Published in final edited form as:

Cochrane Database Syst Rev. ; (9): CD006775. doi:10.1002/14651858.CD006775.pub2.

Punctal occlusion for dry eye syndrome

Ann-Margret Ervin¹, Robert Wojciechowski², and Oliver Schein³

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Maryland, Baltimore, USA

²Inherited Disease Research Branch, National Human Genome Research Institute (NIH), Maryland, Baltimore, USA

³Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Maryland, Baltimore, USA

Abstract

Background—Dry eye syndrome is a disorder of the tear film and is associated with symptoms of ocular discomfort. Punctal occlusion is a mechanical treatment in which the tear drainage system is blocked in order to aid in the preservation of natural tears on the ocular surface.

Objectives—The objective of this review was to assess the safety and efficacy of punctal plugs for the management of dry eye.

Contact person, Ann-Margret Ervin, Assistant Scientist, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, W5010, Baltimore, Maryland, 21205, USA, aervin@jhsph.edu.

Declarations of interest

None known.

Differences between protocol and review

Cochrane methodology regarding assessments of the risk of bias in included studies have been modified and the review authors updated the 'Assessment of risk of bias in included studies' section of the methods to reflect updated methodological considerations.

Contributions of authors

Conceiving the review: AE, RW

Designing the review: AE, RW, OS

Co-ordinating the review: AE

Data collection for the review

- Designing search strategies: AE, RW, OS, CEVG Trials Search Co-ordinator

- Undertaking searches: CEVG Trials Search Co-ordinator

- Screening search results: AE, RW

- Organizing retrieval of papers: AE

- Screening retrieved papers against inclusion criteria: AE, RW

- Appraising quality of papers: AE, RW, OS

- Extracting data from papers: AE, RW

- Writing to authors of papers for additional information: AE

- Providing additional data about papers: AE

- Obtaining and screening data on unpublished studies: AE, RW

Data management for the review

- Entering data into RevMan: AE

- Analysis of data: AE, RW

Interpretation of data

- Providing a methodological perspective: AE, RW, OS

- Providing a clinical perspective: RW, OS

- Providing a policy perspective: RW, OS

- Providing a consumer perspective: AE, RW, OS

Writing the review: AE, RW, OS

Providing general advice on the review: AE, RW, OS

Securing funding for the review: N/A

Performing previous work that was the foundation of the current study: N/A

Guarantor for review: AE

Search methods—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2010, Issue 6), MEDLINE (January 1950 to June 2010), EMBASE (January 1980 to June 2010), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to June 2010), the *meta*Register of Controlled Trials (*mRCT*) (www.controlled-trials.com) and ClinicalTrials.gov (<http://clinicaltrials.gov>). We also searched the Science Citation Index-Expanded database and reference lists of included studies. There were no language or date restrictions in the search for trials. The electronic databases were last searched on 21 June 2010.

Selection criteria—We included randomized and quasi-randomized controlled trials of collagen or silicone punctal plugs in symptomatic participants diagnosed with aqueous tear deficiency or dry eye syndrome.

Data collection and analysis—Two review authors independently assessed trial quality and extracted data. We contacted study investigators for additional information.

Main results—Seven randomized controlled trials including 305 participants (601 eyes) met the inclusion criteria and are summarized in this review. We did not perform meta-analysis due to appreciable variability in interventions and follow-up intervals. Although punctal plugs provided symptomatic improvement and clinical outcomes also improved from baseline measures, few studies demonstrated a benefit of punctal plugs over the comparison intervention. Reported adverse effects included epiphora (overflow of tears), foreign body sensation, eye irritation, and spontaneous plug loss.

Authors' conclusions—This systematic review shows a relative scarcity of controlled clinical trials assessing the efficacy of punctal occlusion therapy in dry eye. Although the evidence is very limited, the data suggest that silicone plugs can provide symptomatic relief in severe dry eye. Moreover, temporary collagen plugs appear similarly effective to silicone plugs on a short-term basis.

Plain language summary

Punctal plugs for dry eye syndrome

Dry eye syndrome, which affects 10% to 20% of adults, is a disorder of the eye's tear film and is associated with symptoms such as burning, foreign body sensation, and fluctuating vision. Punctal plugs are inserted into a small opening in the upper and/or lower eyelid. Seven randomized controlled trials (with a total of 305 participants and 601 eyes) were identified. These trials compared silicone and/or collagen punctal plugs to each other, no treatment, acrylic punctal plugs, or oral pilocarpine (a drug used to increase tear production). Punctal plugs provided symptomatic improvement and clinical outcomes also improved from baseline measurements. Adverse outcomes included epiphora (overflow of tears), foreign body sensation, eye irritation, and spontaneous plug loss. Although individual trials reported improvements among participants assigned to punctal plugs, these trials were too diverse to summarize the effects across all studies.

Background

Description of the condition

Dry eye syndrome or keratoconjunctivitis sicca, is defined as “a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort” (Lemp 1995; Lemp 1998; Pflugfelder 2000). Dry eye affects 10% to 20% of adults, with one to four million aged 65 to 84 affected in the United States (AAO 2003; Schein 1997a). Estimates of dry eye have also been reported in Sweden (15%), India (18.4%), Australia (8.6% to 16.3%), and

Indonesia (27.5%) (Lee 2002; Lemp 1998; McCarty 1998; Sahai 2005). Dry eye has been associated with Sjögren's syndrome, arthritis, diabetes, corneal transplants, multivitamin use, laser in situ keratomileusis (LASIK), and photorefractive keratectomy (PRK) (Dalzell 2003; De Paiva 2006; Moss 2000). Symptoms may include redness, burning, itchiness, foreign body sensation, and in severe cases corneal ulceration and bacterial infection (Lemp 1998; Sheppard 2003; Wilson 2003). Assessments of ocular surface damage and measures of tear stability and hyperosmolality also aid the diagnosis of dry eye syndrome (Lemp 1995). Due to a lack of correlation among self-reported symptoms and clinical measures, it is difficult to precisely identify patients with dry eye (Lemp 1995; Schein 1997).

Artificial tears hydrate the eye and provide limited symptomatic relief with preservative-free tears preferred for long-term use since other formulations may be toxic to the cornea and conjunctival epithelium (Lemp 1994; Pflugfelder 2000). Interventions such as lubricants, bandage contact lenses, estrogens, topical corticosteroids and cyclosporine have also been shown to be effective treatments in selected settings (Lemp 1994; Pflugfelder 2000; Sall 2000; Sheppard 2003; Wilson 2003).

Description of the intervention

Punctal occlusion is a non-pharmacological intervention for dry eye when artificial tears do not effectively ameliorate symptoms (Balaram 2001; Willis 1987). Semi-permanent silicone or temporary collagen punctal plugs are inserted into the upper or lower puncta or both (Lemp 1994). Collagen plugs dissolve within four to seven days while silicone plugs either dislodge spontaneously or are removed by a physician. Permanent occlusion of the puncta is achieved by thermal cautery or argon laser (AAO 2003; Dohlman 1978; Lemp 1994).

How the intervention might work

Although punctal plugs do not completely eliminate the need for artificial tears in most cases, occluding the puncta aids in the preservation of natural tears and improves aqueous tear film quality and quantity (Barnard 1996; Dohlman 1978; Tai 2002). The most common side effects of occlusion are epiphora (overflow of tears), inhibited tear clearance, and desensitization of the corneal surface (Lemp 1994; Sheppard 2003; Tai 2002).

