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Autologous serum eye drops for dry eye

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Abstract

Background

Theoretically, autologous serum eye drops (AS) offer a potential advantage over traditional therapies on the assumption that AS not only serve as a lacrimal substitute to provide lubrication but contain other biochemical components that allow them to mimic natural tears more closely. Application of AS has gained popularity as second-line therapy for patients with dry eye. Published studies on this subject indicate that autologous serum could be an effective treatment for dry eye.

Objectives

We conducted this review to evaluate the efficacy and safety of AS given alone or in combination with artificial tears as compared with artificial tears alone, saline, placebo, or no treatment for adults with dry eye.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 5), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to July 2016), Embase (January 1980 to July 2016), Latin American

and Caribbean Literature on Health Sciences (LILACS) (January 1982 to July 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We also searched the Science Citation Index Expanded database (December 2016) and reference lists of included studies. We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 5 July 2016.

Selection criteria

We included randomized controlled trials (RCTs) that compared AS versus artificial tears for treatment of adults with dry eye.

Data collection and analysis

Two review authors independently screened all titles and abstracts and assessed full-text reports of potentially eligible trials. Two review authors extracted data and assessed risk of bias and characteristics of included trials. We contacted investigators to ask for missing data. For both primary and secondary outcomes, we reported mean differences with corresponding 95% confidence intervals (CIs) for continuous outcomes. We did not perform meta-analysis owing to differences in outcome assessments across trials.

Main results

We identified five eligible RCTs (92 participants) that compared AS versus artificial tears or saline in individuals with dry eye of various origins (Sjögren's syndrome-related dry eye, non-Sjögren's syndrome dry eye, and postoperative dry eye induced by laser-assisted in situ keratomileusis (LASIK)). We assessed the certainty of evidence as low or very low because of lack of reporting of quantitative data for most outcomes and unclear or high risk of bias among trials. We judged most risk of bias domains to have unclear risk in two trials owing to insufficient reporting of trial characteristics, and we considered one trial to have high risk of bias for most domains. We judged the remaining two trials to have low risk of bias; however, these trials used a cross-over design and did not report data in a way that could be used to compare outcomes between treatment groups appropriately. Incomplete outcome reporting and heterogeneity among outcomes and follow-up periods prevented inclusion of these trials in a summary meta-analysis.

Three trials compared AS with artificial tears; however, only one trial reported quantitative data for analysis. Low-certainty evidence from one trial suggested that AS might provide some improvement in participant-reported symptoms compared with artificial tears after two weeks of treatment; the mean difference in mean change in symptom score measured on a visual analogue scale (range 0 to 100, with higher scores representing worse symptoms) was -12.0 (95% confidence interval (CI) -20.16 to -3.84; 20 participants). This same trial found mixed results with respect to ocular surface outcomes; the mean difference in mean change in scores between AS and artificial tears was -0.9 (95% CI -1.47 to -0.33; 20 participants; low-certainty evidence) for fluorescein staining and -2.2 (95% CI -2.73 to -1.67; 20 participants; low-certainty evidence) for Rose Bengal staining. Both staining scales range from 0 to 9, with higher scores indicating worse results. The mean change in tear film break-up time was 2.00 seconds longer (95% CI 0.99 to 3.01; 20 participants; low-certainty evidence) in the AS group than in the artificial tears group. Investigators re-

ported no clinically meaningful differences in Schirmer's test scores between groups (mean difference -0.40 mm, 95% CI -2.91 to 2.11; 20 participants; low-certainty evidence). None of these three trials reported tear hyperosmolarity and adverse events.

Two trials compared AS versus saline; however, only one trial reported quantitative data for analysis of only one outcome (Rose Bengal staining). Trial investigators of the two studies reported no differences in symptom scores, fluorescein staining scores, tear film break-up times, or Schirmer's test scores between groups at two to four weeks' follow-up. Very low-certainty evidence from one trial suggested that AS might provide some improvement in Rose Bengal staining scores compared with saline after four weeks of treatment; the mean difference in Rose Bengal staining score (range from 0 to 9, with higher scores showing worse results) was -0.60 (95% CI -1.11 to -0.09; 35 participants). Neither trial reported tear hyperosmolarity outcomes. One trial reported adverse events; two of 12 participants had signs of conjunctivitis with negative culture that did resolve.

Authors' conclusions

Overall, investigators reported inconsistency in possible benefits of AS for improving participant-reported symptoms and other objective clinical measures. There might be some benefit in symptoms with AS compared with artificial tears in the short-term, but we found no evidence of an effect after two weeks of treatment. Well-planned, large, high-quality RCTs are warranted to examine participants with dry eye of different severities by using standardized questionnaires to measure participant-reported outcomes, as well as objective clinical tests and objective biomarkers to assess the benefit of AS therapy for dry eye.

Plain language summary

Eye drops made from autologous serum as treatment for dry eye

What is the aim of this review?
We conducted this Cochrane review to find out whether autologous serum eye drops work as treatment for dry eye. Cochrane researchers searched for all relevant studies seeking an answer to this question and found five studies.

What are the key messages of this review?
Eye drops containing autologous serum might be better at improving dry eye symptoms than artificial tear drops in the short term (two weeks). We found very little information as to whether autologous serum eye drops work long term or for clinical measures of dry eye.

What was studied in this review?
Dry eye is a common disorder of the tear film, which is a layer of tears covering the surface of the eye. Dry eye affects many adults older than 40 years of age. People with dry eye may feel discomfort in one or both eyes and have sensitivity to light. There are clinical tests that are used by healthcare professionals to measure the amount of tears the eye produces and how fast tears leave the eye. Sometimes these clinical measures do not match the symptoms; a person can have severe dry eye and normal clinical test results, or mild dry eye and abnormal clinical test results.

One common treatment for dry eye is artificial tears, which provide lubrication to the surface of the eye. However, artificial tears lack the biological nutrients found in natural tears that are critical to maintenance of the tear film. Eye drops made by separating liquid and cellular components of the patient's blood, known as autologous serum eye drops, have been shown to possess many of the same biological nutrients found in natural tears. Because of this fact, autologous serum eye drops are believed to be a better tear substitute and have been proposed as treatment for dry eye.

What are the main results of the review?
We found five studies in people with dry eye from Australia, Chile, Japan, and Turkey. These studies compared autologous serum eye drops versus traditional artificial tears or saline solution for treatment of dry eye. We could not combine results of the five studies in analysis owing to differences in what each study evaluated. In one study, people who received autologous serum eye drops showed better improvement in symptoms after two weeks than those who received artificial tears. However, results after longer treatment (four weeks or more) and for other outcomes had problems that prevent us from saying whether autologous serum is truly better than artifical tears or saline. The authors of this review conclude that autologous serum versus artificial tears might provide benefit for treatment of dry eye in the short term. However, the overall benefit seems unclear at this time, and much more research is needed in this area.

How up-to-date is the review?
Cochrane review authors searched for studies that had been published up to July 5, 2016.

Summary of findings

Background

Description of the condition

Dry eye is a common disorder, with an estimated 25% of patients in general ophthalmology or optometry clinics reporting dry eye symptoms (Doughty 1997). It is known that the incidence of dry eye increases with age, and that it is more prevalent in women than in men (McCarty 1998; Schaumberg 2003; Stern 2004). Recently, the Definition and Classification Subcommittee of the International Dry Eye Work Shop (DEWS) redefined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort (including foreign body sensation, dryness or irritation, burning, light sensitivity, redness), visual disturbance, secretion with crusting on the eyelashes, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" (DEWS 2007). Increased tear osmolarity, which causes ocular surface inflammation, is thought to be the central pathogenic mechanism of dry eye (DEWS 2007).

The mechanistic classification of dry eye suggested by DEWS defines two main subtypes: aqueous deficiency and evaporative dry eye, which respectively correspond to disorders of the lacrimal and meibomian glands (DEWS 2007). Disorders of the lacrimal and meibomian glands are usually secondary to systemic disease or local causes. One of the most common systemic diseases causing dry eye is Sjögren's syndrome, which presents as "sicca complex," a combination of dry eye and dry mouth (xerostomia) due to T lymphocyte-mediated destruction of the exocrine glands (Fox 2006; Kumar 2005; Yamada 1990). Other systemic

diseases, such as rheumatoid arthritis, diabetes, and systemic lupus erythematosus; and dermatological conditions, such as acne rosacea and Graves' disease have been reported as causing clinically significant dry eye (Patel 2002). On the other hand, leading causes of non–systemic disease-related dry eye include age-related lacrimal dysfunction (Demato 1984), hormonal changes, drug side effects (e.g., systemic antihistamines, diuretics, topical beta blockers for glaucoma therapies) (Baudouin 2001; Blomquist 2010), and surgical intervention (e.g., photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK); Campos 1992; Noda-Tsuruya 2006; Toda 2004), as well as long-term contact lens use (Lemp 1995).

Dry eye is diagnosed with validated patient symptom questionnaires and a wide array of clinical assessments of the tears and ocular surface. Symptoms of dry eye have been standardized by the use of questionnaires. Patients' most common complaints include dryness or irritation, light sensitivity, foreign body sensation, red eyes, poor vision, daily life limitations, and symptom fluctuation in different environmental conditions. However, researchers have noted no strong correlation between signs and symptoms, particularly in cases of mild dry eye (Begley 2003; Viso 2012). Therefore, the clinical diagnosis of dry eye needs to incorporate objective tests, such as tear osmolarity, tear production assessed by Schirmer's testing, fluorescein clearance, tear film break-up time (TBUT), and demonstration of ocular surface damage through dye staining (fluorescein and lissamine green) (Lemp 1995; Lemp 2011; Perry 2004). Although no gold standard diagnostic test is presently available to identify dry eye, a growing number of studies have suggested that tear osmolarity might be the best single metric for diagnosis and assessment of severity of dry eye (Lemp 2011; Tomlinson 2006). According to Perry 2004, other study authors have suggested that tear film stability determined by TBUT and delayed tear fluorescein clearance (Chodosh 1994; Marci 2000) are reliable ways to assess dry eye.

Description of the intervention

Currently, no cure for dry eye is known. Common treatments are targeted to management of symptoms. The mainstay of conventional therapy consists of application of artificial tears that increase moisture on the ocular surface and provide additional lubrication. Various artificial tear formulations are available; they differ in terms of electrolyte composition, osmolarity, viscosity, the presence of preservatives, and compatible solutes (Lemp 2008). Nelson 1988 found that an unpreserved artificial tear containing 0.1% sodium hyaluronate was effective in improving dry eye symptoms and led to significant improvement in mean tear film osmolarity, break-up times, and conjunctival and corneal staining scores. However, the use of artificial tears has some limitations (Pucker 2016). The composition of natural tears is complex; they consist of water, salts, hydrocarbons, proteins, and lipids for which artificial tears cannot exactly serve as a substitute (Dogru 2011; Quinto 2008). Additionally, frequent application of artificial tears solutions containing chemical preservatives to prevent contamination has been found to induce toxic and allergic reactions, especially among those with sensitive eyes (Baudouin 2010; Dogru 2011; Quinto 2008).

Studies have shown that topical corticosteroids that target the inflammatory pathways associated with ocular inflammation improve symptoms in people with dry eye (de Paiva 2008; Pflugfelder 2004), but their use is limited owing to long-term side effects, including cataracts and increased intraocular pressure (Blomquist 2010). In December 2002, the US Food and Drug Administration (FDA) approved 0.05% solution of cyclosporine A (CsA) as an ocular treatment for people with dry eye (Meadows 2005). Several studies have shown an increase in tear production and in conjunctival goblet cell density with few reported adverse effects following topical application of CsA (Sall 2000; Stevenson 2000; Toker 2010; Wilson 2007).

