT
Li (2016)[28]	37	48.3 (28-62)	SS	AS	50% (8 times/day)	BCL	6 weeks	Fluorometholone	Patients in the BCL group had better OSDI and FS scores than patients in AS group

AS: autologous serum; AT: artificial tears; BCL: bandage contact lens; BS: Behcet's syndrome; CBS: cord blood serum; CED: corneal epithelial defects; CT: conventional treatment; DCL: diabetic corneal lesions; DES: dry eye syndrome; FS: fluorescein staining; IC: GvHD: Graft-versus-Host Disease; HD: Hansen's disease; impression cytology; NA: not available; NHL: non-Hodgkin lymphoma; NSS: normal saline solution; OCI: ocular chemical injury; OCP: ocular cicatricial pemphigoid; OSDI: ocular surface disease index; PED: persistent epithelial defect; PRK: photorefractive keratectomy; PRP: platelet-rich plasma; PS: pterygium surgery; RDS: Riley-Day syndrome; RBS: rose Bengal staining; SCL: soft contact lenses; SJS: Steven-Johnson syndrome; SS: Sjogren's syndrome; ST: Shirmer test; TBUT: tear break-up time. 1Mean age (standard deviation).

Continued on next page.

Table I - Characteristics and main results of the included randomised controlled trials (RCTs) on the use of serum eye drops in ocular surface diseases. *(continued from previous page)*

Study (year)[ref]	Patients (n)	Median age, years (range)	Condition	Product	Concentration (frequency)	Control arm	Duration of treatment/ follow up	Concomitant topical therapy	Main results
Lee (2016)[29]	21	NA	PED	AS+SCL	20% (12 times/day)	No treatment after healing	3 months	Levofloxacin	Prolonged use of AS-SCL decreased recurrence rates
Yilmaz (2016)[30]	24	25 (4)[1]	DES	AS	40%	AT	2 months	None	Significant improvement in OSDI and TBUT scores in AS group
Semeraro (2016)[31]	24	NA	SS	AS	- (5 times/day)	AT	1 year	None	Significant improvement in OSDI in AS group
Sul (2018)[32]	50	NA	PS	AS	50% (8 times/day)	AT	6 months	Dexamethasone, antibiotics	AS accelerated corneal epithelial healing with reduced pain following PS
Akcam (2018)[33]	60	NA	PRK	AS	20% 12 times/day)	AT	1 year	Moxifloxacin, dexamethasone	AS accelerated corneal epithelial healing with reduced pain following PRK

AS: autologous serum; AT: artificial tears; BCL: bandage contact lens; BS: Behcet's syndrome; CBS: cord blood serum; CED: corneal epithelial defects; CT: conventional treatment; DCL: diabetic corneal lesions; DES: dry eye syndrome; FS: fluorescein staining; IC: GvHD: Graft-versus-Host Disease; HD: Hansen's disease; impression cytology; NA: not available; NHL: non-Hodgkin lymphoma; NSS: normal saline solution; OCI: ocular chemical injury; OCP: ocular cicatricial pemphigoid; OSDI: ocular surface disease index; PED: persistent epithelial defect; PRK: photorefractive keratectomy; PRP: platelet-rich plasma; PS: pterygium surgery; RDS: Riley-Day syndrome; RBS: rose Bengal staining; SCL: soft contact lenses; SJS: Steven-Johnson syndrome; SS: Sjogren's syndrome; ST: Shirmer test; TBUT: tear break-up time. 1Mean age (standard deviation)

Figure 2 - Risk of bias graph: review Authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3 - Risk of bias summary: review Authors' judgements about each risk of bias item for each included study.

Table II - Autologous serum eye drop for ocular surface disease: summary of findings.