Nava-Castaneda 2003 compared collagen and silicone punctal plugs to sham treatment in 61 patients with dry eyes and found significant improvement of symptoms such as dryness, itching and burning at four and eight weeks among patients with occluded puncta. The investigators also observed a 93% reduction in conjunctival findings and 91% reduction in the use of adjunctive artificial tears among those treated with silicone and collagen plugs at eight weeks post-implant. Tai 2002 reviewed the charts of 153 dry eye patients (203 eyes) with silicone plugs. Symptoms improved in 74% of eyes at four weeks with a significant reduction in fluorescein staining and use of adjunctive lubrication in the same time period.

Why it is important to do this review

To date, there are no known systematic reviews examining the efficacy of punctal occlusion, specifically punctal plugs, for the management of dry eye. This review summarizes the best available evidence for the use of punctal occlusion in the treatment of dry eye.

Objectives

The objective of this review was to assess the safety and efficacy of punctal plugs for the management of dry eye.

Methods

Criteria for considering studies for this review

Types of studies—We included randomized and quasi-randomized controlled trials for this review. Studies that did not use randomization to allocate participants to treatment groups but used techniques intended to allocate patients in an unbiased fashion were considered quasi-randomized trials. Some examples include allocation based on the day of the week, year of birth, or hospital admission number.

Types of participants—We included symptomatic participants who were diagnosed with aqueous tear deficiency or keratoconjunctivitis sicca (dry eye syndrome). There were no restrictions with respect to age, gender, co-morbidities or use of adjunctive therapy.

Types of interventions—We considered clinical trials in which the lower punctum or upper and lower puncta were occluded with collagen or silicone punctal plugs and compared to each other or other treatments such as artificial tears or diathermy (use of electrodes to heat and contract punctal tissues). Clinical trials in which collagen or silicone plugs were used in conjunction with adjunctive therapies such as artificial tears were also considered for inclusion. We included trials in which occlusion was compared to no treatment, placebo or sham treatments.

Types of outcome measures

Primary outcomes: The primary outcome was subjective report of symptomatic improvement in itching, burning, and other symptoms as defined by included studies within one day to two weeks post-treatment. Since time points for outcome assessments vary appreciably by trial, we considered other time points as reported in included studies.

Secondary outcomes: Secondary outcomes assessed within one day to two weeks post-treatment were included in this review. We also considered other time points as reported in included studies.

Ocular surface staining as defined by the mean change in total Rose Bengal score from baseline to follow-up. We reported change in fluorescein and lissamine green scores where appropriate.

Aqueous tear production as measured by the mean change in Schirmer I test scores (millimeters). We included Schirmer I tests performed with and without anesthesia.

Tear film stability as measured by the mean change in tear film break up time (seconds).

Change in the frequency of artificial tear use as defined by included studies

Adverse outcomes: We reported adverse outcomes such as epiphora, corneal ulcers, and extrusion (total or partial displacement of the plug) of punctal plugs where appropriate. We also summarized other adverse outcomes reported in included studies.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2010, Issue 6), MEDLINE (January 1950 to June 2010), EMBASE (January 1980 to June 2010), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to June 2010), the *meta*Register of Controlled Trials (*mRCT*)

(www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov). We also searched the Science Citation Index-Expanded database and reference lists of included studies. There were no language or date restrictions in the search for trials. The electronic databases were last searched on 21 June 2010.

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

Searching other resources—We searched reference lists of included studies to identify any additional inclusions and also used the Science Citation Index-Expanded database to identify studies that may have cited trials included in this review. We did not handsearch conference proceedings or journals.

Data collection and analysis

Selection of studies—Two review authors independently reviewed titles and abstracts resulting from the literature searches, according to the inclusion criteria stated above. The abstracts were classified as ‘definitely exclude’, ‘unsure’ or ‘definitely include’. We retrieved the full text for abstracts classified as ‘unsure’ by either review author and the study was re-assessed for inclusion. The authors of studies classified as ‘unsure’ were contacted for further clarification, as required, after examining the full text. We resolved any disagreements through discussion. We excluded studies labeled as ‘exclude’ by both review authors from the review and the reasons for exclusion documented. Studies labeled ‘definitely include’ were further assessed for methodological quality.

Data extraction and management—Two review authors independently extracted data using a form developed by the Cochrane Eyes and Vision Group. One review author entered data into RevMan 5.0 and a second author verified all values.

Assessment of risk of bias in included studies—Two authors independently assessed the included studies for sources of systematic bias according to the guidelines in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009a). We evaluated the studies for the following criteria: sequence generation and allocation concealment (selection bias), masking of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. We reported the judgment for each criterion as ‘Yes (low risk of bias)’, ‘No (high risk of bias)’ or ‘Unclear (information is insufficient to assess)’.

We reported the adequacy of sequence generation and allocation concealment. Methods of sequence generation considered to be at low risk of bias include references to random number tables or computer generated random numbers and coin tosses. We considered any method of allocation concealment (such as centralized randomization, use of sequential opaque envelopes) which provides reasonable confidence that the allocation sequence was concealed from participating physicians and patients to be at low risk of bias.

We noted masking of outcome assessors by study outcome. Masking of investigators and participants might not have been possible with the interventions being examined, but was noted where mentioned.

For incomplete outcome data, rates of follow up, reasons for loss to follow-up and analysis by the principle of intention-to-treat (ITT) were examined. We assessed whether follow-up rates for treatment and control arms were similar and whether there were missing data for outcomes of interest. Studies were considered at low risk of bias if there were no missing

data or if participants for whom no outcome data were collected and those who received some or none of the allocated treatment were included in the analysis. We noted the method of data imputation, when appropriate, for included studies.

A study was considered to be at low risk of bias for selective outcome reporting if all pre-specified outcomes of interest in the protocol had been reported in the same manner in the published report.

We examined included studies for other sources of bias and considered studies at low risk of bias if there was no evidence of research misconduct, no potential for bias based on study methodology, or if the study was not stopped early due to evidence of harm or benefit.

We resolved disagreements through discussion. We contacted the authors of the studies for additional information on issues that were unclear from information available in the original report. In case of failure to communicate with the primary investigators, or if there was no response within six weeks, we assessed the methodological quality on the basis of the available information.

Measures of treatment effect—No pooled estimates of treatment effects are included in this review. If considered for a future update, we will calculate a summary risk ratio for dichotomous outcomes including the primary outcome of symptomatic improvement and reports of adverse events. We will verify normality of continuous outcomes and calculate mean differences for secondary outcomes as follows: mean change in Rose Bengal, fluorescein, and lissamine green scores, mean change in tear production as measured by the Schirmer I test, and mean change in tear film break up time. We will calculate standardized mean differences if continuous outcomes are measured using different scales.

Unit of analysis issues—The unit of analysis was eyes. No cross-over trials were included but if cross-over trials are considered during a subsequent update, we will attempt to extract or request from the investigators data to appropriately account for the cross-over design. If we are unable to retrieve these data, we will incorporate statistical techniques to approximate a paired analysis as outlined in Chapter 16.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009b).

Dealing with missing data—We contacted primary authors of included studies to provide missing data such as details regarding study methods, standard deviations and intention-to-treat data. If there was no response from the primary authors within six weeks, we imputed data where possible using available information such as P values or confidence intervals. The assumptions made during imputation are indicated where appropriate.

Assessment of heterogeneity—We did not assess heterogeneity since pooled estimates of the treatment effect were not included in this review. If additional studies are considered during a future update of this review, we will use the I^2 statistic (%) to determine the proportion of variation due to heterogeneity with a value above 50% suggesting considerable statistical heterogeneity. We will also examine the result of the χ^2 test for heterogeneity and the degree of overlap in confidence intervals of included studies. Poor overlap may also suggest the presence of heterogeneity. We will assess clinical and methodological heterogeneity by examining potential variations in participant characteristics, inclusion/exclusion criteria, and assessments of primary and secondary outcomes.