Additional nutritional supplements, such as essential fatty acids including omega-3, linoleic acid, and gamma-linoleic acid, have been proposed as adjuvants in the treatment of dry eye owing to their anti-inflammatory properties (de Paiva 2008). Increased water intake and reduced alcohol consumption are also recommended to improve dry eye symptoms (Dogru 2011). Environmental interventions designed to increase air moisture and reduce particles in the air, including indoor humidifiers and air filters or cleaners, have been shown to reduce dry eye symptoms as well (Dogru 2011). People for whom artificial tears are not sufficient can achieve preservation of the tear film by inserting punctal plugs into the lacrimal ducts; these are designed to reduce drainage of tears through the lacrimal ducts while increasing lubrication on the ocular surface (Ervin 2010; Foulks 2003).

Use of autologous serum eye drops The composition of serum resembles that of tears; most concentrations are equivalent, with the exception that serum has more vitamin A, lysozyme, transforming growth factor-β (TGF-β), and fibronectin, and less immunoglobulin A (IgA), epithelial growth factor (EGF), and vitamin C than are found in tears (Bradley 2008; Joh 1986; Matsumoto 2004; Nelson 1992; Tsubota 1999). Given that many of the essential components in tears are present in serum, use of serum as a tear substitute for maintenance of the ocular surface seems feasible (Imanishi 2000; Kojima 2005b). In 1975, Ralph 1975 initially applied autologous serum eye drops (AS) for dry eye and reported this event. Since that time, AS have become increasingly popular for treating patients with ocular surface diseases, mainly dry eye.

Production of autologous serum eye drops Currently, no forms of AS are commercially available; AS must be compounded with the use of autologous serum. Technological factors affect product quality and properties of AS (Geerling 2004; Liu 2005). Even though methods used for AS preparation, storage, and administration are highly variable, standards have been established to optimize therapeutic effectiveness and product safety (Geerling 2004; Liu 2005). In brief, blood is first drawn from the recipient and is then allowed to clot in the absence of an anticoagulant. Once a clot has formed, the supernatant is centrifuged to separate serum from solid components without inducing hemolysis. After centrifugation, the serum is decanted into a sterile container and may then be diluted to the desired concentration. Autologous serum typically is administered in a 20% concentration, which is based on the concentration of biological factors in actual tears, although higher concentrations (between 50% and 100%) have been used (Dogru 2011; Geerling 2004; Kojima 2008; Quinto 2008). It is known that serum may contain components that are detrimental to the ocular surface. TGF-β, for example, is known to have antiproliferative effects, and high concentrations of TGF-β may suppress wound healing of the ocular surface epithelium (Tsubota 2000). This observation contributed to use of a diluted solution of serum to maintain TGF-β levels that are comparable with those of tears. Preservatives usually are not added to AS, thus reducing the risk of preservative-induced toxicity associated with other dry eye treatments. However, lack of preservatives theoretically increases the risk of ocular infection. Autolgous serum can be stored for less than one month at 4°C while in use, and for up to three months at -20°C (Tsubota 1999). It is important that vials containing autologous serum be kept away from light to avoid degradation of vitamin A.

Indications Autologous serum eye drops have been recommended for treatment of patients with several ocular surface disturbances, such as Sjögren's syndrome-related tear deficiency, non-Sjögren's tear deficiency associated with graft-versus-host disease, neurotrophic keratitis, persistent epithelial defects, superior limbic keratoconjunctivitis, and postoperative dry eye induced by LASIK. People treated with 20% to 50% AS

four to eight times a day have reported subjective improvement in dry eye symptoms; investigators have also noted objective improvement based on fluorescein staining and results of break-up time tests (Chiang 2007; Hyon 2007; Kojima 2005b; Matsumoto 2004; Ogawa 2003; Poon 2001; Tananuvat 2001).

Complications AS usually are well tolerated, and most recipients report less discomfort. Occasionally, patients may experience increased discomfort, slight epitheliopathy (dropout of corneal epithelial cells, akin to fluorescein staining of the surface of the eye), bacterial conjunctivitis, or eyelid eczema (Ogawa 2003; Rocha 2000; Tananuvat 2001). Fox 1984 reported no serious complications but mentioned that other investigators had encountered scleral vasculitis and melting in people with rheumatoid arthritis. McDonnell 1988 described complications such as the deposit of immunoglobulins within the cornea and the presence of corneal peripheral infiltrates with 100% autologous serum treatment in one person.

Risk of infection Some components of serum may have bacteriostatic effects, for example, lysozyme, complement, and IgG; therefore, the addition of another bacteriostatic agent may not be necessary. It has been reported that AS can be used safely in both outpatient and inpatient settings, under a strict protocol of preparation and storage (Langnado 2004; Partal 2011). However, even though AS are prepared under sterile conditions on an individual patient basis, researchers have noted risks for contamination and consequent infection during preparation, storage, and use of the drops (Geerling 2004; Lee 2008).

Selection of people suitable for autologous serum In the United States, the FDA and the American Association of Blood Banks (AABB) have specified criteria for autologous blood donors, which include a minimum hemoglobin concentration of 11 g/dL (hematocrit of 33%) and deferral for conditions presenting risk of bacteremia. Individual blood collection facilities and medical providers may apply additional criteria; these often specify that the patient must be well enough to undergo venipuncture several times a year and to withstand loss of blood (Noble 2004; Roback 2008). Blood collection facilities sometimes specifically defer people considered to be at greatest risk from blood donation, such as those with unstable angina, recent myocardial infarction or cerebrovascular accident, and significant cardiac or pulmonary disease with chronic symptoms who have not been evaluated by the treating physician, and those with untreated aortic stenosis. Children and pregnant women often are excluded (Roback 2008).

To prevent risk of viral transmission to others (e.g., production or nursing staff, children at home who may unintentionally use serum eye drops), it is strongly recommended that the donor be tested for blood-transmitted diseases (e.g., human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis), that hospital staff be cautious of serum production, and that the identity of the recipient be confirmed (Geerling 2004; Yoon 2007). Although significant legal ramifications are associated with potential transmission of blood-based diseases to medical staff as well as serum recipients, no consensus indicates whether people who have blood-transmissible diseases should be disqualified from donating serum for their personal use when medically indicated.

Legal regulations Autologous serum eye drops are unique among ophthalmic therapies in that they are manufactured specifically for each individual and are made from each person's own blood. Regulations on autologous blood donation vary from country to country. In the United States, the Center for Biologics Evaluation and Research (CBER) of the FDA is responsible for the regulation of blood intended for transfusion, as well as blood components and derivatives. In the European Union (EU), the European Parliament and Council has issued several directives on AS (1965/65, 1975/139, 1975/318). However,

these directives had to be taken into account by those passing laws for each member state of the EU (Geerling 2004). For example, the National Blood Service in England and Wales has supplied AS under a drug exemption certificate for the purposes of a clinical trial conducted by the regulatory body in the United Kingdom - the Medicines and Healthcare Regulatory Agency (Noble 2004). When considering integration of AS therapy into treatment regimens, clinicians must take into account special regulations provided by the FDA and other regulatory agencies regarding use of blood products (Geerling 2008; Noble 2004; Roback 2008).

How the intervention might work

Studies have shown that AS contain biochemical factors, such as EGF, vitamin A, TGF-β, fibronectin, substance P, insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), and other cytokines essential for proliferation, differentiation, and maturation of the normal ocular surface epithelium (Gordon 1995; Matsumoto 2004; McCluskey 1987; Nishida 1983; Nishida 1987; Phan 1987; Poon 2001). Therefore, a potential advantage of AS over traditional therapies is that AS serves as a lacrimal substitute that provides lubrication and other biochemical components of tears to assist in corneal and conjunctival epithelium maintenance with limited toxicity (Dogru 2011; Geerling 2004; Liu 2005; Poon 2001; Quinto 2008).

Why it is important to do this review

Autologous serum eye drops for severe dry eye treatment have gained widespread acceptance over the past decade. However, this continues to be a restricted topic because preparation of serum eye drops requires a well-equipped laboratory and trained personnel. Studies conducted recently are controversial with regard to effectiveness of AS for dry eye symptoms (Noble 2004; Tananuvat 2001). Therefore, we conducted a systematic review to determine the efficacy and safety of AS for treatment of patients with dry eye. This review, first published in 2013, found inconsistency in the possible benefits of AS for improving participant-reported symptoms and TBUT and lack of effect based on other objective clinical measures (Pan 2013). We updated this review to determine whether additional evidence is now available.

Objectives

We conducted this review to evaluate the efficacy and safety of AS given alone or in combination with artificial tears as compared with artificial tears alone, saline, placebo, or no treatment for adults with dry eye.

Methods

Criteria for considering studies for this review

Types of studies We included only randomized controlled trials (RCTs) for the purposes of this review. Given the stability of the condition of interest, we also considered cross-over studies in which the sequence of treatments was determined to have been assigned randomly.

Types of participants We included in the review studies conducted in adults (over 18 years of age) with dry eye defined by study investigators with no restrictions based on race or sex.

Types of interventions We included studies that compared application of AS alone or in combination with artificial tears versus artificial tears alone, saline, placebo, or no treatment.

Types of outcome measures Dry eye clinical tests generally do not correlate with patient-reported symptoms. A wide variety of participant-reported outcome scales have led to discrepancies between subjective symptoms and objective clinical tests (Chambers 1999; Fuentes-Paez 2011; Nichols 2004; Patrick 2011). Therefore, we considered both subjective data from participant-reported symptoms regardless of the measurement scale used and objective data obtained from clinical diagnostic tests to analyze fully their effect on the condition.

Primary outcomes We defined symptom improvement as the change from baseline in participant-reported severity and/or frequency of dry eye-related symptoms based on validated patient symptom questionnaires at four weeks after initiation of treatment. Given that trial design, frequency of AS administration, and timing of outcome assessment may vary, we considered all variations in frequency of AS use and other time points as reported by included studies.

Secondary outcomes Investigators reported objective data obtained from ophthalmic examinations and diagnostic tests (Behrens 2006; Tomlinson 2009) two to four weeks after treatment for the following tests.

- Tear hyperosmolarity: mean change in tear osmolarity.
- Ocular staining with fluorescein: mean change in total score from baseline to follow-up.
- Ocular staining with Rose Bengal: mean change in total score from baseline to follow-up.
- Tear film break-up time: mean change in tear film break-up time in seconds. A value less than or equal to five seconds indicates level 3 dry eye severity.
- Schirmer's test: mean change in millimeters with or without anesthesia. A value less than or equal to 5.5 mm/5 min is indicative of dry eye.
- Corneal topography: mean change in tear film break-up time and height of the tear meniscus determined by non-invasive assessment of the tear film.
- Impression cytology: mean change in grades of epithelial metaplasia and goblet cell density.
- Tear fluorescein clearance: mean change in speed of disappearance from the ocular surface of exogenously added fluorescein.
- Conjunctival biopsy: mean change in grades of squamous metaplasia of the conjunctiva.

Adverse effects We tabulated adverse effects (e.g., bacterial and viral infection, eye irritation) reported in the included studies for both AS and control groups.