Patient or population: individuals with dry eye (xerophthalmia); ***settings***: eye clinic; ***intervention***: autologous serum ; ***comparison***: artificial tears.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect: mean difference (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	*Corresponding risk*				
	Artificial tears	*Autologous serum*				
Schirmer test Score <4 mm indicates severe dry eye. Follow up: 2-6 weeks.	The mean score ranged across control groups from 4.00 to 10.10	The mean score in the intervention groups was 1.05 higher (0.17 lower to 2.26 higher)	1.05 (−0.17-2.26)	496 (5 studies, 7 data sets). Two studies used a cross-over design.	⊕⊖⊖⊖[1] very low	On average, it is unclear whether or not use of AS compared to AT increases the score at short-term follow up. The between group differences were small and unlikely to be clinically important.
Tear film break-up time (TBUT) A TBUT <10 seconds is considered abnormal. Follow-up: 2-6 weeks.	Mean score range across control groups: 3.00-12.50 seconds	Mean score in the intervention groups was 2.68 seconds higher (1.33-4.03 higher)	2.68 seconds (1.33-4.03)	544 (6 studies, 8 data sets). Three studies used a cross-over design and paired data were available from two of these.	⊕⊕⊖⊖[2] low	On average, compared to AT, at short-term follow up AS increases in TBUT of 2.68 seconds.
Fluorescein staining Range of scale: 0-9, where a higher score is worse. Follow-up: 2-6 weeks.	The mean score ranged across control groups from 2.00 to 8.00	The mean score in the intervention groups was 0.61 lower (1.50 lower to 0.28 higher)	−0.61 (−1.50-0.28)	400 (4 studies, 5 data sets). One study used a cross-over design.	⊕⊖⊖⊖[1] very low	On average, it is unclear whether or not use of AS compared to AT decreases the fluorescein staining score at short term follow up. The between group differences were small and unlikely to be clinically important.
Ocular surface disease index (OSDI) Participant- reported symptoms. Range of scale: 0-100, with scores 0 to 12 representing normal, 13 to 22 representing mild DES, 23 to 32 representing moderate DES, and greater than 33 representing severe DES. Follow-up: 2-4 weeks.	The mean score ranged across control groups from 24.90 to 30.00	The mean score in the intervention groups was 11.17 lower (16.58 to 5.77 lower)	−11.17 (−16.58 - −5.77)	224 (3 studies; 4 data sets).	⊕⊕⊖⊖[3] low	On average, compared to AT, at short-term follow up AS decreases OSDI of 11.17.

*The basis for the assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference. AS: autologous serum; AT: artificial tears;

GRADE Working Group grades of evidence:

- high quality: further research is very unlikely to change our confidence in the estimate of effect.
- moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- very low quality: we are very uncertain about the estimate.

[1]Down-graded because of imprecision (95% CI includes line of no effect), for inconsistency (due to substantial heterogeneity, I^2>80%), and because of high risk of bias or unclear risk of bias in some of the included studies.

[2]Down-graded because of inconsistency (due to substantial heterogeneity, I^2>80%) and because of high risk of bias or unclear risk of bias in some of the included studies.

[3]Down-graded because of inconsistency (due to substantial heterogeneity, I^2>80%) and for imprecision (studies include relatively few patients and thus have a wide CI around the estimate of the effect).

Blood Transfus 2019; 17: 200-9 DOI 10.2450/2019.0080-19

allocation[16,21-23,25,26,30]. Nine studies were graded at low risk of detection bias due to the fact that the assessor was blinded to treatment allocation. Nine studies were graded at unclear risk of detection bias due to the fact that they did not provide information to allow judgement to be made about high or low risk of bias related to the blinding of outcome assessors. Two studies[15,31] were graded at high risk of bias.

Incomplete outcome data

Two studies[17,27] were judged at high risk of attrition bias because there was a high proportion of withdrawals. Two other studies[19,20] were judged at unclear risk of bias. The remaining studies were judged at low risk of bias.

Selective reporting

Although the protocols of the studies were not always available on prospective registers of clinical trials, we judged the large majority of the included studies at low risk of reporting bias because the outcomes reporting was complete. Two studies were judged at unclear risk of reporting bias because reported information was not sufficient to allow review authors to extract usable data[15,20].

Other potential sources of bias

We judged two studies to be at high risk for other sources of bias because of imbalance at baseline[19,27].

Effects of interventions

For the Summary of findings for the main comparison see Table II, Figures 4-7, *Online Supplementary Content, Table SI and Figures S1-S6*. Outcomes were reported after a short follow-up period (up to 6 weeks) and/or at additional follow-up periods (2-12 months).