Assessment of reporting biases—Since pooled estimates of treatment effect across studies were not included, we did not examine funnel plots to assess reporting biases.

Data synthesis—We did not perform meta-analysis due to variability in interventions and follow-up intervals for the primary and secondary outcomes of interest. We will use the following guidelines for future updates of this review: If the I^2 statistic suggests considerable heterogeneity, as defined above in ‘Assessment of heterogeneity’, we will not combine the results in a meta-analysis and will instead present a narrative summary. If considerable heterogeneity does not exist based on the I^2 statistic and an inspection of the forest plot, we will combine the results of included trials in a meta-analysis using a random-effects model. A fixed-effect model will be used if the number of trials is less than three and there is no statistical, clinical, or methodological heterogeneity. In this instance, the fixed-effect model will provide a more robust estimate of the treatment effect.

Subgroup analysis and investigation of heterogeneity—Sufficient data were not available to conduct subgroup analyses. We will use the following guidelines for future updates of this review: If there is considerable statistical heterogeneity, evidence of potential clinical or methodological heterogeneity, and data are available, we will conduct a subgroup analysis of tear deficient classifications of dry eye as defined by the National Eye Institute/ Industry Workshop on Clinical Trials in Dry Eyes (Lemp 1995).

Sensitivity analysis—We did not perform sensitivity analyses. We will consider sensitivity analyses during future updates of this review to determine the impact of excluding studies with lower methodological quality, industry funding and those unpublished at the time of this review. We will also conduct sensitivity analyses to determine the impact of including quasi-randomized trials.

Results

Description of studies

Studies assessed for inclusion are described in the Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search—The electronic search identified a total of 115 titles and abstracts. We retrieved the full text of 19 articles and assessed the studies for inclusion in the review. Six reports were eligible for inclusion and 13 were excluded. One additional included study was identified from the list of references from the protocol version of this systematic review and from a search of the Science Citation Index-Expanded database.

Included studies—The seven studies (305 participants, 601 eyes) included in this review are described in the ‘Characteristics of included studies’ table and the intervention categories summarized in Table 1.

Studies that include collagen punctal plugs: Farrell 2003 compared collagen punctal plugs in the lower puncta versus the lower and upper puncta among a sample of 62 patients (121 eyes) with Sjögren’s syndrome or primary/secondary keratoconjunctivitis sicca. Participants were randomized to receive collagen punctal plugs in the 1) lower puncta only (investigator followed the steps of inserting a plug in the upper puncta but with no actual plugs inserted) or 2) upper and lower puncta. Participants returned at five and 12 days after receiving punctal plugs.

Lowther 1995 compared collagen punctal plugs to sham treatment among a sample of 32 hydrogel contact lens patients (64 eyes) with bilateral dry eye. One eye was randomized to receive collagen plugs in the lower and upper puncta while the steps of inserting a punctal plug were performed in the fellow eye (although no plug was actually inserted). Participants

continued wearing hydrogel contact lenses and returned for follow-up five days after receiving punctal plugs.

Tsifetaki 2003 compared collagen plugs to oral pilocarpine (oral pilocarpine was also compared to artificial tears) among a sample of 85 female patients diagnosed with Sjögren's syndrome. Patients with diabetes, heart disease, renal failure, gastrointestinal disease, multiple sclerosis, or any other eye disease were excluded from the study. Twenty-eight participants were randomized to oral pilocarpine, 28 to collagen punctal plugs, and 28 to artificial tears only. Artificial tears were also provided to participants receiving collagen plugs and oral pilocarpine. Participants returned weekly during the first month of follow-up and then once per month for up to 12 weeks.

Studies that include silicone punctal plugs

Burgess 2008 compared silicone punctal plugs to acrylic plugs among a sample of 21 dry eye patients (36 eyes) who used artificial tears for more than six months with no improvement. Patients who wore contact lenses or received punctal plugs within the previous six months were excluded from the study. Eighteen eyes were randomized to receive acrylic plugs and 18 to receive silicone plugs. Participants returned for follow-up approximately 11 weeks after occlusion.

Mansour 2007 compared silicone punctal plugs to no occlusion among a sample of 20 Sjögren's patients (40 eyes) with no ocular surface co-morbidities, no prior punctal occlusion or prior eye surgery. One eye was randomized to occlusion of the upper and lower puncta with silicone punctal plugs while the fellow eye remained unoccluded. Participants returned at least six months after occlusion for follow-up assessments.

Studies that include both collagen and silicone punctal plugs—Altan-Yaycioglu 2005 compared collagen to silicone punctal plugs among a sample of 24 patients (48 eyes) with dry eye syndrome who used artificial tears with no improvement. Excluded were patients with prior punctal occlusion, eyelid or blinking abnormalities, or previous nuclear scintigraphy. Twenty-two eyes were randomized to receive bilateral collagen punctal plugs in the lower puncta and 26 eyes received bilateral silicone punctal plugs in the lower puncta. Follow-up measurements were taken immediately after occlusion with the exception of ocular surface staining which was performed three days after occlusion.

Nava-Castaneda 2003 compared collagen plus silicone plugs to sham treatment among a sample of 61 patients (121 eyes) 18 to 80 years of age with two subjective symptoms of dry eye, ocular surface abnormalities as demonstrated by fluorescein score > 1, and conjunctivitis of 1 month. Patients were excluded if dry eye attributed to other ocular conditions or if diagnosed with asthma. Thirty-one eyes were randomized to receive collagen and silicone punctal plugs and 30 were randomized to sham occlusion. Participants were followed-up one hour and two, four, and eight weeks after occlusion.

Excluded studies—We excluded the remaining 13 studies, listed in the 'Characteristics of excluded studies' table with reasons for exclusion.

Risk of bias in included studies

Figure 1 presents a summary of the risk of bias for the included studies.

Allocation—Sequence generation was judged to be at low risk of bias for four studies (Burgess 2008; Mansour 2007; Nava-Castaneda 2003; Tsifetaki 2003). All studies used some form of a computer generated randomization scheme. Sequence generation was not

discussed in the remaining three included studies (Altan-Yaycioglu 2005; Farrell 2003; Lowther 1995).

Allocation concealment was judged to be at low risk of bias for the Nava-Castaneda 2003 study only. Random assignments were prepared by an external statistical committee and then placed in sealed envelopes. The randomization schedule was also maintained by the statistical committee. The remaining six trials did not include a discussion of allocation concealment.

Blinding—Masking was judged to be at low risk of bias for five of the seven included studies (Burgess 2008; Farrell 2003; Lowther 1995 ; Nava-Castaneda 2003; Tsifetaki 2003). In all of these studies, the outcome assessors were masked and in four of the five trials the participants were also masked to treatment assignment. Masking was judged to be at high risk of bias in the Mansour 2007 study. The investigators reported that the same investigator performed all measurements and was presumably unmasked to treatment assignment. In the Altan-Yaycioglu 2005 study, the nuclear medicine specialist evaluating the lacrimal scintigraphy images was masked to treatment assignment, but lacrimal scintigraphy was not a measurement included in this review. It is unclear whether or not other outcome assessors were masked during this study.

Incomplete outcome data—The domain incomplete outcome data was judged to be at low risk of bias for three of the seven included studies (Farrell 2003; Lowther 1995; Nava-Castaneda 2003). There was no loss to follow-up or missing data reported and this was confirmed by a review of the number randomized versus the number analyzed in the results.

The Mansour 2007 study was judged to be at high risk of bias for incomplete outcome data. Six participants were excluded from the analysis because of spontaneous plug loss and one excluded after an inflammatory reaction to plug material.