Quality of life measures We planned to record health-related quality of life data obtained by any validated measure (e.g., activities of daily vision scale) in the included studies.

Economic data We planned to document cost analyses and other data on economic outcomes reported by the included studies.

Search methods for identification of studies

Electronic searches We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 5), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to July 2016), Embase (January 1980 to July 2016), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to July 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 5 July 2016.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), the ISRCTN (Appendix 5), ClinicalTrials.gov (Appendix 6), and the ICTRP (Appendix 7).

Searching other resources We also searched the Science Citation Index-Expanded database (December 2016) and reference lists of included studies. We did not handsearch conference proceedings or journals.

Data collection and analysis

Selection of studies Two review authors independently reviewed the titles and abstracts of all records identified via electronic and manual searches. We classified each record as relevant, potentially relevant, or definitely not relevant. We resolved discrepancies through consensus and obtained full-text reports of all relevant or potentially relevant records. Two review authors assessed full-text reports for final inclusion of studies in this review. We resolved discrepancies through consensus. For studies that we excluded after review of the full text, we documented reasons for exclusion (see Characteristics of excluded studies).

Data extraction and management Two review authors extracted data independently using the data extraction form developed by Cochrane Eyes and Vision for this review. We resolved discrepancies by discussion and contacted study authors for additional data when necessary. One review author entered all data into Review Manager 5 (RevMan 2014), and a second review author confirmed all entered data.

Assessment of risk of bias in included studies Two review authors assessed risk of bias independently according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Review authors were not masked to any trial details during this assessment. We considered the following risk of bias parameters for each of the included studies: sequence generation and allocation concealment (selection bias); masking (blinding) of participants and researchers during and after treatment (performance bias), as well as during outcome assessment (detection bias); completeness of follow-up for primary and secondary outcomes (attrition bias); and selective outcome reporting (reporting bias). We applied a judgement of "low risk," "unclear risk," or "high risk" to each of the above parameters for each included study.

For cross-over trials, we considered additional methodological assessments of risk of bias, including whether investigators provided a washout period, the number lost to follow-up after each phase, and whether study authors reported data for each phase or by treatment, as described in Chapter 16 of the

Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011b).

Measures of treatment effect We did not conduct summary meta-analyses of treatment effects in this review. If sufficient data are available for future updates, we will calculate summary risk ratios (RRs) for dichotomous outcomes of interest (proportion of participants reporting improvement in dry eye-related symptoms). We will dichotomize ordinal data to reflect varying degrees of symptom improvement ("some improvement") and will perform sensitivity analyses while using different cut points (Patrick 2011). For continuous scales of participant-reported outcomes, we will calculate standardized mean differences (SMDs) to account for variation in measurement scales. We will summarize continuous data from objective ocular tests by calculating mean differences from baseline to follow-up between treatment and control arms (ocular surface staining, Schirmer's test, and tear break-up time).

We will use the generic inverse variance method to summarize treatment effects in studies that reported between-group measures of effect and variance estimates. We will not include quantitative data from cross-over trials, which report only first phase data, given the risk of bias for incomplete outcome reporting (Higgins 2011b).

Unit of analysis issues The unit of analysis was the individual participant, who was randomized to each treatment arm in two cross-over trials (Celebi 2014; Urzua 2012) and in one of the two parallel-group trials (Kojima 2005a). The other parallel-group trial randomized participants to each intervention and included in the analyses both eyes of each participant independently (Noda-Tsuruya 2006). We reported results using the unit of analysis reported by individual studies. One trial used a paired-eye design, in which researchers evaluated each eye of each participant and considered the eye the unit of analysis (Tananuvat 2001).

Dealing with missing data We contacted study authors of included trials for clarification or retrieval of missing primary and secondary outcome data. We did not conduct any imputations when study authors did not provide missing data and instead relied on data provided in published reports. For future summary meta-analyses, when trial authors are unable to provide information on missing data, we plan to conduct sensitivity analyses by assuming that all participants with missing data in the treated group had the worse outcome (if dichotomous); and that all participants with missing data in the treated group did not have the worse outcome.

Assessment of heterogeneity We assessed clinical and methodological heterogeneity by examining characteristics of study participants, treatment and control comparisons, and assessments of primary and secondary outcomes. Owing to differences in outcome assessments and time points across trials, we did not consider meta-analysis to be appropriate for this review.

If future updates of this review include meta-analyses, we will examine consistency across studies by using the I^2 test (Higgins 2003), and we will regard a value greater than 50% as indicating substantial statistical heterogeneity. We also will inspect forest plots to determine the degree of overlap of confidence intervals among included studies. Little overlap is another indication of the presence of heterogeneity.

Assessment of reporting biases We were not able to conduct meta-analysis and could not assess reporting bias through inspection of funnel plots. We assessed studies for selective outcome reporting at the trial level as part of the "Risk of bias" assessment.

Data synthesis Data were insufficient to allow review authors to conduct a meta-analysis, as planned in the protocol of this review (Pan 2011). We provided a narrative summary of results in place of statistical summary analyses.

For future updates, we will conduct a random-effects meta-analysis when we find clinical, methodological, and statistical homogeneity among included studies. When fewer than three studies are included in a meta-analysis, we will use a fixed-effect model. We will not combine studies in a meta-analysis when we detect substantial heterogeneity among included studies.

Subgroup analysis and investigation of heterogeneity Data were insufficient to allow review authors to conduct a subgroup analysis for this review. If adequate data are obtained in future updates, we will stratify by underlying cause of dry eye symptoms, including tear deficiencies (Sjögren's syndrome), non–Sjögren's syndrome–related dry eye, evaporative dry eye (blepharitis or meibomian gland dysfunction (MGD)), and complications of LASIK.

Sensitivity analysis We did not conduct a sensitivity analysis for this review. For future updates, we will investigate the impact of studies with lower methodological quality (i.e., high risk of bias for random sequence generation or incomplete outcome data for primary or secondary outcomes) and of unpublished studies by performing sensitivity analyses.

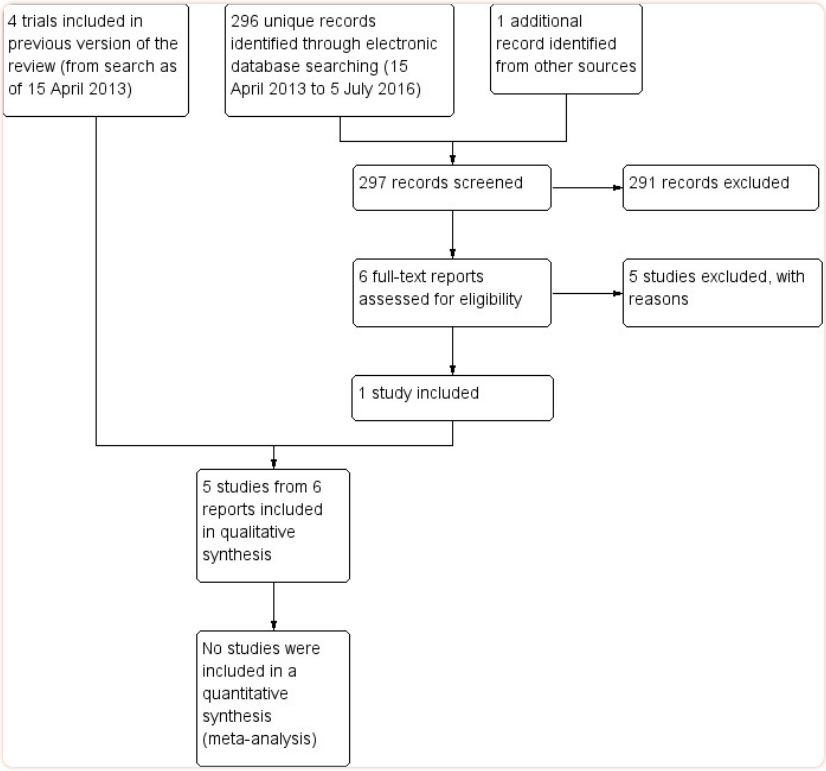
Summary of findings We assessed the certainty of evidence for each outcome in this review by using the GRADE classification method (GRADEpro 2014). The GRADE approach considers five criteria when used to assess the certainty of evidence, including risk of bias, indirectness, heterogeneity, imprecision, and publication bias. Two review authors independently graded each outcome as very low, low, moderate, or high, and resolved disagreements by discussion. We summarized the main findings of GRADE assessments for each outcome in a "Summary of findings" table. In the absence of a core outcome set for dry eye, we selected the seven outcomes presented in the "Summary of findings" table as the primary outcomes (symptom improvement), as well as adverse events and the first five listed secondary outcomes (tear hyperosmolarity, ocular staining with fluorescein, ocular staining with Rose Bengal, tear film break-up time, and Schirmer's test score).

Results

Description of studies

Results of the search We identified a total of 402 titles and abstracts through electronic searches performed as of April 2013 (Pan 2013). After removing duplicates, we screened 360 titles and abstracts. We identified 30 reports of 29 studies as potentially relevant for this review. After full-text review of the 30 reports, we included three full-text reports from three trials (Noda-Tsuruya 2006; Tananuvat 2001; Urzua 2012) and one full-text report and conference abstract report of findings from another trial (Kojima 2005a) (see Characteristics of included studies).

Updated electronic searches yielded 296 additional records as of July 5, 2016 (Figure 1). We identified one potentially relevant record by searching the Science Citation Index for trials that cited included studies. Of 297 unique records identified, we excluded 291 records by screening titles and abstracts, and five upon review of full-text reports (Fea 2016; Hwang 2014; Li 2015; Mukhopadhyay 2015; NCT02752763). We included one new trial (Celebi 2014) in the update of this review.



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Results obtained by searching for studies for inclusion in the review.

Included studies

Participants All study participants in the five trials included in this review had dry eye (149 eyes of 92 participants). Causes of dry eye included post LASIK (Noda-Tsuruya 2006), non-Sjögren's syndrome (Urzua 2012), and a mix of Sjögren's and non-Sjögren's conditions (Celebi 2014; Kojima 2005a; Tananuvat 2001). Three trials specifically included participants with dry eye refractory to conventional therapy (e.g., artificial tears, topical cyclosporine) (Celebi 2014; Tananuvat 2001; Urzua 2012). The number of participants in these studies ranged from 12 to 27, and average age ranged between 30 and 65 years. Two trials were conducted in Japan (Kojima 2005a; Noda-Tsuruya 2006), and one each in Australia (Tananuvat 2001), Chile (Urzua 2012), and Turkey (Celebi 2014). Most trials enrolled both men and women and enrolled more women than men, except for Noda-Tsuruya 2006, which included only men with post-LASIK dry eye.

Interventions All five trials evaluated 20% AS and gave instructions to participants to apply drops four, five, or six times daily, as well as similar instructions for storage of AS study vials across trials. Investigators instructed participants to refrigerate the eye drop bottle in use while freezing the rest. Duration of AS use ranged from two weeks to six months across trials. Three trials compared AS versus artificial tears using a parallel-group (Kojima 2005a) or cross-over (Celebi 2014; Urzua 2012) study design; two trials used a parallel-group (Noda-Tsuruya 2006) or paired-eye (Tananuvat 2001) study design to compare 20% AS with saline. Both cross-over trials included a washout between treatment periods to minimize carry-over effects. In two trials, participants in both treatment groups received additional topical treatments: preservative-free artificial tears as needed (Tananuvat 2001) and low-dose steroids, antibiotics, and hyaluronic acid after the LASIK procedure (Noda-Tsuruya 2006).