Schirmer test

Usable data of the Schirmer test were available from five trials[18,20,26,27,30]. Two studies used a cross-over design, and for these studies we summarised data from the first cross-over period as in a parallel analysis and paired data from both cross-over periods[26,30]. For the follow up at 2-6 weeks pooled data from four trials (7 data sets, 496 eyes)

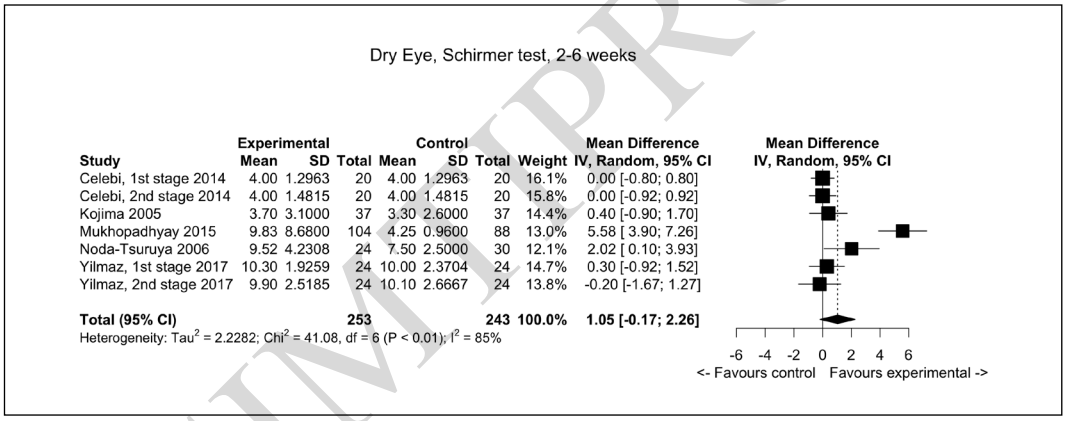

Figure 4 - Forest plot of comparison.
Outcome: Schirmer test at 2-6 weeks using paired data.
CI: conficence interval; SD: standard deviation.

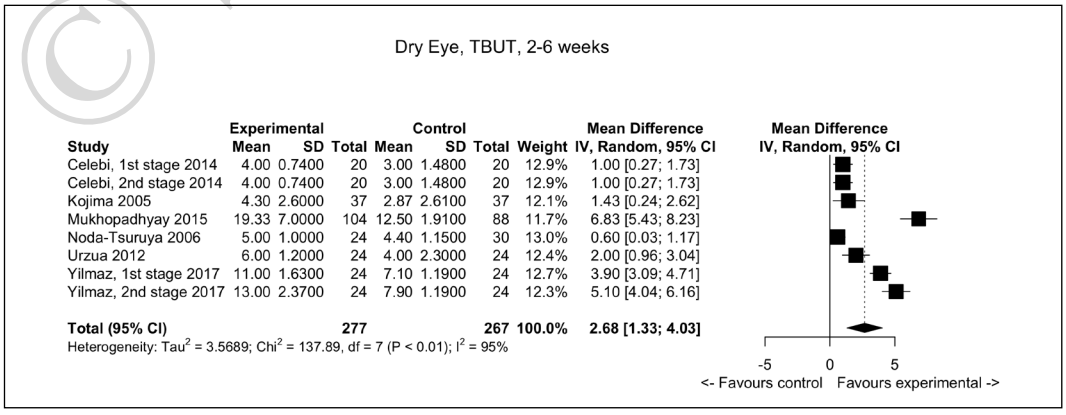

Figure 5 - Forest plot of comparison.
Outcome: tear film break-up time (TBUT) at 2-6 weeks using paired data.
CI: conficence interval; SD: standard deviation.

showed no clear between-group differences in Schirmer test (MD 1.05; 95% CI: −0.17-2.26; I^2=85%); very low quality evidence down-graded for serious risk of bias, for inconsistency (due to substantial heterogeneity), and for imprecision (95% CI include line of no effect) (Table II and Figure 4). Not surprisingly, the results were much the same when the analysis used the data of cross-over trial as a parallel analysis (*Online Supplementary Content, Table SI and Figure S1*), thus supporting the absence of a carry-over effect after a week washout period.