Altan-Yaycioglu 2005, Burgess 2008, and Tsifetaki 2003 were all judged as unclear for risk of bias on this parameter. In the Altan-Yaycioglu 2005 study, the investigators did not report sample sizes in the results section, so it was unclear if all participants completed follow-up examinations. It should be noted that most outcomes were assessed immediately after insertion of the punctal plugs with the exception of ocular surface staining which was assessed three days after occlusion. Burgess 2008 did not include sample sizes for all outcomes, so it was unclear if all randomized participants completed follow-up examinations. In the Tsifetaki 2003 study, one participant was lost to follow-up and one participant discontinued due to local infection, but it is not clear if these participants were excluded from the analyses.

Selective reporting—We did not have access to study protocols or other related materials so we were unable to assess the risk of bias for selective outcome reporting. This parameter is reported as “unclear” for all included studies.

Other potential sources of bias—We were unable to assess the risk of bias for other potential sources of bias. This parameter is reported as “unclear” for all included studies.

Effects of interventions

Studies that include collagen punctal plugs

Symptomatic improvement: Farrell 2003 reported median McMonnies symptom scores for participants receiving collagen punctal plugs in the lower puncta versus the upper and lower puncta for the right and left eyes separately (higher scores denoting increased symptom

reports). The median (range) values for the right eye at baseline, five days, and 12 days post occlusion were 7 (3 to 12), 3 (0 to 8), and 3 (0 to 10) respectively for participants with collagen plugs in their lower puncta and 7 (6 to 13), 3 (0 to 11), and 3 (0 to 7) respectively for participants with collagen plugs in their lower and upper puncta. These differences were not statistically significant.

Lowther 1995 noted the number of eyes with dryness, burning, soreness, and grittiness at baseline and five days follow-up among a group of participants receiving a collagen punctal plug in one eye and sham occlusion in the contralateral eye. All eyes in the study (32 participants, 64 eyes) experienced dryness at baseline; at follow-up, 12 (37.5%) collagen and 15 (46.9%) sham occlusion eyes were dry. Burning was experienced in 17 (53.1%) collagen and 15 (46.9%) sham occlusion eyes at baseline; at follow-up, six (18.8%) collagen and five (15.6%) sham occlusion eyes experienced burning. Nine (28.1%) collagen and seven (21.9%) sham occlusion eyes experienced soreness at baseline with five (15.6%) collagen and six (18.8%) sham eyes experiencing at follow-up. Grittiness was experienced in 11 (34.3%) collagen and eight (25%) sham eyes at baseline. These numbers decreased to six (18.8%) and seven (21.9%) respectively at follow-up.

Tsifetaki 2003 reported significant subjective improvement in ocular symptoms of participants receiving oral pilocarpine (90% improvement) when compared to participants receiving collagen punctal plugs (60% improvement) at 12 weeks with more participants randomized to oral pilocarpine benefiting from treatment ($P < 0.05$, Chi² test).

Ocular surface staining: Lowther 1995 reported mean fluorescein ocular surface staining scores (0 no staining to 4 heavy staining) for patients receiving a collagen punctal plug in one eye and sham occlusion in the contralateral eye. At baseline, mean scores were 0.78 and 0.69 respectively for collagen and sham occlusion eyes. At five days post occlusion, mean scores were 0.63 and 0.59. These differences were not statistically significant.

Tsifetaki 2003 noted significant differences in Rose Bengal ocular surface staining scores with participants receiving oral pilocarpine showing more improvement at 12 weeks than participants randomized to collagen punctal plugs. Mean difference $\pm$ standard deviation in right and left eyes at follow-up respectively were -1 ± 1.3 and -1.1 ± 1.0 oral pilocarpine; -0.9 ± 1.2 and -0.5 ± 0.9 collagen punctal plugs ($P < 0.05$, Wilcoxon rank sum test).

Aqueous tear production: Tsifetaki 2003 noted no difference in Schirmer scores when oral pilocarpine was compared to collagen punctal plugs. Mean difference $\pm$ standard deviation in right and left eyes at follow-up respectively were 0.3 ± 1.1 and 1.2 ± 1.3 mm oral pilocarpine; 0.2 ± 0.4 and 0.7 ± 0.8 mm collagen punctal plugs.

Tear film stability: Lowther 1995 reported mean tear break up time (TBUT) for patients receiving a collagen punctal plug in one eye and sham occlusion in the contralateral eye. At baseline, mean TBUTs were 8.59 and 8.78 seconds respectively for collagen and sham occlusion eyes. At five days follow-up, mean TBUTs were 7.44 and 7.56 seconds. These differences were not statistically significant.

Studies that include silicone punctal plugs

Symptomatic improvement: Burgess 2008 reported no difference in mean subjective symptom score when silicone and acrylic punctal plugs were compared. Baseline and approximately 11 weeks follow-up mean $\pm$ standard deviation scores were 29.6 ± 16.9 and 21.0 ± 14.5 respectively among participants with silicone plugs; 38.9 ± 16.7 and 21.9 ± 18.8 among participants with acrylic plugs ($P = 0.102$, Wilcoxon rank sum test).

Mansour 2007 noted discomfort scores for silicone punctal plug and contralateral unoccluded eyes (summary score of 0 to 10 with higher denoting more discomfort) at baseline and at approximately six weeks follow-up. Silicone punctal plug mean $\pm$ standard deviation scores were 7.08 ± 1.75 and 5.00 ± 2.24 respectively; 6.77 ± 6.00 and 6.00 ± 2.00 among unoccluded eyes.

Ocular surface staining: Burgess 2008 found no differences in Rose Bengal and fluorescein ocular surface staining when silicone and acrylic punctal plugs were compared. Rose Bengal baseline and approximately 11 weeks follow-up mean $\pm$ standard deviation scores were 3.09 ± 2.98 and 0.55 ± 0.93 respectively among participants with silicone plugs; 4.80 ± 2.39 and 1.00 ± 0.71 among participants with acrylic plugs ($P = 0.429$, Wilcoxon rank sum test). Fluorescein baseline and approximately 11 weeks follow-up mean $\pm$ standard deviation scores were 3.50 ± 4.29 and 1.63 ± 3.65 respectively among participants with silicone plugs; 4.11 ± 4.30 and 2.06 ± 2.48 among participants with acrylic plugs ($P = 0.776$, Wilcoxon rank sum test).

Mansour 2007 reported Rose Bengal ocular surface staining scores for silicone punctal plug and contralateral unoccluded eyes at baseline and at approximately six weeks follow-up. Silicone punctal plug mean $\pm$ standard deviation scores were 7.31 ± 1.11 and 6.23 ± 1.96 respectively; 7.31 ± 1.18 and 7.00 ± 1.15 among unoccluded eyes.

Aqueous tear production: Burgess 2008 found no difference in mean Schirmer scores when silicone and acrylic punctal plugs were compared. Baseline and approximately 11 weeks follow-up mean $\pm$ standard deviation scores were 2.60 ± 2.59 and 3.80 ± 2.08 mm respectively among participants with silicone plugs; 1.80 ± 1.37 and 4.87 ± 5.45 mm among participants with acrylic plugs (1.87 mm, 95% CI -1.59 to 5.33 ; $P = 0.154$, t test).

Mansour 2007 reported Schirmer scores for silicone punctal plug and contralateral unoccluded eyes at baseline and at approximately six weeks follow-up. Silicone punctal plug mean $\pm$ standard deviation scores were 2.69 ± 1.65 and 4.85 ± 4.62 respectively; 7.31 ± 1.18 and 7.00 ± 1.15 among unoccluded eyes.

Tear film stability: Burgess 2008 reported no difference in tear film break up time when silicone and acrylic punctal plugs were compared. Baseline and approximately 11 weeks follow-up mean $\pm$ standard deviation scores were 2.31 ± 1.14 and 3.50 ± 2.50 seconds respectively among participants with silicone plugs; 2.28 ± 0.96 and 3.86 ± 2.34 seconds among participants with acrylic plugs (0.40 seconds, 95% CI -1.11 to 1.91 ; $P = 0.414$, t test).