Outcomes The five included trials used different methods to evaluate participant-reported symptom improvement at different follow-up times. For each method used, higher values represented more severe symptoms/discomfort, and a decrease in values from baseline would suggest improvement in symptoms. Two studies described participant-reported symptoms at one-month follow-up - the primary outcome for this review (Celebi 2014; Tananuvat 2001); however, Celebi 2014 used a cross-over design and reported only between-group P values. The other three trials presented participant-reported symptoms noted at additional follow-up periods between two weeks' (Kojima 2005a; Urzua 2012) and six months' follow-up (Noda-Tsuruya 2006). Tananuvat 2001 additionally assessed study participants during follow-up visits at one week and two months and graded symptoms of dry eye (discomfort, foreign body sensation, dryness, and photophobia) as grade 0, no symptoms; 1, mild; 2, moderate; and 3, severe. Kojima 2005a used a visual analogue scale to assess pain symptom scores ranging from 0 to 100 points, where 0 represents absence of any pain and 100 represents intense and unbearable pain. The visual analogue scale is 10 cm long, and participants mark their responses on the scale. Noda-Tsuruya 2006 used a written questionnaire to assess dry eye symptoms; participants graded “typical dry eye symptoms” as 0, none; 1, mild; 2, moderate; 3, strong; and 4, very strong. Celebi 2014 and Urzua 2012 used the Ocular Surface Disease Index (OSDI), recommended by the International Dry Eye Workshop (Ozcura 2007), to evaluate participant-reported improvement in dry eye symptoms.

Although all studies provided measures of TBUT, tear secretion (Schirmer's test), and fluorescein staining, investigators did not follow the same procedures and reported additional differences in the time points at which they collected data. We believe that variation in procedures used to evaluate objective clinical tests would not influence the ability of investigators to compare treatment effects across studies; however, variation in the time points at which outcomes were assessed precluded pooling of data across trials. Kojima 2005a and Noda-Tsuruya 2006 observed TBUT after instilling 2 µL of 1% Rose Bengal mixed with 1% fluorescein and saline into the cul-de-sac; Celebi 2014 used 5 µL of fluorescein sodium; and Tananuvat 2001 placed a fluorescein strip moistened with saline into the lower cul-de-sac. Urzua 2012 provided no additional description of how investigators evaluated TBUT.

Celebi 2014, Tananuvat 2001, and Noda-Tsuruya 2006 specified that they performed Schirmer's test with anesthesia, and Kojima 2005a performed Schirmer's test without anesthesia.

Kojima 2005a and Noda-Tsuruya 2006 carried out scoring of fluorescein staining of the ocular surface by dividing the cornea into upper, middle, and inferior compartments, and by grading each compartment on a scale of 0 to 3 points (maximum: 9 points). Tananuvat 2001 did not divide the cornea into thirds and grad-

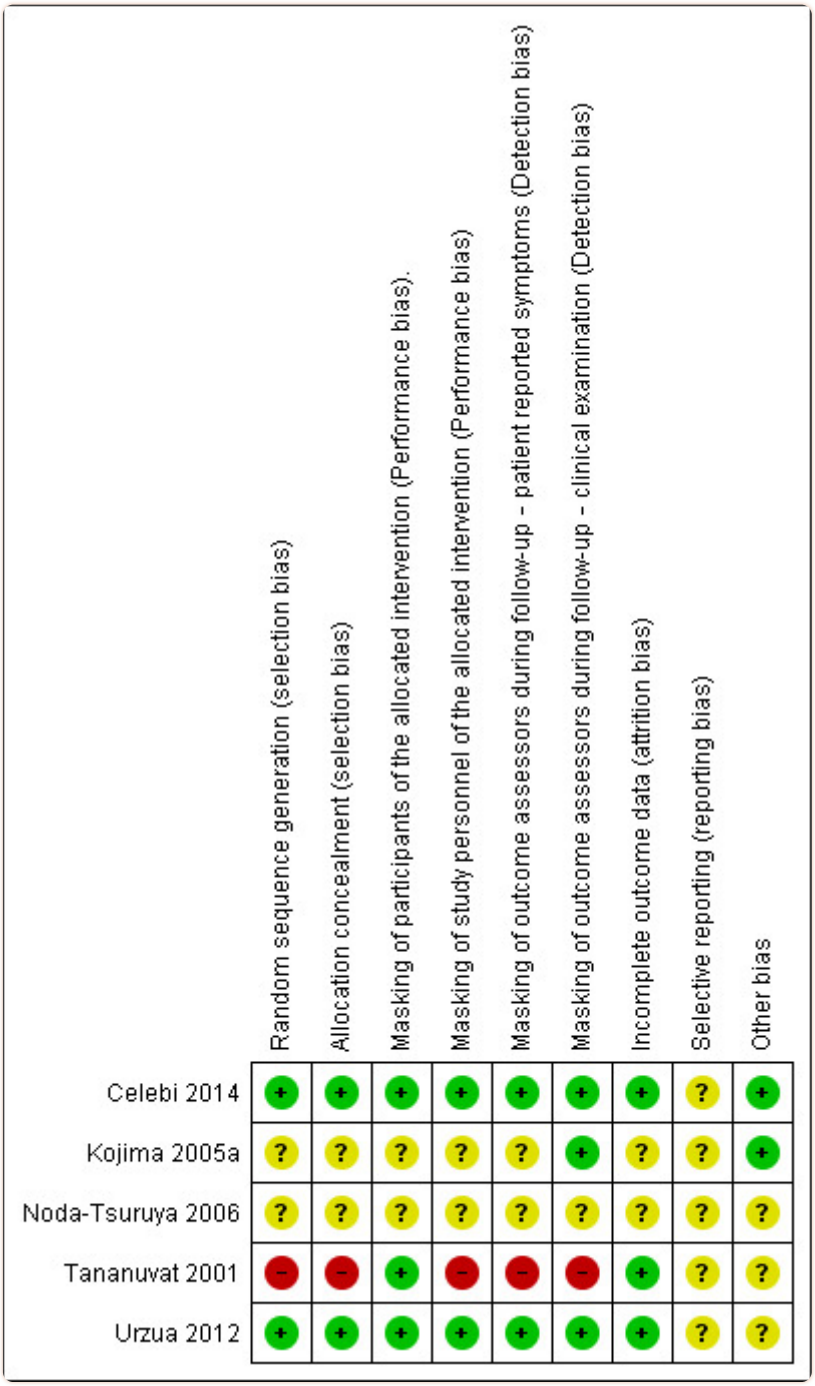
ed fluorescein staining of the cornea from 0 to 3. Celebi 2014 and Urzua 2012 used the Oxford Scale (six categories; 0 to 5, where 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe) to evaluate fluorescein staining (Bron 2003). The three trials measuring this outcome (Kojima 2005a; Noda-Tsuruya 2006; Tananuvat 2001) did not report details of the procedures used to evaluate Rose Bengal staining. Only one trial (Tananuvat 2001) evaluated conjunctival impression cytology and frequency of other topical lubricants.

Tananuvat 2001 was the only study that reported results from impression cytology and adverse events. No trial reported outcomes related to tear osmolarity, corneal topography, tear fluorescein clearance, conjunctival biopsy, quality of life, or costs.

Excluded studies We excluded 30 studies after full-text review (see Characteristics of excluded studies). Conference abstracts reported two studies (Harritshoj 2011; Jaksche 2005); we found one study in a clinical trial registry record (NCT02752763); and we identified the remainder from full-text publications. Most excluded studies were non-randomized studies or reviews. We excluded five RCTs because investigators did not compare AS versus artificial tears or placebo (Fea 2016; Jaksche 2005; Li 2015; Noble 2004; Yoon 2007).

Risk of bias in included studies

Figure 2 presents a summary of the risk of bias for included studies. For two studies (Kojima 2005a; Noda-Tsuruya 2006), most risk of bias domains were unclear owing to insufficient description in trial reports.



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Methodological quality summary: risk of bias review authors' judgements about each risk of bias item for each included study.

Allocation

Sequence generation and allocation concealment We judged risk of bias domains for sequence generation and allocation concealment to have low risk in two studies (Celebi 2014; Urzua 2012) and unclear risk in two studies (Kojima 2005a; Noda-Tsuruya 2006). Although the trials assessed to have unclear risk of bias

specified randomization of participants, neither of the published reports described in sufficient detail methods used to generate the allocation sequence or ways investigators implemented allocation concealment. One study used block randomization, with block sizes of two resulting in alternating treatment assignment; we judged this study to have high risks of bias for sequence generation and allocation concealment as investigators were unmasked and assignments provided in a block size of two could be known (Tananuvat 2001).

Masking (performance bias and detection bias)

Masking of participants and study personnel We judged masking of participants and study personnel to the allocated intervention to introduce low risk of bias in two studies (Celebi 2014; Urzua 2012) and unclear risk in two studies (Kojima 2005a; Noda-Tsuruya 2006). Published reports for Kojima 2005a and Noda-Tsuruya 2006 provided a full description of measures used to achieve masking; investigators specified a prospective randomized design without clearly reporting masking of participants or study personnel. Researchers conducted the third trial as a single masked study, with participants masked to treatment assignments and investigators unmasked (Tananuvat 2001). We judged this trial to be at low risk of bias for masking participants and at high risk of bias for not masking study personnel.

Participants allocated to the AS group had to undergo blood extraction as part of the serum production process. All five trials (Celebi 2014; Kojima 2005a; Noda-Tsuruya 2006; Tananuvat 2001; Urzua 2012) reported specific instructions provided for preservation and storage of AS. It is not clear at what point in the randomization process participants were subjected to serum collection procedures, or whether investigators provided the same storage instructions to all participants regardless of treatment assignment. Two studies (Celebi 2014; Urzua 2012) implemented a cross-over study design, which maintained participant masking, whereby all participants underwent venous blood draw for preparation of their AS. Additional measures taken in these trials included use of opaque flasks and instructions to keep all study medications frozen to ensure participant masking.

Masking of outcome assessors Investigators considered outcome assessments in two main categories: assessment of participant-reported symptoms; and assessment of objective clinical examinations. We assessed Celebi 2014 and Urzua 2012 as having low risk of bias for both participant-reported outcomes and objective clinical tests because participants and outcome assessors were masked. We judged masking of outcome assessors for participant-reported symptoms to introduce unclear risk for two studies (Kojima 2005a; Noda-Tsuruya 2006). Neither study provided a full description of how study authors recorded participant-reported outcomes and whether study personnel collecting this information were aware of each participant's treatment assignment. Two studies asked participants to complete a written questionnaire or an analogue pain scale (Kojima 2005a; Noda-Tsuruya 2006). We judged masking of outcome assessors for the objective clinical examination to introduce unclear risk of bias for one study (Noda-Tsuruya 2006) but low risk for the other (Kojima 2005a). One study kept investigators unmasked; we determined that this study was at high risk of bias for all outcome assessments (Tananuvat 2001).

Incomplete outcome data We judged the domain for incomplete outcome data to be at low risk of bias for three studies (Celebi 2014; Tananuvat 2001; Urzua 2012) because these studies reported no losses to follow-up and no missing data. One study (Noda-Tsuruya 2006) reported the number of eyes for each outcome at all time points across both treatment arms, but investigators did not provide reasons for missing

outcome data; the number of analyzed eyes was variable throughout the intervention, and this resulted in a judgement of unclear risk of bias. One trial (Kojima 2005a) excluded two eyes from analyses in the full-text report but not in the conference abstract for the same trial, with no explanation for the discrepancy.