Tear film break-up time (TBUT)

Pooled data from six trials (8 data sets, 544 eyes) showed a slightly higher increase in TBUT scores in autologous serum compared to control (MD 2.68; 95% CI: 1.33-4.03; I^2=95%); low-quality evidence, down-graded for serious risk of bias and for inconsistency (Table II and Figure 5). The results were much the same in the analysis of parallel data (*Online Supplementary Content, Table SI and Figure S2*).

Fluorescein staining

Pooled data from four trials (5 data sets, 400 eyes) showed no clear between-group differences in fluorescein staining (MD −0.61; 95% CI: −1.50-0.28; I^2=95%); very low quality evidence, downgraded for inconsistency, serious risk of biases and serious imprecision (Figure 6). The results were much the same in the analysis of parallel data (*Online Supplementary Content, Table SI and Figure S3*).

Ocular surface disease index

Pooled data from three trials (5 data sets, 224 eyes) showed a greater decrease in OSDI in AS compared to control (MD −11.17; 95% CI: −16.58 - −5.77; I^2=93%); low quality evidence, downgraded for inconsistency and imprecision) (Figure 7).

For the Schirmer test, fluorescein staining and TBUT data were also available at additional follow-up timing (from 2 to 12 months)[15,17,20,28,31]. For the Schirmer test, pooled data from four studies showed no clear between-group differences (MD, −0.11; 95% CI: −0.36-0.14, I^2=0); low-quality evidence, down-graded for risk of bias and imprecision (*Online Supplementary Content*, *Table SI and Figure S4*). Likewise, at 2-12 months, no clear between-group differences were found in the results of the flurescein staining test (MD, 0.92; 95% CI: −0.01-1.85; I^2=86); very-low quality evidence, down-graded for risk of bias, inconsistency and imprecision (*Online Supplementary Content*, *Table SI and Figure S5*) and TBUT (MD, 0.91; 95% CI: −0.53-2.36; I^2=93; very-low quality evidence, down-graded for risk of bias, inconsistency and imprecision (*Online Supplementary Content, Table SI and Figure S6*).

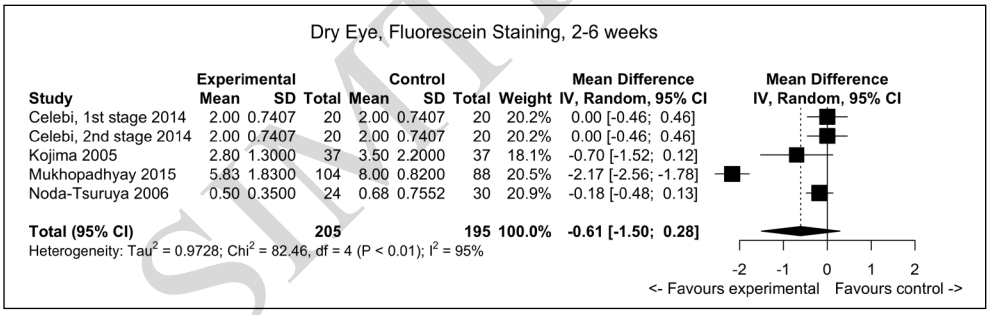

Figure 6 - Forest plot of comparison.
Outcome: fluorescein staining at 2-6 weeks using paired data.
CI: conficence interval; SD: standard deviation.

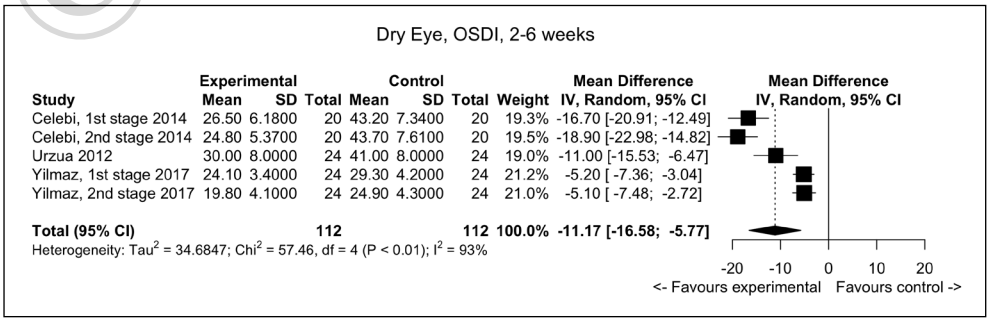

Figure 7 - Forest plot of comparison.
Outcome: Ocular Surface Disease Index (OSDI) at 2-6 weeks using paired data.
CI: conficence interval; SD: standard deviation.