Artificial tear use: In the Burgess 2008 study, silicone and acrylic punctal plugs reduced the use of tear supplements in 10 (55.6%) and 11 (61.1%) participants respectively, but the difference in mean improvement in artificial tear use (as measured by the symptom score) was not statistically significant (mean 1.55, 95% CI -1.50 to 4.60 ; $P = 0.27$, t test).

Adverse outcomes: One acrylic punctal plug participant experienced epiphora, one silicone punctal plug participant experienced intermittent ocular irritation, and two silicone and one acrylic punctal plug participants experienced temporary foreign body sensation in the Burgess 2008 study.

Spontaneous plug loss occurred in six eyes with silicone punctal plugs in the Mansour 2007 study and six participants receiving silicone punctal plugs in the Burgess 2008 study.

Studies that include both collagen and silicone punctal plugs

Symptomatic improvement: In the Nava-Castaneda 2003 study, investigators compared summary and individual dry eye symptom scores among participants receiving collagen and silicone punctal plugs and those receiving no occlusion (sham occlusion) at baseline and at one hour, two, four, and eight weeks follow-up. There were no differences in total dry eye symptom score at one hour, but significant differences at two weeks (24.2 ± 18.9 collagen/silicone; 33.2 ± 11.4 sham; $P = 0.028$, t test), four weeks (9.7 ± 8.0 collagen/silicone; 33.1 ± 13.7 sham; $P < 0.001$, t test), and eight weeks (2.5 ± 3.1 collagen/silicone; 30.7 ± 14.8 sham; $P < 0.001$, t test) follow-up. There were also significant differences in the frequency of individual symptom scores at two weeks (burning, foreign body sensation, light sensitivity), four weeks (dryness, itching, burning, foreign body sensation, fluctuating vision, light sensitivity), and eight weeks (dryness, watery eyes, itching, burning, foreign body sensation, fluctuating vision, light sensitivity) with participants in the collagen/silicone group reporting lower frequency of these symptoms.

Ocular surface staining: Altan-Yaycioglu 2005 reported no difference in Rose Bengal ocular surface staining scores when collagen and silicone punctal plugs were compared. Baseline and three days follow-up mean $\pm$ standard deviation scores were 6.63 ± 0.84 and 1.90 ± 0.81 respectively among participants receiving collagen plugs; 6.61 ± 0.89 and 2.07 ± 0.79 among participants receiving silicone plugs.

Nava-Castaneda 2003 found differences in fluorescein ocular surface staining scores at two, four, and eight weeks follow-up among participants receiving collagen and silicone punctal plugs compared to those receiving sham occlusion (scores of 0: absent to 4: severe) with active treatment participants showing reduced staining. The mean $\pm$ standard deviation scores were 1.3 ± 0.8 collagen/silicone; 2.1 ± 0.9 sham; $P = 0.001$, t test at two weeks; 0.7 ± 0.7 collagen/silicone; 2.1 ± 1.0 sham; $P < 0.001$, t test at four weeks, and at eight weeks 0.2 ± 0.4 collagen/silicone; 1.7 ± 1.0 sham; $P < 0.001$, t test.

Aqueous tear production: Altan-Yaycioglu 2005 reported no difference in mean Schirmer I scores when collagen and silicone punctal plugs were compared. Baseline and immediately after occlusion mean $\pm$ standard deviation scores were 1.35 ± 0.49 and 5.77 ± 0.75 mm respectively among participants with collagen plugs; 1.38 ± 0.49 and 5.96 ± 0.87 mm among participants with silicone plugs.

Tear film stability: Altan-Yaycioglu 2005 reported no difference in the mean change in tear film stability when collagen and silicone punctal plugs were compared. Baseline and immediately after occlusion mean $\pm$ standard deviation scores were 5.50 ± 1.25 and 12.20 ± 2.50 seconds respectively among participants with collagen plugs; 5.42 ± 1.42 and 12.40 ± 2.50 seconds among participants with silicone plugs.

Artificial tear use: Topical artificial tear use was significantly less frequent among participants receiving collagen and silicone punctal plugs compared to those receiving sham occlusion at two, four, and eight weeks follow-up in the Nava-Castaneda 2003 study. The mean $\pm$ standard deviation scores were 2.1 ± 1.1 collagen/silicone; 3.5 ± 0.7 sham; $P = 0.004$, t test at two weeks; 1.8 ± 0.9 collagen/silicone; 3.6 ± 0.7 sham; $P < 0.001$ at four weeks, and at eight weeks 0.9 ± 0.7 collagen/silicone; 3.6 ± 0.9 sham; $P < 0.001$.

Adverse outcomes: One participant receiving collagen and silicone punctal plugs experienced epiphora in the Nava-Castaneda 2003 study.

Discussion

Summary of main results

The electronic searches identified seven reports of randomized clinical trials of the use of either collagen or silicone punctal occlusion in the treatment of dry eye that satisfied our inclusion criteria. Of these, three reported on the use of collagen punctal plugs alone, two on use of silicone plugs alone, one on use of silicone and collagen plugs, and one reported on the effectiveness of a combined treatment with collagen and silicone occlusion. Although the literature does not unequivocally validate punctal occlusion as an effective treatment for dry eye, the combined evidence lends support to its usefulness in dry eye management.

This review shows a relative lack of strong evidence supporting the efficacy of collagen punctal plugs as a treatment modality for dry eye, partly due to a lack of consistency in experimental design and analytical strategies across studies. The studies included in this review, however, do not report on the use of collagen canalicular occlusion as a means of predicting the efficacy of permanent occlusion, a purpose for which collagen plugs are intended. Comparing occlusion of both puncta to a sham procedure in the contralateral eye, Lowther 1995 reported no statistically significant effects on either objective or subjective measures of dry eye after five days of occlusion with collagen plugs. Tsifetaki 2003 showed oral pilocarpine to be more effective than collagen punctal plugs after 12 weeks of dry eye treatment in Sjögren's syndrome patients. In addition, patients randomized to punctal occlusion showed significant subjective improvement of dry eye symptoms compared to an artificial tears-only control group. Their results, however, should be interpreted with caution as collagen plugs would have long been dissolved at the time of follow-up. Furthermore, while oral pilocarpine is used to treat the complications of Sjögren syndrome (which include dry eye), it is not conventionally used in treating isolated dry eye. Hence, comparisons of the efficacy of punctal occlusion versus oral pilocarpine may have limited applicability in non-Sjögren patients. Farrell 2003 showed that treatment with collagen punctal plugs improved tear status in aqueous-deficient dry eyes. This effect was seen when occluding either the lower puncta only, or after insertion of collagen plugs in both the lower and upper puncta. Nevertheless, since no sham group was used in the study, treatment efficacy of punctal occlusion must be inferred from comparisons to baseline measurements.

Studies of permanent silicone or combined silicone/collagen punctal occlusion in the treatment of dry eye show some evidence of their clinical efficacy. However, a lack of consistency in study design and analytical strategies do not permit a quantitative analysis of the combined results. Burgess 2008 reported similar subjective and objective improvement in dry eyes treated with either silicone or acrylic punctal plugs. A lack of a sham/no treatment group, however, limits the study's interpretability to pre- and post-treatment comparisons. In addition, a serious statistical flaw, wherein 36 eyes of 21 participants were treated as independent in the analyses, calls into question the validity of their results. Mansour 2007 reported significant improvement in both Rose Bengal staining and level of discomfort in severe dry eyes secondary to Sjögren syndrome treated with punctal occlusion compared to untreated contralateral eyes. Their sample size, however, was limited to 13 patients after excluding 6 participants who suffered spontaneous plug loss and one who developed an inflammatory reaction to the plug material. Altan-Yaycioglu 2005 reported on the effect of collagen and silicone plugs on objective measures of tear film integrity. Schirmer I scores, Rose Bengal scores, and TBUTs all improved significantly at three-days treatment for both silicone and collagen plug treatment groups.

