PROTOCOL

# Safety and Efficacy of Ayurvedic Interventions in the Management of Conjunctivitis: A Protocol for a Systematic Review

V Krishna Kumar[1], Alok Kumar Srivastava[2], Pallavi N Kamble[3], Pratap Makhija[4]


## Abstract

**Background:** Conjunctivitis is a common condition of the eye that occurs worldwide and affects all ages and social strata, affecting more than 2% of the population. Conventional treatment has many options for treating the disease. Despite adequate treatment options, patients continue to suffer troublesome symptoms. Complementary and alternative medicine (CAM) therapies may play a significant role here. Systematic reviews on this topic have been published for herbal medicines. Data are available on plenty of studies individually proving efficacy and safety of various *Shodhana*, *Shamana*, and *Netra Kriyakalpa* in conjunctivitis. However, systematic review of Ayurveda interventions for conjunctivitis is unavailable. This study aims at a thorough review of published clinical data of safety and efficacy of Ayurvedic interventions in the management of conjunctivitis.

**Materials and methods:** A systematic review of randomized controlled trials (RCTs), quasi-randomized controlled trials (QRCTs), controlled clinical trials (CCTs), and multiple arms clinical trials on conjunctivitis published till date will be conducted. Studies having patients fulfilling the diagnostic criteria based on the symptomatology of *Abhishyanda* (HF-1) explained in classic Ayurveda texts and conjunctivitis of all ages and either sex will be included. Studies in which Ayurvedic treatments (*Shamana*, *Shodhana*, or/and *Netra Kriyakalpa*) with any dose, type, schedule, drug, dosage form, and advised *Pathayapathya* (lifestyle changes) as intervention or control will be selected. The primary outcome will be the response to treatment and onset of serious adverse events.

**Ethics and dissemination:** Formal ethical approval will be obtained. The results will be disseminated through a peer-reviewed publication.

**Trial registration number:** International prospective register for systematic reviews (PROSPERO) number CRD42019129436.


**Keywords:** Ayurveda, Conjunctivitis, Efficacy, Protocol for a systematic review, Safety.

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## Introduction

Conjunctivitis is a common condition of the eye that occurs worldwide and affects all ages and social strata,[1] affecting more than 2% of the population.[2] Due to its common occurrence, contagiousness, and potentially debilitating morbidity, conjunctivitis is a global economic burden.[1] It is caused by a variety of bacterial or viral pathogens but may also be caused by allergies, irritants, or medications. Most types are self-limiting, but some may progress and cause serious complications. Many cases of bacterial conjunctivitis are self-limiting; and in uncomplicated cases, no treatment is required. However, antibiotics can be used to treat conjunctivitis caused by gonorrhea or chlamydia and conjunctivitis in contact lens wearers. Viral conjunctivitis treatment is supportive. Antihistamines and mast cell stabilizers relieve the symptoms of allergic conjunctivitis.[1]

The CAM therapies may play a significant role here. Systematic reviews on this topic have been published for herbal medicines.[3] Data on plenty of studies individually proving the efficacy and safety of various *Shodhana* (purification procedures), *Shamana* (pacifying treatment), and *Netra Kriyakalpa* (ocular therapeutics) in conjunctivitis are available. *Shodhana* procedures include *Virechana* (therapeutic purgation), *Nasya* (nasal medication), *Basti* (therapeutic enema), and *Raktamokshana* (bloodletting) depending on the *Dosha* (body humor) involved. *Snehapana* (oleation) and *Swedana* (sudation) are administered as prepreparatory procedures before *Shodhana*. *Netra Kriyakalpa* includes *Tarpana* (administration of medicated ghee over eyes), *Putapaka* (administration of specially prepared *Putapaka rasa* over eyes), *Aschotana* (eye drops), *Seka* (ocular irrigation),[4] *Anjana* (medicated collyrium),[5] and *Bidalaka* (application of medicated paste over eyelids).[6] They are selected alone or in combination depending on disease condition. Other treatments include *Shirovasti* (retention of medicated oil over scalp),[4] *Dhoomapana* (medicated smoke), *Lepa* (application of medicated paste over scalp), and *Kavalagraha* (gargling with medicinal liquids).[7] However, systematic review of Ayurveda interventions in conjunctivitis has not been carried out. So it is planned to systematically review published clinical data of safety and efficacy of Ayurvedic interventions in the management of conjunctivitis. Secondary aim of the study is to do meta-analysis of the eligible studies.