Discussion

In the last 40 years, blood-derived topical therapy has been used in a wide array of clinical conditions[40,41]. In particular, thanks to their properties of mimicking the composition and function of natural tears, over the last decades, serum eye drops have been increasingly used in a variety of ocular surface disorders, including mainly dry eye disease. Following the first reports documenting that serum eye drops provide improved tear film stability, ocular surface health, and subjective comfort in refractory dry eye syndrome, a number of systematic reviews and meta-analyses have tried to perform a pooling analysis of data to assess the possible clinical benefit of this treatment; however, results have been inconclusive[3,5,7,9,10]. A Cochrane review published in 2017 on the use of serum eye drops in patients with dry eye, collecting data from five RCTs with 92 participants, concluded that autologous serum eye drops provided some benefit in improving patient-reported symptoms in the short term (2 weeks) but not over long-term periods[10].

Our systematic review included 19 trials evaluating autologous serum *vs* controls (artificial tears alone, saline, placebo, bandage contact lenses, umbilical cord serum, hyaluronic acid or no treatment) in the treatment of ocular surface diseases, including dry eye syndrome and other clinical conditions (persistent epithelial defect, post-surgical status, post-chemical damage). Due to the clinical heterogeneity of these conditions, we limited the quantitative synthesis (meta-analysis) to ten studies evaluating autologous serum *vs* artificial tears in the treatment of dry eye syndrome, a very common disorder associated with potential damage of the ocular surface that can result in superficial erosions of the cornea and conjunctival epithelial defects[12]. Three of these studies had a cross-over design, but we believe that the inclusion of cross-over design in our review was appropriate given the relative stability of dry eye and the absence of a carry-over effect after 1-week washout between treatment periods. The results of the meta-analysis showed that autologous serum eye drop may not result in higher Schirmer test score and fluorescein staining score in the short term (2-6 weeks) and medium/long term (2-12 months follow up) compared to artificial tears in patients with eye dry syndrome. Some benefit at short-term follow up for the outcome TBUT and OSDI was observed. The available evidence for all the comparisons was rated as low or very low quality due to inconsistency, imprecision, and risk of bias in most of the selected studies. The results of our research are in agreement with those of the Cochrane systematic review and meta-analysis[10]. However, our more recent quantitative analysis included a larger number of trials and patients (10 RCTs with 353 patients). In addition to the existing literature, in this systematic review we tried to find some clinical evidence also for other clinical conditions other than dry eye syndrome that lead to severe ocular surface disease (i.e., post-chemical or -surgical injury) or for other blood-derived topical products (i.e., allogeneic serum eye drops and umbilical cord blood serum)[42-45], but the paucity of studies retrieved did not allow us to perform a qualitative pooling analysis of the data.

Conclusions

As outlined by other authors[10], we observed a wide inter-studies heterogeneity, mainly due to differences in procedures for production of autologous serum and protocols for clinical application. Indeed, as reported in Table I, a consistent number of trials concomitantly used additional local therapy to autologous serum eye drops in both cases and controls, which meant that the effect of this blood-derived product in dry eye syndrome could not be properly evaluated. Given this, adequately powered and well-designed randomised trials are needed to evaluate the long-term clinical benefit of serum eye drops in ocular surface disorders.

Acknowledgements

The Authors thank Professor Marilyn Scopes (Italian Foundation for Research on Anaemia and Haemoglobinopathies, Genoa, Italy) for her precious assistance with language editing and proofreading, and Mrs. Martina Amerini (Italian Foundation for Research on Anaemia and Haemoglobinopathies, Genoa, Italy) for general administrative support and assistance in writing this manuscript.

Disclosure of conflicts of interest

Giancarlo M. Liumbruno is the Editor-in-Chief of Blood Transfusion. As a result, this manuscript was subjected to an additional external review. The other Authors declare no conflicts of interest.