Selective reporting We found all studies to be at unclear risk of reporting bias. For one study, we were able to confirm prespecified outcomes described in the ClinicalTrials.gov record against the corresponding publication (Urzua 2012), but we did not have access to study protocols or other related materials for the other studies. Although Urzua 2012 reported data for all outcomes as described in trial registry record, the study used a cross-over design and outcome data were not reported in a way that we could compare outcomes between treatment groups appropriately. Celebi 2014 also used a cross-over design and did not report outcome data in a way that we could analyzed the data appropriately. For Noda-Tsuruya 2006 and Tananuvat 2001, reported information was insufficient for review authors to extract usable data for quantitative summary analyses.

Other potential sources of bias We were unable to fully assess other potential sources of bias for two studies that we judged to have unclear risk of bias. In one study (Tananuvat 2001), participants in both groups were able to use artificial tears lubricants. The estimated treatment effect of AS may have been influenced if additional lubricants had a perceived therapeutic effect on the outcomes of interest and were used in different frequencies by each group. Another study (Noda-Tsuruya 2006) reported a discrepancy between the unit of randomization (individual) and the unit of analysis (eyes); this may have led to biased treatment effects with no consideration of within-participant correlation. On review of predefined inclusion criteria, we identified a discrepancy with inclusion criteria listed in the published report for one study; this led us to judge this study as having unclear risk of bias (Urzua 2012). Furthermore, Celebi 2014 and Urzua 2012 used a cross-over design but did not provide sufficient information to account for the design, so review authors could analyze the data. For one study, we found sufficient information (appropriate study design, proper ethical conduct, no involvement from industry) to establish low risk of other potential bias (Kojima 2005a).

Effects of interventions

See: Table 1; Table 2

Summary of findings for the main comparison

Summary of findings: autologous serum compared with artificial tears

Autologous serum compared with artificial tears for dry eye

Patient or population: participants with dry eye
Settings: eye clinics
Intervention: autologous serum 20%
Comparison: artificial tears

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk Artificial tears	Corresponding risk Autologous serum				
Participant-reported symptoms Range of scale: 0-100, where a higher score is worse Follow-up: 2-4 weeks	Mean change in symptom score in the control group was 7.2 point improvement	Mean change in symptom score in the autologous serum group was **12.0 points more improved** (20.16 to 3.84 more improved)		20 (1 RCT)	⊕⊕⊖⊖ **low**[a,b]	Trial investigators of 2 other studies reported more symptomatic improvement in the autologous serum group than in the artificial tears group; however, studies used a cross-over design and did not provide sufficient data for comparison of treatments between groups
Tear hyperosmolarity Follow-up: 2-4 weeks	Not reported					
Fluorescein staining Range of scale: 0-9, where a higher score is worse	Mean change in fluorescein score in the control group was 0.2 point	Mean change in fluorescein score in the autologous serum group was **0.9 points more**		20 (1 RCT)	⊕⊕⊖⊖ **low**[a,b]	Trial investigators of 2 other studies reported a non-significant difference in

[a]Downgraded (-1) for imprecision (wide confidence intervals)

[b]Downgraded (-1) for unclear risk of bias, such as performance and detection bias (lack of masking) and reporting bias (lack of quantitative data from relevant trials)

Summary of findings 2

Summary of findings: autologous serum compared with saline

Autologous serum compared with saline for dry eye **Patient or population:** participants with dry eye **Settings:** eye clinics **Intervention:** autologous serum 20% **Comparison:** saline						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Saline	**Autologous serum**				
Participant-reported symptoms Follow-up: 2-4 weeks	See comment					Trial investigators of 2 studies reported no difference in symptom scores between groups; however, studies did not provide sufficient data for comparison of treatments between groups
Tear hyperosmolarity Follow-up: 2-4 weeks	Not reported					
Fluorescein staining Range of scale: 0-9, where a higher score is worse Follow-up: 2-4 weeks	See comment					Trial investigators of 2 studies reported no difference in fluorescein staining scores between groups; however, studies did not provide sufficient

[a]Downgraded (-3) for high or unclear risk of selection, performance, detection, and reporting bias

We could not combine included studies in meta-analyses owing to heterogeneity in the time points at which primary and secondary outcomes were reported and insufficient reporting of descriptive statistics (means and standard deviations) necessary for computing treatment effect estimates. Two studies implemented a cross-over design but did not report the necessary summary statistics from a paired analysis (i.e., mean difference from paired t-test and corresponding confidence interval or P value) to account for participant-level differences in AS and artificial tears (Celebi 2014; Urzua 2012). We therefore provide only a narrative description of reported findings from each trial.

We analyzed improvement in symptoms at any follow-up time point and adverse events at the end of the study. For all secondary outcomes, we present data reported between two weeks and four weeks.

20% autologous serum versus artificial tears Three of the five included trials measured effects of 20% autologous serum (AS) using preservative-free artificial tears as a control. Two trials used a cross-over design and used two different brands of artificial tears (Celebi 2014; Urzua 2012); one trial used a parallel-group design and did not state which brand of artificial tears was used (Kojima 2005a).

Improvement in symptoms Celebi 2014 was the only included trial to report results for the specified primary outcome - change from baseline in participant-reported symptoms - at the specified primary outcome time point for this review of one month's follow-up. However, all included trials presented participant-reported symptoms at various follow-up times.

Both cross-over trials - Celebi 2014 and Urzua 2012 - used the Ocular Surface Disease Index (OSDI) to measure improvement in symptoms. The OSDI questionnaire consists of 12 questions, which respondents rank from 0 to 4. A score of 0 indicates "none of the time," 1 indicates "some of the time," 2 "half the time," 3 "most of the time," and 4 "all of the time" (Ozcura 2007). The total score is calculated using the following formula: OSDI = ((sum of scores for all answered questions) × 100]/[(total number of questions) × 4) (Ozcura 2007). Total scores can range from 0 to 100; any score above 46 is considered high (Ozcura 2007). Kojima 2005a used a visual analogue scale to assess improvement in symptoms.

Two weeks' follow-up Two trials assessed participant-reported symptoms after two weeks of treatment. Urzua 2012, which used a cross-over design, reported data only as pooled OSDI values after treatment with AS versus artificial tears, regardless of the phase in which the participant received treatment. Trial investigators reported a 51% decrease in OSDI score in the AS group and a 22% decrease in the artificial tears group, but these data do not account for the cross-over design and do not provide a between-group comparison.

In Kojima 2005a, mean change (and standard deviation (SD)) from baseline at two weeks' follow-up measured on the visual analogue scale was -19.2 ± 8.8 for the 20% AS group and -7.2 ± 9.8 for the artificial tears group, resulting in a difference in mean change from baseline of -12.00 (95% confidence interval (CI) -20.16 to -3.84; 20 participants; Analysis 1.1). This difference suggests a greater decrease in pain/dry eye symptoms in the 20% AS group compared with the artificial tears group after two weeks; however, the upper limit of the 95% confidence interval translates to a difference of less than 0.5 cm on the visual analogue scale.

We graded the certainty of evidence for symptom improvement at two weeks' follow-up as low, after down-grading for imprecision (-1) and unclear risk of bias (-1).

Four weeks' follow-up One trial assessed participant-reported symptoms after two weeks of treatment. Using a cross-over design, Celebi 2014 assigned participants to a sequence of 20% AS then artificial tears, or a sequence of artificial tears then 20% AS. Each phase in each sequence lasted one month and was preceded by a washout period. Investigators reported mean OSDI scores for each group at the end of each phase, but these data do not account for the cross-over design, nor do they allow assessment of the change in OSDI scores between groups. At the end of the first phase, Celebi 2014 reported that the mean OSDI score in the AS 20% group was lower than in the artificial tears group, although scores for both groups fell within the moderate OSDI category.

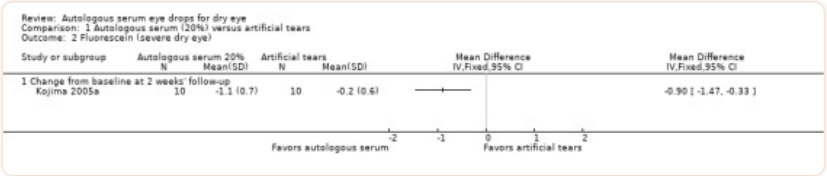
Three months' follow-up After completion of a two-week washout phase, Celebi 2014 recorded OSDI scores again to serve as a baseline for both groups, but these data do not account for the cross-over design nor allow assessment of the change in OSDI scores between groups. Similar to one-month follow-up, Celebi 2014 reported that the mean OSDI score in the AS 20% group was lower than in the artificial tears group, although scores for both groups fell within the moderate OSDI category.

Six months' follow-up Celebi 2014,Kojima 2005a, and Urzua 2012 did not report improvement in symptoms at six months' follow-up.

Tear hyperosmolarity None of the included trials reported this outcome.

Ocular surface staining

Fluorescein staining Three studies reported results of fluorescein staining. In Kojima 2005a, mean change and SD for fluorescein staining from baseline to two weeks was -1.1 ± 0.7 for the 20% AS group and -0.2 ± 0.6 for the artificial tears group, resulting in a difference in the mean change from baseline of -0.90 (95% CI -1.47 to -0.33; 20 participants; Analysis 1.2). Researchers did not consider this difference to be clinically important and classified fluorescein staining scores for both groups as abnormal (defined as a fluorescein staining score > 1) at baseline and at follow-up. Urzua 2012 and Celebi 2014 reported a non-significant difference between groups in mean Oxford Scale scores for fluorescein staining; however, data from these trials do not account for the cross-over design, nor do they provide sufficient information for comparison of scores between treatment groups.



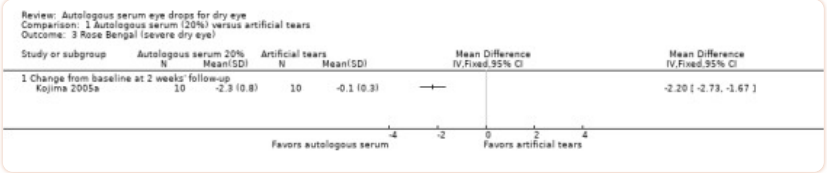
1.2

Analysis

Comparison 1 Autologous serum (20%) versus artificial tears, Outcome 2 Fluorescein (severe dry eye).

We graded the certainty of evidence for fluorescein staining as low, after downgrading for imprecision (-1) and unclear risk of bias (-1).

Rose Bengal staining One study reported results for Rose Bengal staining. In Kojima 2005a, the mean change and SD in Rose Bengal staining from baseline to two weeks was -2.3 ± 0.8 for the 20% AS group and -0.1 ± 0.3 for the artificial tears group, resulting in a difference in the mean change from baseline of -2.20 (95% CI -2.73 to -1.67; 20 eyes; Analysis 1.3). This difference may be considered clinically important; however, study investigators classified Rose Bengal staining scores in both groups as abnormal (defined as a Rose Bengal staining score > 1) at baseline and at follow-up.