The most convincing evidence of the efficacy of lacrimal occlusion therapy for dry eye was reported by Nava-Castaneda 2003, who structured a progressive therapeutic regimen involving temporary collagen plugs followed by permanent silicone plug implantation. Dry

eye patients were randomized to either a treatment or a sham group, and outcomes were assessed at one hour and two, four and eight weeks post-treatment. The authors reported highly significant improvements in moisturizing agent use, fluorescein staining, ocular discomfort, and visual performance in the treated group. Importantly, the therapeutic benefits of punctal occlusion increased significantly as the duration of treatment increased. This suggests that follow-up periods of eight or more weeks may be necessary to properly evaluate the effect of lacrimal occlusion therapies on dry eye.

Adverse outcomes—Only Tsifetaki 2003 reported adverse outcomes in studies of collagen plugs-only treatment; one participant of 28 discontinued the study due to a local infection. The most common adverse outcomes in silicone plug studies were: spontaneous plug loss (six of 28 in Mansour 2007, six of 20 in Burgess 2008); epiphora (one case each in Burgess 2008 and Nava-Castaneda 2003, four in Farrell 2003); ocular irritation or foreign body sensation (three cases in Burgess 2008); and local inflammatory reaction to silicone (one case in Mansour 2007). In addition, Mansour 2007 reported one case of corneal melting and perforation, and Nava-Castaneda 2003 reported one instance of corneal ulceration. Both of these serious conditions were thought to be unrelated to the punctum plug.

Overall completeness and applicability of evidence

Quantitative assessments of the seven included studies were not possible due to significant clinical and methodological heterogeneity. As a result, the evidence for punctal occlusion in the treatment of dry eye-related symptoms is incomplete.

Quality of the evidence

Only one study (Nava-Castaneda 2003) utilized a sham group as a basis for comparison. Although Tsifetaki 2003 did not perform a sham procedure on untreated participants, their study included a control group randomized to artificial tears only. Two studies (Lowther 1995; Mansour 2007) compared outcomes of treated eyes to untreated contralateral eyes, offering internal controls by which to compare therapeutic efficacy of punctal occlusion. Farrell 2003 compared both lower and upper punctal occlusion to lower punctum occlusion only. The two remaining studies (Altan-Yaycioglu 2005; Burgess 2008) contrasted the relative clinical efficacy of two different punctal plug types. This lack of consistency in experimental design makes comparisons between studies problematic and limits the interpretability of the findings. Nevertheless, there is a general trend across studies showing the benefit of punctal occlusion therapy; only Lowther 1995 reported no improvement in objective clinical outcomes following punctal plug insertion. It should be noted, however, that Lowther 1995 was the one included study to specifically recruit contact lens wearers, and its five-day follow-up period limits its applicability to short course treatment.

Follow-up periods were variable across studies. As expected, a shorter timeline was used for studies of dissolvable collagen plugs. These studies do not address the question of the long-term clinical effectiveness of punctal occlusion in the treatment of chronic dry eye. However, Tsifetaki 2003 reported using permanent collagen plugs and a follow-up period of up to 12 weeks. It is not clear whether they erroneously reported collagen plugs as “permanent” and used an inappropriate follow-up period, or whether permanent (silicone or polydioxanone) plugs were actually used in the study. Moreover, their findings of better clinical and subjective outcomes for oral pilocarpine therapy versus punctal occlusion in Sjögren’s patients are unlikely to be pertinent to non-syndromic dry eye.

Authors' conclusions

Implications for practice

This systematic review shows a relative scarcity of controlled clinical trials assessing the efficacy of punctal occlusion therapy in dry eye. Although the evidence is very limited, the data suggest that silicone plugs can provide symptomatic relief in severe dry eye. Moreover, temporary collagen plugs appear similarly effective to silicone plugs on a short-term basis. However, the usefulness of collagen plugs for predicting the success of long-term silicone punctal occlusion remains to be investigated. Although one study of collagen implants reported similar outcomes for lower canalicular-only versus upper- and lower-canalicular occlusion, there remains insufficient evidence to assess whether these treatment modalities are clinically equivalent.

Implications for research

The major limiting factor in our ability to evaluate the efficacy of punctal occlusion therapy in the treatment of dry eye remains a scarcity of clinical trials in the area. Moreover, a lack of adequate standardization across studies with respect to study design, follow-up periods and outcomes assessment further complicates any comparisons. In order to minimize the likelihood of potential sources of bias, randomization and concealment allocation should be strictly adhered to, and a sham procedure should be carried out whenever possible.

Given the bilateral nature of non-structural dry eye disease, untreated contralateral eyes offer a convenient matched control group. Hence, uniocular trials can be appropriate when properly executed (although possible asymmetries between eyes should be accounted-for in study designs and analyses). It should also be noted that tear film abnormalities in one eye often produce excess tearing bilaterally. This reflex tearing could be an important source of bias in uniocular trials of lacrimal occlusion therapy in dry eye.

A properly-selected group receiving a sham treatment (where the steps of inserting a plug are simulated but no actual plugs are inserted), together with appropriate masking procedures, can provide adequate control for most potential biases and allow for a direct computation of treatment effect. Masking of study participants is not possible in a study that includes a no treatment control group without sham occlusion. Although pre- to post-treatment comparisons provide estimates of treatment effects, these studies are more susceptible to placebo effect and observer bias than well-designed uniocular trials, or studies that incorporate a group randomized to sham occlusion. In addition, comparison of different treatment modalities such as silicone versus collagen or acrylic plugs may not be sufficiently informative given that the efficacy of any one of these therapies has not been established with a high degree of certainty.

Since the benefit of punctal occlusion has been shown to increase over a period of at least eight weeks (Nava-Castaneda 2003), a relatively long follow-up period (up to several months) should be used in order to evaluate the full therapeutic effect of silicone punctal occlusion therapy. There is also a need for studies assessing the use of temporary collagen implants for predicting the effectiveness of long-term silicone plug therapy. Finally, it is unclear whether both lower and upper lacrimal occlusion provides additional benefit to lower punctum-only treatment of dry eye. Future studies should investigate whether occlusion of lower canaliculi only is sufficient in treating dry eye.

In our opinion, additional well-designed randomized controlled trials of lacrimal occlusion therapy in dry eye are needed. Ideal study designs should include masking of participants and outcome assessors; adequate follow-up periods; and appropriate comparison groups. Samples should be large enough to provide sufficient statistical power to detect clinically

relevant treatment effect sizes of the primary outcomes, and analyses should be appropriate to the study's design and outcome measures. Moreover, standardization of outcome measures and follow-up periods across studies would be beneficial to maximize study comparability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of support

Internal sources

National Human Genome Research Institute Intramural funds, National Institutes of Health, USA

This research was supported in part by the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health

External sources

Contract N01-EY-2-1003 and Grant 1 U01 EY020522-01, National Eye Institute, National Institutes of Health, USA

The authors would like to thank Iris Gordon, Trials Search Co-ordinator, Cochrane Eyes and Vision Group (CEVG), for designing the search strategy and conducting the electronic searches. We also acknowledge the CEVG editorial team's support during the preparation of this protocol and thank Marie Diener-West and Michael Lemp for their comments.