References

1) Ralph RA, Doane MG, Dohlman CH. Clinical experience with a mobile ocular perfusion pump. Arch Ophthalmol 1975; **93**: 1039-43.
2) Fox RI, Chan R, Michelson JB, et al. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. Arthritis Rheum 1984; **27**: 459-61.
3) Giannaccare G, Versura P, Buzzi M, et al. Blood derived eye drops for the treatment of cornea and ocular surface diseases. Transfus Apher Sci 2017; **56**: 595-604.
4) Anitua E, Muruzabal F, Tayebba A, et al. Autologous serum and plasma risg in growth factors in ophthalmology: preclinical and clinical studies. Acta Ophthalmol 2015; **93**: e605-14.
5) Soni NG, Jeng BH. Blood-derived topical therapy for ocular surface diseases. Br J Ophtalmol 2016; **100**: 22-7.
6) Piccin A, Di Pierro AM, Canzian L, et al. Platelet gel: a new therapeutic tool with great potential. Blood Transfus 2017; **15**: 333-40.

7) van der Meer PF, Seghatchian J, Marks DC. Quality standards, safety and efficacy of blood-derived serum eye drops: a review. Transfus Apher Sci 2016; **54**: 164-7.
8) Marshall LL, Roach JM. Treatment of dry eye disease. Consult Pharm 2016; **31**: 96-106.
9) Rauz S, Koay SY, Foot B, et al. The Royal College of Ophthalmologists guidelines on serum eye drops for the treatment of severe ocular surface disease: full report. Eye 2017; doi: 10.1038/eye.2017.209. [Epub ahead of print].
10) Pan Q, Angelina A, Marrone M, et al. Autologous serum eye drops for dry eye. Cochrane Database Syst Rev 2017; **2**: CD009327.
11) Kirmani BH, Jones SG, Datta S, et al. A meta-analysis of platelet gel for prevention of sternal wound infections following cardiac surgery. Blood Transfus 2017; **15**: 57-65.
12) Clayton JA. Dry eye. N Engl J Med 2018; **378**: 2212-23.
13) Imanishi J, Kamiyama K, Iguchi I, et al. Growth factors: importance in wound healing and maintenance of transparency of the cornea. Prog Retin Eye Res 2000; **19**: 113-29.
14) De Pascale MR, Lanza M, Sommese L, Napoli C. Human serum eye drops in eye alterations: an insight and a critical analysis. J Ophtalmol 2015; **2015**: 396410.
15) Tananuvat N, Daniell M, Sullivan LJ, et al. Controlled study of the use of autologous serum in dry eye patients. Cornea 2001; **20**: 802-6.
16) Vajpayee RB, Mukerji N, Tandon R, et al. Evaluation of umbilical cord serum therapy for persistent corneal epithelial defects. Br J Ophthalmol 2003; **87**: 1312-6.
17) Noble BA, Loh RS, MacLennan S, et al. Comparison of autologous serum eye drops with conventional therapy in a randomised controlled crossover trial for ocular surface disease. Br J Ophthalmol 2004; 88: 647-52.
18) Kojima T, Ishida R, Dogru M, et al. The effect of autologous serum eye drops in the treatment of severe dry eye disease: a prospective randomized case-control study. Am J Ophthalmol 2005; **139**: 242-6.
19) Schulze SD, Sekundo W, Kroll P. Autologous serum for the treatment of corneal epithelial abrasions in diabetic patients undergoing vitrectomy. Am J Ophthalmol 2006; **142**: 207-11.
20) Noda-Tsuruya T, Asano-Kato N, Toda I, Tsubota K. Autologous serum eye drops for dry eye after LASIK. J Refract Surg 2006; **22**: 61-6.
21) Sharma N, Goel M, Velpandian T, et al. Evaluation of umbilical cord serum therapy in acute ocular chemical burns. Invest Ophthalmol Vis Sci 2011; **52**: 1087-92.
22) Urzua CA, Vasquez DH, Huidobro A, et al. Randomized double-blind clinical trial of autologous serum versus artificial tears in dry eye syndrome. Curr Eye Res 2012; **37**: 684-8.
23) Panda A, Jain M, Vanathu M, et al. Topical autologous platelet-rich plasma eyedrops for acute corneal chemical injury. Cornea 2012; **31**: 989-93.
24) Cho YK, Huang W, Kim GY, Lim BS. Comparison of autologous serum eye drops with different diluents. Curr Eye Res 2013; **38**: 9-17.