1.3

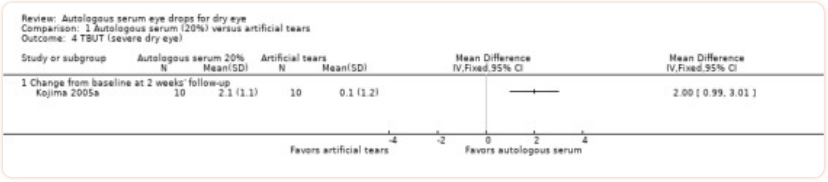
Analysis

Comparison 1 Autologous serum (20%) versus artificial tears, Outcome 3 Rose Bengal (severe dry eye).

We graded the certainty of evidence for fluorescein staining as low, after downgrading for imprecision (-1) and unclear risk of bias (-1).

Tear film break-up time (TBUT) Three studies reported results for TBUT. Kojima 2005a reported mean change and SD from baseline to two weeks' follow-up of 2.1 ± 1.1 seconds for the 20% AS group and 0.1 ± 1.2 seconds for the artificial tears group, resulting in a mean difference of 2.00 seconds (95% CI 0.99 to 3.01) between 10 participants in each treatment group (Analysis 1.4). Trial investigators did not consider this difference to be clinically important, and TBUT at baseline and follow-up in both groups indicated dry

eye (TBUT ≤ 5 seconds; Behrens 2006). Celebi 2014 and Urzua 2012 reported differences in TBUT between groups as 1 and 2 seconds, respectively; however, data from these trials do not account for the cross-over design, nor do they provide sufficient information for comparison of scores between treatment groups.



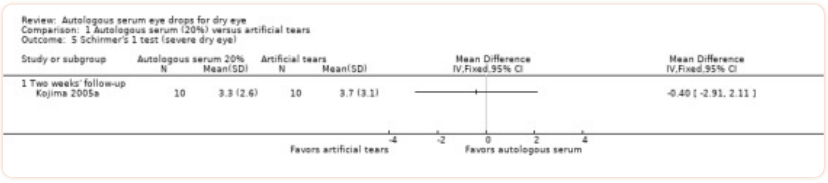
1.4

Analysis

Comparison 1 Autologous serum (20%) versus artificial tears, Outcome 4 TBUT (severe dry eye).

We graded the certainty of evidence for fluorescein staining as low, after downgrading for imprecision (-1) and unclear risk of bias (-1).

Schirmer's test Kojima 2005a performed Schirmer's test without anesthesia. At two weeks' follow-up, the mean and SD for the 20% AS group was 3.3 ± 2.6 mm compared with 3.7 ± 3.1 mm for the artificial tears group, resulting in a mean difference of -0.40 (95% CI -2.91 to 2.11 mm; 20 participants; Analysis 1.5). Investigators did not consider this difference to be clinically important, and Schirmer's test values in both groups indicated severe dry eye (< 4 mm). Celebi 2014 reported no difference in Schirmer's test scores between groups; however, data from this trial do not account for the cross-over design, nor do they provide sufficient information for comparison of scores between treatment groups.



1.5

Analysis

Comparison 1 Autologous serum (20%) versus artificial tears, Outcome 5 Schirmer's 1 test (severe dry eye).

We graded the certainty of evidence for fluorescein staining as low, after downgrading for imprecision (-1) and unclear risk of bias (-1).

Corneal topography None of the included trials reported this outcome.

Impression cytology Celebi 2014,Kojima 2005a, and Urzua 2012 did not report this outcome.

Tear fluorescein clearance None of the included trials reported this outcome.

Conjunctival biopsy None of the included trials reported this outcome.

Adverse events Celebi 2014,Kojima 2005a, and Urzua 2012 did not report adverse events at any time point.

20% autologous serum versus saline Two of the five included trials measured effects of 20% AS versus saline eye drops (Noda-Tsuruya 2006; Tananuvat 2001). We did not perform meta-analysis owing to insufficient data; Tananuvat 2001 did not report the number of participants per group nor SDs for outcomes.

Improvement in symptoms

Two weeks' follow-up Noda-Tsuruya 2006 and Tananuvat 2001 did not report improvement in symptoms at two weeks.

Four weeks' follow-up At four weeks' follow-up, Tananuvat 2001 reported that the mean composite symptom score was 5.36 for the 20% AS group and 6.45 for the saline group. We could not analyze the difference between 20% AS and saline groups owing to insufficient data; however, trial investigators reported that mean symptom scores were not statistically significantly different ($P > 0.05$) between groups over a two-month treatment period.

Six months' follow-up Noda-Tsuruya 2006 did not report descriptive statistics (mean and SD) for 27 post-LASIK participants (54 eyes) as measured by a five-point questionnaire. However, in a narrative description, trial investigators reported that they found no statistically significant differences ($P > 0.05$) in participant-reported symptoms between the 12 participants (24 eyes) in the 20% AS group and the 15 participants (30 eyes) in the artificial tears group before and after LASIK surgery through six months' follow-up.

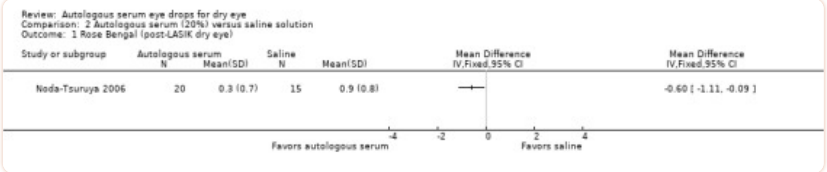
Tear hyperosmolarity None of the included trials reported this outcome.

Ocular surface staining

Fluorescein staining Both studies assessed fluorescein staining. Noda-Tsuruya 2006 reported mean and SD among 20 eyes at one month's follow-up for the 20% AS group (0.5 ± 0.7) but did not provide data for the 23 eyes in the control group. Tananuvat 2001 reported a mean score of 1.55 for the 20% AS group and 1.55 for the saline group (12 participants in total).

Rose Bengal staining Both studies assessed Rose Bengal staining. Noda-Tsuruya 2006 reported that means and SDs were 0.3 ± 0.7 for the 20% AS group and 0.9 ± 0.8 for the saline group, resulting in a mean difference in Rose Bengal staining score of -0.60 (95% CI -1.11 to -0.09; 35 eyes) one month after LASIK (

Analysis 2.1). Investigators did not consider this difference clinically important. Tananuvat 2001 reported that the mean for Rose Bengal staining was the same for both 20% AS and control groups at one month's follow-up (mean 4.22 points for both groups).



2.1

Analysis

Comparison 2 Autologous serum (20%) versus saline solution, Outcome 1 Rose Bengal (post-LASIK dry eye).

We graded the certainty of the evidence for fluorescein staining as very low, after downgrading for high or unclear risk of selection, performance, detection and reporting bias (-3).

Tear film break-up time (TBUT) One study reported TBUT at two to four weeks' follow-up. Tananuvat 2001 reported means (in seconds) of 0.55 for the 20% AS group and 0.64 for the control group.

Schirmer's test Noda-Tsuruya 2006 performed Schirmer's test with anesthesia; however, trial investigators reported only that they detected no differences between treatment groups and provided no descriptive statistics (mean and SD).

Corneal topography None of the included trials reported this outcome.

Impression cytology Only one study reported results from impression cytology according to conjunctival differentiation separated into six stages scored from 0 to 6 (Tananuvat 2001). At two months' follow-up, the mean score was 1.57 for the 20% AS group and 2.17 for the saline group after two months' follow-up. Trial investigators reported that the mean difference between groups at two months' follow-up was non-significant ($P > 0.05$).

Tear fluorescein clearance None of the included trials reported this outcome.

Conjunctival biopsy None of the included trials reported this outcome.

Adverse events Tananuvat 2001 reported that two of 12 participants had signs of conjunctivitis with negative culture; in both cases, symptoms resolved later with proper treatment. It was not stated whether investigators assigned affected eyes to the AS group or to the control group. Microbiological culture of serum stored at -20°C for up to two months showed no growth. All returned serum bottles underwent culture, and only one sample exhibited mixed organisms, including yeast. Investigators detected no cases of infectious conjunctivitis and no other adverse reactions.

Discussion

Several studies (Fox 1984; Kojima 2005a; Noda-Tsuruya 2006; Tananuvat 2001; Tsubota 1996; Tsubota 1999; Tsubota 2000) have described the use of autologous serum eye drops (AS) to treat people with dry eye. Our aim in performing this systematic review was to analyze evidence of the highest quality from randomized controlled trials (RCTs) to determine the efficacy and safety of AS in treating people with dry eye. However, most of the published literature is limited to retrospective case reports and non-randomized case series.

Summary of main results

We identified five RCTs that investigated effects of AS compared with artificial tears or saline in participants with a variety of causes of dry eye (Celebi 2014; Kojima 2005a; Noda-Tsuruya 2006; Tananuvat 2001; Urzua 2012). Celebi 2014 used a cross-over design to compare 20% AS (four times daily) versus artificial tears in participants with severe dry eye. Kojima 2005a evaluated the effectiveness of 20% AS after a two-week treatment interval (six times a day) in participants with severe Sjögren's and non-Sjögren's syndrome dry eye. Urzua 2012 used a cross-over design to compare two-week treatment intervals with 20% AS and artificial tears in 12 adult participants with severe non-Sjögren's syndrome dry eye. Tananuvat 2001 investigated the efficacy of 20% AS in 12 participants with bilateral severe dry eye over a two-month treatment interval (six times daily). Noda-Tsuruya 2006 assessed the efficacy of 20% AS (five times daily) for post-laser-assisted in situ keratomileusis (LASIK) dry eye from one week to six months.

Although precise measurement of symptoms is an important part of the dry eye diagnosis, no universally accepted standardized method is known for recording patient-reported symptoms; it has been commonly observed that participant-reported symptoms do not correlate with objective clinical test results (Alfonso 1999; Lin 2003; Schein 1997; Viso 2012). Although Celebi 2014 and Urzua 2012 both used the Ocular Surface Disease Index (OSDI), other studies in this review applied different methods to measure participant-reported symptoms. With consideration of the wide array of subjective questionnaires and scales used to measure participant symptoms and differences in length of follow-up, the five trials comparing AS versus artificial tears or saline did not consistently observe improvement in participant-reported symptoms. This might be due to variety in the type and severity of dry eye among participants in these studies.

Reported data from the included studies show that 20% AS were not associated with significant improvement in tear film stability as measured by tear break-up time (TBUT), aqueous tear production as measured by Schirmer’s test, or improvement in the condition of the ocular surface as measured by fluorescein or Rose Bengal staining compared with preservative-free artificial tears or saline. Tananuvat 2001 further found that 20% AS did not significantly change impression cytology among participants with severe bilateral dry eye.

Four of the five included studies did not report outcomes for adverse events or complications. One study (Tananuvat 2001) reported conjunctivitis in two participants, with cultures showing no growth followed by resolution of symptoms. All used AS containers returned by study participants for culture; one sample showed mixed organisms, including yeast, but investigators detected no infectious conjunctivitis nor adverse reactions among study participants.

Overall completeness and applicability of evidence

A major difficulty that review authors encountered in summarizing the results of included studies was heterogeneity among participant populations, interventions, and comparisons**,** as well as variation in procedures performed to prepare AS. We could not conduct summary meta-analyses because of additional differences in follow-up intervals and incomplete descriptive statistics for reported treatment outcomes. Also, each study included a sample size with too few participants to detect meaningful differences between groups for many outcomes. Thus, we were able to draw conclusions on the basis of qualitative assessment of trial reports.