References to studies

Included studies

- Altan-Yaycioglu 2005. Altan-Yaycioglu R, Gencoglu EA, Akova YA, Dursun D, Cengiz F, Akman A. Silicone versus collagen plugs for treating dry eye: results of a prospective randomized trial including lacrimal scintigraphy. *American Journal of Ophthalmology*. 2005; 140(1):88–93. [PubMed: 15939391]
- Burgess 2008. Burgess PI, Koay P, Clark P. SmartPlug versus silicone punctal plug therapy for dry eye: a prospective randomized trial. *Cornea*. 2008; 27(4):391–4. [PubMed: 18434839]
- Farrell 2003. Farrell J, Patel S, Grierson DG, Sturrock RD. A clinical procedure to predict the value of temporary occlusion therapy in keratoconjunctivitis sicca. *Ophthalmic & Physiological Optics*. 2003; 23(1):1–8. [PubMed: 12535050]
- Lowther 1995. Lowther GE, Semes L. Effect of absorbable intracanalicular collagen implants in hydrogel contact lens patients with symptoms of dryness. *International Contact Lens Clinic*. 1995; 22:238–43. Lowther, GE.; Semes, L. Effect of intracanalicular collagen implants on drying symptoms and the tear film of hydrogel contact lens patients. *American Academy of Optometry*; 1991 Dec; Anaheim (CA). 1991. p. Abstract number 75
- Mansour 2007. Mansour K, Leonhardt CJ, Kalk WW, Bootsma H, Bruin KJ, Blanksma LJ. Lacrimal punctum occlusion in the treatment of severe keratoconjunctivitis Sicca caused by Sjogren syndrome: a uniocular evaluation. *Cornea*. 2007; 26(2):147–50. [PubMed: 17251802]
- Nava-Castaneda 2003. Nava-Castaneda A, Tovilla-Canales JL, Rodriguez L, Tovilla Y, Pomar JL, Jones CE. Effects of lacrimal occlusion with collagen and silicone plugs on patients with conjunctivitis associated with dry eye. *Cornea*. 2003; 22(1):10–4. [PubMed: 12502940]
- Tsifetaki 2003. Tsifetaki N, Kitsos G, Paschides CA, Alamanos Y, Eftaxias V, Voulgari PV, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjogren's syndrome: a randomised 12 week controlled study. *Annals of the Rheumatic Diseases*. 2003; 62(12):1204–7. [PubMed: 14644860]

Excluded studies

- Charnetski-Sites 2001. Charnetski-Sites, C.; Bucci, FA, Jr. Do silicone punctal plugs impact tear lactoferrin levels following LASIK. American Academy of Optometry; 2001 Dec; Philadelphia (PA). 2001. p. Abstract 203
- Geldis 2008. Geldis JR, Nichols JJ. The impact of punctal occlusion on soft contact lens wearing comfort and the tear film. *Eye & Contact Lens*. 2008; 34(5):261–5. [PubMed: 18779665]
- Giovagnoli 1992. Giovagnoli D, Graham SJ. Inferior punctal occlusion with removable silicone punctal plugs in the treatment of dry-eye related contact lens discomfort. *Journal of the American Optometric Association*. 1992; 63(7):481–5. [PubMed: 1506612]
- Goto 2003. Goto E, Yagi Y, Kaido M, Matsumoto Y, Konomi K, Tsubota K. Improved functional visual acuity after punctal occlusion in dry eye patients. *American Journal of Ophthalmology*. 2003; 135(5):704–5. [PubMed: 12719079]
- Guzey 2001. Guzey M, Ozardali I, Kilic A, Basar E, Dogan Z, Satıcı A, et al. The treatment of severe trachomatous dry eye with canalicular silicone plugs. *Eye*. 2001; 15(Pt 3):297–303. [PubMed: 11450724]
- Hamano 2002. Hamano T. Atelocollagen punctal occlusion for the treatment of the dry eye. *Advances in Experimental Medicine & Biology*. 2002; 506(Pt B):1283–4. [PubMed: 12614068]
- Murube del Castillo 1995. Murube del Castillo J, Olivares C, Murube E. Treatment of dry eye by punctum patch. *Orbit*. 1995; 14(1):1–7.
- Nishii 2004. Nishii M, Yokoi N, Komuro A, Kinoshita S. Clinical investigation of extrusion of a new punctal plug(Flex Plug). *Nippon Ganka Gakkai Zasshi*. 2004; 108(3):139–43. [PubMed: 15103949]
- Ozkan 2001. Ozkan Y, Bozkurt B, Gedik S, Irkeç M, Orhan M. Corneal topographical study of the effect of lacrimal punctum occlusion on corneal surface regularity in dry eye patients. *European Journal of Ophthalmology*. 2001; 11(2):116–9. [PubMed: 11456010]
- Patten 1976. Patten JT. Punctal occlusion with n-butyl cyanoacrylate tissue adhesive. *Ophthalmic Surgery*. 1976; 7(2):24–6. [PubMed: 945531]
- Sharpe 2001. Published data only (unpublished sought but not used). Sharpe J, Connor C. The effect of site selection for punctal occlusion on patient symptom relief. American Academy of Optometry 2001 Dec Philadelphia (PA) 2001: Abstract number 299.
- Virtanen 1996. Virtanen T, Huotari K, Harkonen M, Tervo T. Lacrimal plugs as a therapy for contact lens intolerance. *Eye*. 1996; 10(Pt 6):727–31. [PubMed: 9091371]
- Ward 2001. Ward, HJ. A preliminary comparison of superior to inferior silicone punctal occlusion in hydrogel contact lens wearers with dry eye signs and symptoms. American Academy of Optometry; 2001 Dec; Philadelphia (PA). 2001. p. Abstract number 300

Other references

Additional references

- AAO 2003. American Academy of Ophthalmology (AAO). [accessed 27 April 2010] Cornea/External Disease Panel; Preferred Practice Pattern for Dry Eye Syndrome. Sep. 2003 p. 1-21. <http://one.aao.org/CE/PracticeGuidelines/default.aspx>
- Balaram 2001. Balaram M, Schaumberg DA, Dana MR. Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome. *American Journal of Ophthalmology*. 2001; 131(1):30–6. [PubMed: 11162976]
- Barnard 1996. Barnard NA. Punctal and intracanalicular occlusion - a guide for the practitioner. The College of Optometrists. *Ophthalmic and Physiological Optics*. 1996; 16(Suppl 1):S15–22. [PubMed: 8796195]
- Dalzell 2003. Dalzell MD. Dry eye: prevalence, utilization, and economic implications. *Managed Care*. 2003; 12(12 Suppl):9–13. [PubMed: 14723108]
- De Paiva 2006. De Paiva CS, Chen Z, Koch DD, Hamill MB, Manuel FK, Hassan SS, et al. The incidence and risk factors for developing dry eye after myopic LASIK. *American Journal of Ophthalmology*. 2006; 141(3):438–45. [PubMed: 16490488]