25) López-García JS, García-Lozano I, Rivas L, et al. Autologous serum eye drops diluted with sodium hyaluronate: clinical and experimental comparative study. Acta Ophthalmol 2014; **92**: e22-9.
26) Celebi AR, Ulusoy C, Mirza GE. The efficacy of autologous serum eye drops for severe dry eye syndrome: a randomized double-blind crossover study. Graefes Arch Clin Exp Ophthalmol 2014; **252**: 619-26.
27) Mukhopadhyay S, Sen S, Datta H. Comparative role of 20% cord blood serum and 20% autologous serum in dry eye associated with Hansen's disease: a tear proteomic study. Br J Ophthalmol 2015; **99**: 108-12.
28) Li J, Zhang X, Zheng Q, et al. Comparative evaluation of silicone hydrogel contact lenses and autologous serum for management of Sjögren syndrome-associated dry eye. Cornea 2015; **34**: 1072-8.
29) Lee YK, Lin YC, Tsai SH, et al. Therapeutic outcomes of combined topical autologous serum eye drops with silicone-hydrogel soft contact lenses in the treatment of corneal persistent epithelial defects: a preliminary study. Cont Lens Anterior Eye 2016; **39**: 425-430.
30) Yılmaz U, Küçük E, Koç Ç, Gökler E. Comparison of autologous serum versus preservative free artificial tear in patients with dry eyes due to systemic isotretinoin therapy. Curr Eye Res 2017; **42**: 827-31.
31) Semeraro F, Forbice E, Nascimbeni G, et al. Effect of autologous serum eye drops in patients with Sjögren syndrome-related dry eye: clinical and in vivo confocal microscopy evaluation of the ocular surface. In vivo 2016; **30**: 931-8.
32) Sul S, Korkmaz S, Alacamli G, et al. Application of autologous serum eye drops after pterygium surgery: a prospective study. Graefes Arch Clin Exp Ophthalmol 2018; **256**: 1939-43.
33) Akcam HT, Unlu M, Karaca EE, et al. Autologous serum eye-drops and enhanced epithelial healing time after photorefractive keratectomy. Clin Exp Optom 2018; **101**: 34-7.
34) Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. III: the issue of carry-over. Statist Med 2002; **21**: 2161-73.
35) Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014; **14**: 135.
36) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; **7**: 177-88.
37) Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions - Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available at: http://www.cochranehandbook.org.
38) Schünemann HJ, Oxman AD, Higgins JP, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at: http://www.cochranehandbook.org. Accessed on: 30/03/2019.
39) Guyatt GH, Oxman AD, Kunz R, et al. What is 'quality of evidence' and why is it important to clinicians? BMJ 2008; **336**: 995-8.
40) Clendenen N, Ginde A. Efficacy of platelet-rich plasma as conservative treatment in orthopaedics. Blood Transfus 2018; **16**: 473-4.
41) Franchini M, Cruciani M, Mengoli C, et al. Efficacy of platelet-rich plasma as conservative treatment in orthopaedics: a systematic review and meta-analysis. Blood Transfus 2018; **16**: 502-13.
42) Pupella S, Bianchi M, Ceccarelli A, et al. A cost analysis of public cord blood banks belonging to the Italian Cord Blood Network. Blood Transfus 2018; **16**: 313-20.
43) Sacchi N. Is it time to re-think a sustainable banking model for the Italian Cord Blood Network? Blood Transfus 2018; **16**: 221-3.
44) Valle V, Screnci M, Murgi E, et al. Collection of umbilical cord blood for banking: collection rate and factors influencing collection. Blood Transfus 2017; **15**: 587-8.
45) Yoon KC. Use of umbilical cord serum in ophthalmology. Chonna Med J 2014; **50**: 82-5.

Arrived: 3 April 2019 - Revision accepted: 15 May 2019
Correspondence: Massimo Franchini
Department of Haematology and Transfusion Medicine
"Carlo Poma" Hospital
Strada Lago Paiolo 1
46100 Mantua, Italy
e-mail: massimo.franchini@asst-mantova.it