Participant characteristics The causes of dry eye described for included participants may not be representative of all people with dry eye who potentially may benefit from AS. One study (Kojima 2005a) reported previous punctal occlusion as an exclusion criterion, and people with previous punctal occlusion were eligible for inclusion in another (Tananuvat 2001). One trial included participants with post-LASIK dry eye (Noda-Tsuruya 2006). Three trials enrolled participants with both severe Sjögren's and non-Sjögren's syndrome dry eye (Celebi 2014; Kojima 2005a; Tananuvat 2001), and another (Urzua 2012) enrolled participants with severe non-Sjögren's syndrome dry eye only.

Interventions and comparisons It is worth noting that investigators in Tananuvat 2001 instructed participants in the intraindividual study, in which participants used AS in one eye and placebo in the fellow eye, to use non-hyaluronan and unpreserved saline-based artificial tears as needed. These researchers also reported prior punctal occlusion in 75% of participants at the beginning of the study, adding further to the heterogeneity among included studies.

Preparation and storage of AS Currently, neither regulatory guidelines nor standard protocols have been provided for the manufacture of AS for dry eye. Critical steps in the production of AS, such as clotting time, centrifugation, and dilution, can influence the biochemical properties of AS and may lead to variable efficacy and treatment outcomes. In this review, only one study reported clotting time of two hours following venipuncture (Urzua 2012), and the other studies did not report clotting time. Geerling 2004 in Germany proposed two hours of clotting time at room temperature followed by optimal centrifugation of whole blood at 3000 × g for 15 minutes. Included studies reported variation in centrifugation speed and time, including 1500 revolutions per minute (rpm) for five minutes (Kojima 2005a), 2200 rpm for 20 minutes (Noda-Tsuruya 2006), 4200 rpm for 15 minutes (Tananuvat 2001), and 3500 rpm for five minutes (Urzua 2012). It has been demonstrated that higher concentrations of epithelial growth factor (EGF) and lower concentrations of transforming growth factor-beta (TGF-β) are obtained at higher centrifugation speed (Liu 2005; Pancholi 1998; Phasukkijwatana 2011). Although none of the included trials measured the concentrations of biologically active components within AS, concentrations of EGF, TGF-β, or other biological factors might be different across the included studies owing to variation in the rpm used for centrifugation. It is interesting to note that the trials included in this review compared 20% AS versus non-hyaluronan and unpreserved saline-based artificial tears or saline. Although results from in vitro studies show the greatest cell proliferation, with serum concentrations ranging from 12.5% to 25% (Geerling 2004; Liu 2005), 20% AS was the only concentration evaluated in the five trials included in this review.

Instructions given to study participants for storing AS were similar across included studies. Specifically, investigators instructed participants to keep vials containing AS in the freezer (-20°C) for up to three months and in a refrigerator at 4°C for two weeks after thawing. The AS storage instructions given to study participants have been shown to be effective in preventing contamination and deterioration of biological growth factors (Geerling 2004). Kojima 2005a reported an additional precaution to protect serum vials from ultraviolet light because vitamin A is easily degraded by light. A study from Thailand (Phasukkijwatana 2011) demonstrated that the stability of biologically active components within AS could be maintained for up to six months when stored at -20°C. However, the US Food and Drug Administration has not approved a standard procedure for preparing AS.

Quality of the evidence

Review authors identified only five small RCTs conducted in single-center settings; they included 92 total participants with severe Sjögren's-related dry eye, non-Sjögren's dry eye, and post-LASIK dry eye. The small number of participants is insufficient for review authors to detect or rule out meaningful beneficial or harmful effects of AS, or to provide precise estimates of individual outcomes. For many outcomes, data were insufficient for quantitative analysis. For the few outcomes for which analysis was possible, we assessed the certainty of evidence as low or very low.

We found that two studies had unclear risk of bias for masking participants. Given the primary outcome (i.e., change in participant-reported symptoms), the results of individual trials could have been influenced if participants were aware of their treatment assignment. However, complete masking may not have been feasible, given the necessary venipuncture involved in AS production. Also, variation in instructions reported for proper storage of AS compared with artificial tears might have led to participant knowledge of treatment assignments.

Potential biases in the review process

We employed a comprehensive search strategy to identify potentially eligible trials to minimize selection bias. Throughout the review process, two review authors assessed all potentially eligible studies and completed data extraction independently to minimize errors. Although we sought unpublished data from investigators of all included trials to supplement data provided in the published reports, we were unable to conduct quantitative synthesis for any of the outcomes specified for this review. The limited number of included trials precluded evaluation of potential publication bias through examination of funnel plots.

Agreements and disagreements with other studies or reviews

In the 2011 Prefered Practice Patterns, the American Academy of Ophthalmology (AAO) suggested that autologous serum drops improve ocular symptoms and conjunctival and corneal staining in severe dry eye (AAO 2011). Conclusions of the AAO were described as level "A III," and the AAO did not incorporate findings or conclusions from any of the five RCTs included in our review. Another evidence-based review (Akpek 2011) found level II B evidence for serum eye drops in Sjögren's syndrome dry eye that reflects the

absence of reliable evidence to support treatment decisions. The Akpek 2011 review discussed none of the five trials included in our review; this review focused on individuals with Sjögren's syndrome dry eye only, and review authors evaluated two studies that we excluded from our review (Noble 2004; Yoon 2007).

Authors' conclusions

Implications for practice

Current evidence suggests that 20% AS might provide some benefit in improving patient-reported symptoms over the short term (two weeks), but longer periods of follow-up provide no evidence of improvement over longer periods. Objective clinical measures of the ocular surface showed no clear effect.

Preparation, manufacturing, and storage of AS require a well-established, specialized service and strict aseptic processing. Procedures for AS production (clotting time, centrifugation, and concentration), including the proper solute for making AS, need to be optimized for clinical application of AS in people with dry eye. In addition, clinicians should carefully consider and document all applicable legislative restrictions and should obtain informed consent from each patient.

Implications for research

Well-planned, large-scale, high-quality randomized controlled trials are needed, with participants stratified by age and severity of dry eye, to compare AS versus artificial tears (or other treatments), and to evaluate additional concentrations of AS. These studies must include a random sequence generation protocol and appropriate concealment of treatment assignments before allocation. Future studies should attempt to ensure that both participants and study investigators (clinical staff and outcome assessors) are masked to treatment assignments to limit potential bias in participant-reported outcomes. We recommend that randomization in such trials be stratified by participant age and severity of dry eye-related symptoms. Future studies should utilize standardized and validated scoring systems of dry eye clinical severity, as well as symptom questionnaires. Objective biomarkers, which have been reported as a parallel index to the dry eye severity scale, such as tear osmolarity, tear cytokines, and HLA-DR expression by ocular surface cells (Lemp 2011; Tomlinson 2006; Versura 2012), should be applied as outcomes in conjunction with participant symptoms. Cost comparisons also would be of interest. Analyses should include both short-term (two to four weeks) and long-term (six to 12 months) outcomes. Data on adverse outcomes, including complications, infection, and tolerance of AS, should be documented.

What's new

Date	Event	Description
10 February 2017	New search has been performed	Issue 2, 2017: We updated electronic searches on July 5, 2016
10 February 2017	New citation required but conclusions have not changed	Issue 2, 2017: Updated searches yielded 1 new trial (Celebi 2014)

History

Protocol first published: Issue 9, 2011
Review first published: Issue 8, 2013

Date	Event	Description
15 October 2013	Amended	We made revisions in accordance with MECIR reporting standard guidelines

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Appendices

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Dry Eye Syndromes] explode all trees
#2 dry near eye*
#3 ocular near dry*
#4 MeSH descriptor: [Tears] explode all trees
#5t ear* near/2 film*
#6 xerophthalmi*
#7 keratoconjunctivi*
#8 sjogren* near syndrome

#9 steven* johnson syndrome*
#10 MeSH descriptor: [Pemphigoid, Benign Mucous Membrane] explode all trees
#11 cicatricial pemphgoid*
#12 blepharoconjunctiviti*
#13 MeSH descriptor: [Meibomian Glands] explode all trees
#14 meibomian
#15 lacrimal
#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 MeSH descriptor: [Serum] explode all trees
#18 autologous near/2 serum*
#19 #17 or #18
#20 #16 and #19

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp dry eye syndromes/
14. (dry adj2 eye$).tw.
15. (ocular adj2 dry$).tw.
16. exp tears/
17. (tear adj2 film$).tw.
18. xerophthalmi$.tw.
19. keratoconjunctiviti$.tw.
20. Sjogren$ syndrome.tw.
21. Stevens Johnson syndrome/
22. Steven$ Johnson syndrome$.tw.
23. Pemphigoid, Benign Mucous Membrane/
24. cicatricial pemphigoid$.tw.
25. blepharoconjunctiviti$.tw.
26. meibomian glands/
27. meibomian.tw.
28. lacrimal.tw.
29. or/13-28
30. exp serum/

31. (autologous adj2 serum$).tw.
32. or/30-31
33. 29 and 32
34. 12 and 33

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. dry eye/
34. (dry adj2 eye$).tw.
35. (ocular adj2 dry$).tw.

36. (tear adj2 film$).tw.
37. xerophthalmia/
38. xerophthalmi$.tw.
39. keratoconjunctivitis sicca/
40. keratoconjunctiviti$.tw.
41. Sjogren syndrome/
42. Sjogren$ syndrome.tw.
43. Stevens Johnson syndrome/
44. Steven$ Johnson syndrome$.tw.
45. mucous membrane pemphigoid/
46. cicatricial pemphigoid$.tw.
47. blepharoconjunctiviti$.tw.
48. meibomian gland/
49. meibomian.tw.
50. lacrimal apparatus/
51. lacrimal fluid/
52. lacrimal.tw.
53. or/33-52
54. exp serum/
55. (autologous adj2 serum$).tw.
56. or/54-55
57. 53 and 56
58. 32 and 57

Appendix 4. LILACS search strategy

dry eye and autologous

Appendix 5. ISRCTN search strategy

dry eye AND autologous

Appendix 6. ClinicalTrials.gov search strategy

Dry Eye AND Autologous

Appendix 7. ICTRP search strategy

dry eye OR dry eyes = Condition AND Autologous = Intervention

Notes

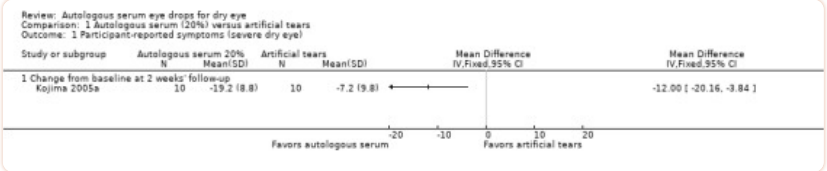
New search for studies and content updated (no change to conclusions)

Data and analyses

Comparison 1

Autologous serum (20%) versus artificial tears

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant-reported symptoms (severe dry eye)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Change from baseline at 2 weeks' follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Fluorescein (severe dry eye)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Change from baseline at 2 weeks' follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Rose Bengal (severe dry eye)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Change from baseline at 2 weeks' follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 TBUT (severe dry eye)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Change from baseline at 2 weeks' follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Schirmer's 1 test (severe dry eye)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Two weeks' follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]



1.1

Analysis

Comparison 1 Autologous serum (20%) versus artificial tears, Outcome 1 Participant-reported symptoms (severe dry eye).