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**Conflict of interest:** None

## Materials and Methods

### Study Design

The RCTs, QRCTs, CCTs, and multiple-arm clinical trials published till date will be included. There will be no language restrictions. The search will be rerun just before the final analyses and further studies retrieved for inclusion.

### Participants

Studies with patients fulfilling the diagnostic criteria based on the symptomatology of *Abhishyanda* explained in classic Ayurveda texts and conjunctivitis of all ages and either sex will be included.

### Interventions

Of interest are Ayurvedic treatments (*Shamana*, *Shodhana*, or/and *Netra Kriyakalpa*) with any dose, type, schedule, drug, dosage form, and advised *Pathayapathya* (lifestyle changes) as intervention or control. We will also consider studies in which patients in all groups of study may receive other non-Ayurveda interventions. We will also include placebo and/or sham therapy and/or *Shamana* therapy and/or *Shodhana* therapy and/or *Netra Kriyakalpa* and/or non-Ayurveda interventions as control.

### Outcome

Primary outcomes will be response to treatment (improvement in subjective and/or objective criteria of assessment) and serious adverse events (resulting in death, disability, or incapacity; life-threatening complications, leading to hospitalization or prolongation of hospitalization). Secondary outcomes involve withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment and the number of patients with a specific adverse event.

### Timing and Effect Measures

No restrictions will be made in the inclusion of study in review by primary outcomes. Administration timings vary from 7 days to 6 months which will be included as different categories of medications are used. For secondary outcomes, timing is during the study period or up to 1 month after completion of the study.

### Search Strategy

PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), DHARA portal, Google Scholar, and online clinical trial registers will be searched. Manual search will be done in central and departmental libraries of Institute for Post Graduate Teaching and Research in Ayurveda, Gujarat Ayurved University, Jamnagar with due permissions and Ayurveda Research Database by MS Baghel will also be searched. Manual search will also be done in the central and departmental libraries of Govt. Ayurveda College, Thiruvananthapuram. For electronic search, the following search strategy will be used—Ayurveda OR Ayurvedic OR Ayurvedic treatment OR Aschyotana OR Bidalaka OR Seka OR Tarpana OR Putapaka OR Anjana OR Pindi OR Netra Kriyakalpa OR Nasya OR Eye Drops OR Triphala OR Abhishyanda OR Vatika Abhishyanda OR Paittika Abhishyanda OR Kaphaja Abhishyanda OR Raktaja Abhishyanda OR Utklishta AND conjunctivitis OR pink eye in titles, abstract, or keywords.

### Study Selection

Two review authors KKV and KPN will independently assess the title and abstract identified during the search. Authors will read potentially eligible articles in full to determine whether they meet the eligibility criteria. Disagreements will be discussed with the third review author AKS. If necessary, more information about a particular study will be obtained from the contact person (authors) of that study through e-mail or telephone.

### Data Extraction

Predefined form will be drafted to extract data from the included studies for assessment of study quality and data analysis. Data will be extracted independently by two review authors KKV and KPN. Any disagreement will be discussed and settled with third author AKS, wherever necessary. All three review authors will independently assess the quality of reporting trial using consolidated standards of reporting trials-2010 checklist for quality assessment of the included parallel-group RCT[8] and transparent reporting of evaluations with non-randomized designs-2004 checklist[9] for quality assessment of included nonrandomized trial. Assessment will be done under three categories, "yes" reporting, "no" reporting, and "incomplete" reporting. Two points will be given for each item if it is reported completely. In case of incomplete reporting only one point will be given to that item and no point for "no" reporting. Results will be interpreted in terms of percentage (%) of the mean of each three category reporting items. Data abstracted will include study setting, study population, participant demographics and baseline characteristics, details of the intervention and control conditions, methodology, recruitment and study completion rates, outcomes, and times of measurement. Two authors KKV and KPN will independently assess the risk of bias in the included studies. The RCTs will be assessed with the help of the Cochrane tool of Risk of bias[10] and non-randomized trials will be assessed with the risk of bias in non-randomized studies of interventions tool.[11] Disagreements between these review authors will be resolved by discussion, with the involvement of the third review author AKS if necessary and the results will be interpreted.