- Dohlman 1978. Dohlman CH. Punctal occlusion in keratoconjunctivitis sicca. *Ophthalmology*. 1978; 85(12):1277–81. [PubMed: 745834]
- Glanville 2006. Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association*. 2006; 94(2):130–6. [PubMed: 16636704]
- Higgins 2009a. Higgins, JPT.; Altman, DG.; Green, S., editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2*. The Cochrane Collaboration; 2009. Chapter 8: Assessing risk of bias in included studies. [updated September 2009] Available from www.cochrane-handbook.org
- Higgins 2009b. Higgins, JPT.; Deeks, JJ.; Altman, DG.; Green, S., editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2*. The Cochrane Collaboration; 2009. Chapter 16: Special topics in Statistics. [updated September 2009] Available from www.cochrane-handbook.org
- Lee 2002. Lee AJ, Lee J, Saw SM, Gazzard G, Koh D, Widjaja D, et al. Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. *British Journal of Ophthalmology*. 2002; 86(12):1347–51. [PubMed: 12446361]
- Lemp 1994. Lemp MA. Management of the dry-eye patient. *International Ophthalmology Clinics*. 1994; 34(1):101–13. [PubMed: 8169064]
- Lemp 1995. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. *The CLAO Journal*. 1995; 21(4):221–32. [PubMed: 8565190]
- Lemp 1998. Lemp MA. Epidemiology and classification of dry eye. *Advances in Experimental Medicines & Biology*. 1998; 438:791–803.
- McCarty 1998. McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology*. 1998; 105(6):1114–9. [PubMed: 9627665]
- Moss 2000. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Archives of Ophthalmology*. 2000; 118(9):1264–8. [PubMed: 10980773]
- Pflugfelder 2000. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five-year review. *Cornea*. 2000; 19(5):644–9. [PubMed: 11009316]
- Sahai 2005. Sahai A, Malik P. Dry eye: prevalence and attributable risk factors in a hospital-based population. *Indian Journal of Ophthalmology*. 2005; 53(2):87–91. [PubMed: 15976462]
- Sall 2000. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *CsA Phase 3 Study Group*. *Ophthalmology*. 2000; 107(4):631–9. [PubMed: 10768324]
- Schein 1997. Schein OD, Tielsch JM, Munoz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly. A population-based perspective. *Ophthalmology*. 1997; 104(9):1395–401. [PubMed: 9307632]
- Schein 1997a. Schein OD, Munoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. *American Journal of Ophthalmology*. 1997; 124(6):723–8. [PubMed: 9402817]
- Sheppard 2003. Sheppard JD. Dry eye moves beyond palliative therapy. *Managed Care*. 2003; 12(12 Suppl):6–8. [PubMed: 14723107]
- Tai 2002. Tai MC, Cosar CB, Cohen EJ, Rapuano CJ, Laibson PR. The clinical efficacy of silicone punctal plug therapy. *Cornea*. 2002; 21(2):135–9. [PubMed: 11862081]
- Willis 1987. Willis RM, Folberg R, Krachmer JH, Holland EJ. The treatment of aqueous-deficient dry eye with removable punctal plugs. A clinical and impression-cytologic study. *Ophthalmology*. 1987; 94(5):514–8. [PubMed: 3601366]
- Wilson 2003. Wilson SE. Inflammation: a unifying theory for the origin of dry eye syndrome. *Managed Care*. 2003; 12(12 Suppl):14–9. [PubMed: 14723109]

Appendices

1 CENTRAL search strategy

- #1 MeSH descriptor Dry Eye
- #2 dry near eye*
- #3 ocular near dry*
- #4 MeSH descriptor Tears
- #5 tear*
- #6 MeSH descriptor Xerophthalmia
- #7 xerophthalmi*
- #8 MeSH descriptor Vitamin A Deficiency
- #9 Vitamin A deficien*
- #10 MeSH descriptor Keratoconjunctivitis Sicca
- #11 keratoconjunctivi*
- #12 MeSH descriptor Sjogren's Syndrome
- #13 sjogren* near syndrome
- #14 MeSH descriptor Stevens-Johnson Syndrome
- #15 steven* johnson syndrome*
- #16 MeSH descriptor Pemphigoid, Benign Mucous Membrane
- #18 blepharoconjunctiviti*
- #19 MeSH descriptor Meibomian Glands
- #20 meibomian
- #21 MeSH descriptor Lacrimal Apparatus Diseases
- #22 lacrimal
- #23 MeSH descriptor Corneal Diseases
- #24 cornea*
- #25 MeSH descriptor Conjunctival Diseases
- #26 conjunctiv*
- #27 (#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)
- #28 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
- #29 (#27 OR #28)
- #30 (occlu* or plug*) near puncta*
- #31 (#29 AND #30)

2 MEDLINE (OVID) search strategy

1. randomized controlled trial.pt.
2. (randomised 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\$.tw.
18. exp xerophthalmia/
19. xerophthalmi\$.tw.
20. exp vitamin A deficiency/
21. (vitamin A adj3 deficien\$.tw.
22. exp keratoconjunctivitis sicca/
23. keratoconjunctiviti\$.tw.
24. exp Sjogren's syndrome/
25. Sjogren\$ syndrome.tw.
26. exp Stevens Johnson syndrome/
27. Steven\$ Johnson syndrome\$.tw.
28. exp Pemphigoid, Benign Mucous Membrane/
29. cicatricial pemphigoid\$.tw.
30. blepharoconjunctiviti\$.tw.
31. exp meibomian glands/
32. meibomian.tw.
33. exp lacrimal apparatus diseases/
34. lacrimal.tw.

35. exp corneal diseases/
36. cornea\$.tw.
37. exp conjunctival diseases/
38. conjunctiv\$.tw.
39. or/13–38
40. ((occlu\$ or plug\$) adj2 puncta\$).tw.
41. 39 and 40
42. 12 and 41

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

3 EMBASE (OVID) search strategy

1. exp randomised controlled trial/
2. exp randomisation/
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. exp dry eye/
34. (dry adj2 eye\$).tw.
35. (ocular adj2 dry\$).tw.
36. exp lacrimal fluid/
37. tear\$.tw.
38. exp xerophthalmia/
39. xerophthalmi\$.tw.
40. exp Retinol deficiency/
41. (vitamin A adj3 deficien\$).tw.
42. exp keratoconjunctivitis sicca/
43. keratoconjunctiviti\$.tw.
44. exp Sjogren syndrome/
45. Sjogren\$ syndrome.tw.
46. exp Stevens Johnson syndrome/
47. Steven\$ Johnson syndrome\$.tw.
48. exp Bullous skin disease/
49. cicatricial pemphigoid\$.tw.
50. blepharoconjunctiviti\$.tw.
51. exp meibomian gland/
52. meibomian.tw.
53. exp lacrimal apparatus/
54. exp lacrimal fluid/
55. lacrimal.tw.
56. exp cornea disease/
57. cornea\$.tw.
58. exp conjunctiva disease/
59. conjunctiv\$.tw.

- 60. or/33–59
- 61. ((occlu\$ or plug\$) adj2 puncta\$).tw.
- 62. 60 and 61
- 63. 32 and 62

4 LILACS search strategy

eye\$ and puncta\$

5 metaRegister of Controlled Trials search strategy

punctal occlusion

6 ClinicalTrials. gov search strategy

punctal occlusion

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Altan-Yaycioglu 2005	?	?	?	?	?	?
Burgess 2008	+	?	+	?	?	?
Farrell 2003	?	?	+	+	?	?
Lowther 1995	?	?	+	+	?	?
Mansour 2007	+	?	-	-	?	?
Nava-Castaneda 2003	+	+	+	+	?	?
Tsifetaki 2003	+	?	+	?	?	?

Figure 1.
Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Table 1

Interventions of Included Studies

Study	Interventions
Studies that include collagen punctal plugs	
Farrell 2003	Collagen punctal plugs in the lower puncta compared to collagen punctal plugs in the lower and upper puncta
Lowther 1995	Collagen punctal plugs compared to sham treatment
Tsifetaki 2003	Collagen punctal plugs compared to oral pilocarpine
Studies that include silicone punctal plugs	
Burgess 2008	Silicone punctal plugs compared to acrylic punctal plugs
Mansour 2007	Silicone punctal plugs compared to no occlusion
Studies that include both collagen and silicone punctal plugs	
Altan-Yaycioglu 2005	Collagen punctal plugs compared to silicone punctal plugs
Nava-Castaneda 2003	Collagen plus silicone punctal plugs compared to sham treatment