Comparison 2

Autologous serum (20%) versus saline solution

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rose Bengal (post-LASIK dry eye)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Celebi 2014

Methods	**Study design:** 2-period cross-over, randomized controlled trial **Unit of randomization:** individual **Number randomized:** Total: 20 participants Per sequence: 10 randomized to each sequence **Unit of analysis:** individual **Number analyzed:** Total: 20 participants Per sequence: 10 per sequence
Participants	**Country:** Turkey **Mean age:** 56 years **Gender:** 18 women; 2 men **Underlying conditions:** severe, refractory dry eye **Inclusion criteria:** Severe DES, defined as tear BUT < 5 seconds, Schirmer's test score with anesthesia < 5 mm, corneal and conjunctival fluorescein staining ≥ grade 1 according to the Oxford Scale, and OSDI score > 40, refractory to conventional treatment (e.g., artificial tears, sodium hyaluronate, cyclosporine) **Exclusion criteria:** Active ocular infection or any other inflammation not associated with dry eye, eyelid or eyelash abnormality, associated glaucoma, graft-versus-host disease, severe anemia, uncontrolled cerebrovascular and cardiovascular disease, history of refractive surgery, current contact lens use or use of any type of topical eye drops other than dry eye medications, severe associated ocular allergy, pregnant or lactating women, inability to complete the study protocol
	Sequence 1: washout - 20% AS - washout - artificial tears **Sequence 2:** washout - artificial tears - washout - 20% AS AS protocol: 20% AS solution used 4 times a day for 1 month Artificial tears protocol: artificial tears (Refresh) used 4 times a day for 1 month Washout protocol: preservative-free isotonic saline (0.9% sodium chloride) used 4 times a day for 2 weeks **Length of follow-up:** Planned: 3 months

Kojima 2005a

Methods	**Study design:** parallel-group, randomized controlled trial **Unit of randomization:** individual **Number randomized:** Total: 20 participants (37 eyes) Per group: 10 participants **Unit of analysis:** individuals **Number analyzed:** Total: 20 participants Per group: 10 participants
Participants	**Country:** Japan **Mean age:** AS: 62 years Artificial tears: 65 years **Gender:** AS: 8 women; 2 men Artificial tears: 8 women; 2 men **Underlying conditions:** 8 of 10 participants in the AS group and 9 of 10 participants in artificial tears group had Sjögren's syndrome **Inclusion criteria:** All participants met diagnostic criteria of the Japanese Dry Eye Research Group: Schirmer's 1 test < 5 mm, or tear film BUT < 5 seconds **Exclusion criteria:** History of punctal occlusion, ocular or systemic disease, or history of drug or contact lens use that would alter the ocular surface
Interventions	**Intervention 1:** 20% AS (saline) **Intervention 2:** preservative-free artificial tears **Length of follow-up:** Planned: 2 weeks Actual: 2 weeks
	Participant questionnaire: Absence of any pain constituted a score of 0 points on visual analogue pain scales; intense, unbearable pain was considered a full pain score of 100 points **Tear function:**Tear film BUT was measured 3 times, and the mean value was calculated. Tear film BUT was considered abnormal if < 5 seconds. Schirmer's test was considered abnormal if < 5 mm.

[Noda-Tsuruya 2006]

	Study design: parallel-group, randomized controlled trial **Unit of randomization:** individual **Number randomized:** Total: 27 participants (54 eyes) Per group: AS: 12 participants (24 eyes) Saline: 15 participants (30 eyes) **Unit of analysis:** eyes **Number analyzed:** **1 month** BUT: AS 20, saline 23 Schirmer's: AS 20, saline 19 Rose Bengal: AS 20, saline 15 Fluorescein: AS 20, saline 23 **3 months** BUT: AS 18, saline 15 Schirmer's: AS 16, saline 15 Rose Bengal: AS 16, saline 11 Fluorescein: AS 18, saline 15 **6 months** BUT: AS 8, saline 10 Schirmer's: AS 8, saline 10 Rose Bengal: AS 6, saline 10
Methods	Fluorescein: AS 8, saline 10 **Country:** Japan **Mean age:** 30 years **Gender:** 100% men **Underlying conditions:** All participants had LASIK surgery 1 week before the start of the study **Concurrent dry eye treatments:** One week after LASIK surgery, all participants received topical steroids, antibiotics, and hyaluronic acid eye drops 5 times per day and discontinued use at 1 week postoperatively **Inclusion criteria:** post-LASIK, men "All patients revealed normal findings by routine preoperative ophthalmologic examination including tear function and vital

Tananuvat 2001

Methods	**Study design:** paired-eye, randomized controlled trial **Unit of randomization:** eyes **Number randomized:** Total: 26 eyes of 13 participants Per group: 13 eyes of 13 participants **Unit of analysis:** eyes **Number analyzed:** Total: 12 eyes of 12 participants Per group: 12 eyes of 12 participants
Participants	**Country:** Australia **Mean age:** 60 years **Gender:** Men: 5 Women: 7 **Underlying conditions:** 5 participants had Sjögren's syndrome: 2 had primary Sjögren's syndrome and 3 had secondary Sjögren's syndrome. Non-Sjögren's-type dry eyes included non-Hodgkin's lymphoma (n = 1), graft-versus-host disease (n = 1), Stevens-Johnson syndrome (n = 1), rheumatoid arthritis (n = 1), and idiopathic (n = 3) **Concurrent dry eye treatments:** artificial tears as needed **Inclusion criteria:** "Patients with bilateral severe dry eye were enrolled in this study. All had low Schirmer test scores and positive rose bengal staining and symptoms of dry eye despite frequent lubricants or previous punctal occlusion" **Exclusion criteria:** "Patients were excluded if they had active ocular infection or inflammation not related to dry eye, had ocular surgery within 3 months, were monocular, or had other conditions that may mimic dry eye symptoms such as allergic conjunctivitis or lid or lash abnormalities"
	Intervention 1: 20% AS **Intervention 2:** unpreserved saline solution and dilute fluorescein solution **Length of follow-up:** Planned: 2 months

Urzua 2012

Methods	**Study design:** 2-period cross-over, randomized controlled trial **Unit of randomization:** individual **Number randomized:** 12 participants **Unit of analysis:** individual **Number analyzed:** 12 participants
Participants	**Country:** Chile **Mean age:** 52 years **Gender:** 11 women; 1 man **Underlying conditions:** severe non-Sjögren's dry eye **Inclusion criteria:** At least 18 years old with severe dry eye, as defined by OSDI score ≥ 40, tear BUT < 5 seconds, cornea-conjunctival epithelial defects measured by fluorescein staining and evaluation using Oxford score and Schirmer's score < 5 mm/5 min; "all had used previous treatment with artificial tears with preservative" **Exclusion criteria:** Ocular surface disease other than dry eye, severe anemia, previous use of autologous serum or concomitant use of other topical ocular drug (i.e., topical steroids or cyclosporine), hypersensibility to any proposed interventions, inability to complete study protocol
Interventions	**Sequence 1:** 20% AS - washout - artificial tears **Sequence 2:** artificial tears - washout - 20% AS AS protocol: 20% AS solution used 4 times a day for 2 weeks Artificial tears protocol: artificial tears (Systane) used 4 times a day for 2 weeks Washout protocol: 0.9% sodium chloride used 4 times a day for 1 week **Length of follow-up:** Planned: 5 weeks Actual: 5 weeks
Outcomes	**Participant questionnaire:** score reduction in OSDI **Tear function:**tear BUT (in seconds) **Ocular surface:**corneal-conjunctival staining according to the Oxford Scale score (6 categories) **Vision:** best-corrected visual acuity **Trial registration:** NCT00779987

APL: autologous platelet lysate.

AS: autologous serum eye drops.

BCVA: best-corrected visual acuity.

DES: dry eye syndrome.

BUT: break-up time.

LASIK: laser-assisted in situ keratomileusis.

OSDI: ocular surface disease index.

TBUT: tear film break-up time.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Albegger 1972	Not a randomized controlled trial
Alvarado 2004	Non-randomized case series
Anderson 2004	Non-randomized case series
Badami 2009	Non-randomized case series
Bradley 2008	Non-randomized case series
Brown 2005	Non-randomized case series
Chiang 2007	Non-randomized case series
Craig 2008	Non-randomized case series
Fea 2016	Randomized trial comparing autologous platelet lysate drops with artificial tears
Fuchsluger 2005	Non-randomized case report
Geerling 2002	Overview about efficacy and recommendations for autologous serum for dry eye disease; not a randomized controlled trial
Geerling 2004	Non-randomized case series
Geerling 2008	Review of autologous blood products in the treatment of dry eye; not a randomized controlled trial
Harritshoj 2011	Retrospective study investigating allogenic (donor) serum
Hwang 2014	Non-randomized case series
Hyon 2007	Retrospective study
Jaksche 2005	Randomized trial comparing 50% autologous serum drops with 100% autologous serum drops
Koffler 2006	Non-randomized case series
Kojima 2005b	Non-randomized case series
Kojima 2008	Non-randomized case series
Li 2015	Randomized trial comparing autologous serum eye drops with bandage contact lenses
Messmer 2005	Not a randomized controlled trial
Movahedan 2006	Non-randomized case series
Mukhopadhyay 2015	Randomized trial in participants with Hansen's disease (leprosy); comparison of cord blood serum eye drops vs autologous serum eye drops vs artificial tears
NCT02752763	Randomized trial in participants using isotretinoin (vitamin A derivative); comparison of autologous serum eye drops vs artificial tears
Noble 2004	Conventional treatment arm with different pharmacological agents for each participant

Differences between protocol and review

We conducted GRADE assessments of the certainty of evidence and included a "Summary of findings" table, in accordance with Cochrane standards.

Contributions of authors

Conceiving of the review: AA.
Designing the review: AA, QP.
Co-ordinating the review: MM.
Collecting data for the review:
- Designing search strategies: AA, Iris Gordon (Cochrane Eyes and Vision Informationist).
- Undertaking searches: Iris Gordon.
- Screening search results: QP, AA, AZ, MM, TH, LT.
- Organizing retrieval of papers: MM.
- Screening retrieved papers against inclusion criteria: QP, AA, AZ, MM, TH, LT.
- Appraising the quality of papers: QP, AA, AZ, MM.
- Extracting data from papers: QP, AA, AZ, MM.
- Writing to authors of papers for additional information: AZ, MM.
- Providing additional data about papers: MM.
- Obtaining and screening data on unpublished studies: AZ, MM.

Managing data for the review:
- Entering data into RevMan: MM.
- Checking data once entered into RevMan: QP.

Interpreting data:
- Providing a methodological perspective: MM.
- Providing a clinical perspective: QP, AA, AZ, WJS, TH, LT, EKA.
- Providing a policy perspective: QP, AA, WJS, EKA.
- Providing a consumer perspective: AA, EKA.

Writing the review: QP, AA, AZ, MM.
Performing previous work that was the foundation of the current study: AA, EKA.
Serving as guarantor for the review: MM.
Updating the review:
- Updating and undertaking searches: Iris Gordon.
- Screening retrieved papers against inclusion criteria: QP, Cochrane Eyes and Vision.
- Appraising the quality of papers: QP, MM.
- Extracting data from papers: QP, MM.
- Writing the review: QP.
- Commenting on and approving the review update: QP, AA, MM, WJS, EKA.

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  The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

Declarations of interest

QP: none known.
AA: none known.
MM: none known.
WJS: none known.
EKA: none known.

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