### Data Synthesis

The results will be synthesized and presented in count, percentage, and frequency in a narrative manner. Two investigators including the consultant (statistics) will analyze the data by using the software. Dichotomous data will be presented and combined using relative risks and continuous data will be summarized by arithmetic means and standard deviations, and all data will be combined by using weighted mean differences; both will be accompanied by 95% confidence intervals. Medians and ranges will be reported in tables. Arithmetic means and standard deviations will be used to summarize continuous data when the data are assumed to be normally distributed. Separate summary effect estimates will also be generated for studies that meet and do not meet the individual quality criterion. Heterogeneity among trials will be assessed by inspecting forest plots, to look for overlapping confidence intervals, applying the Chi-square test, with a $p$ value of 0.05 indicating statistical significance, and using the $I^2$ test with a value of 50% to denote moderate levels of heterogeneity. If heterogeneity is detected and it is still considered clinically meaningful to combine studies, then a random-effects model will be used. A sensitivity analysis to investigate the robustness of the results to the quality components will be done, provided there are sufficient trials. A funnel plot will be utilized to indicate publication bias, heterogeneity of results, or differences in the methodological quality. Heterogeneity in studies will be explored, and if sufficient studies are identified and included in this review, a meta-analysis based on the methodological quality of the studies is possible.

For individual trials, wherever possible, mean differences (and 95% confidence intervals) will be reported.

## Conclusion

This systematic review will give more precise estimates of the effectiveness of Ayurvedic interventions in conjunctivitis and thus would give evidence to make health decisions nationally, regionally, and globally for this condition and give way for future research. In case enough data is available, meta-analysis will also be conducted. It will also show the relative efficacy and safety of *Shodhana*, *Shamana*, and *Netra Kriyakalpa* in conjunctivitis.

## Author's Contribution

VV Krishna Kumar, Alok K Srivastava, Pallavi N Kamble, and Pratap Makhija drafted the manuscript. All authors contributed to developing the selection criteria, the risk of bias assessment strategy, and data extraction criteria. VV Krishna Kumar developed the search strategy. All authors read, provided feedback, and approved the final manuscript.

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# हिन्दी सारांश

## कंजक्टिवाइटिस के प्रबंधन में आयुर्वेदिक चिकित्सा की सुरक्षितता और प्रभावकारिता: एक सिस्टेमेटिक रिव्यू के लिए प्रोटोकॉल

**कृष्णकुमार वी., आलोककुमार श्रीवास्तव, पल्लवी एन. कांबले, प्रताप माखीजा**

**परिचय:** कंजंक्टिवाइटिस आंख की एक सामान्य व्याधि है जो पूरे विश्व में पायी जाती है और सभी उम्र और सामाजिक स्तर को प्रभावित करती है, जिससे दो प्रतिशत से अधिक आबादी प्रभावित होती है। पारंपरिक उपचार में बीमारी के इलाज के लिए कई विकल्प होते हैं लेकिन उपचार के पर्याप्त विकल्पों के बावजूद, रोगियों को परेशान करने वाले लक्षण दिखाई देते हैं। पूरक एवं वैकल्पिक चिकित्सा उपचार यहाँ एक महत्वपूर्ण भूमिका निभा सकता है। इस विषय पर कई व्यवस्थित समीक्षायें हर्बल दवाओं के लिए प्रकाशित की गई हैं। कंजक्टिवाइटिस में विभिन्न शोधन, शमन और नेत्र क्रियाकल्प की प्रभावकारिता और सुरक्षा को व्यक्तिगत रूप से साबित किया गया है। हालाँकि, कंजंक्टिवाइटिस के लिए आयुर्वेद चिकित्सा के लिए कोई सिस्टेमेटिक रिव्यू नहीं किया गया है। यह अध्ययन कंजक्टिवाइटिस के प्रबंधन में आयुर्वेदिक चिकित्सा की सुरक्षितता और प्रभावकारिता को देखते हुए प्रकाशित नैदानिक आंकड़ों की गहन समीक्षा के उद्देश्य से है।

**विधियाँ और विश्लेषण:** हम रैंडमाइज्ड कंट्रोल ट्रायल, क्वासी रैंडमाइज्ड कंट्रोल ट्रायल, रैंडमाइज्ड कंट्रोलड् क्लीनिकल ट्रायल, मल्टीपल आर्म क्लीनिकल ट्रायल की एक सिस्टेमेटिक रिव्यू करेंगे, जो 1990 से आज तक प्रकाशित हैं। इस समीक्षा में आयुर्वेद के विभिन्न ग्रंथों मे वर्णित सभी वय एवं लिंग मे पाये जाने वाले कंजंक्टिवाइटिस से संबन्धित लक्षणों के आधार पर निर्धारित अध्ययनों को सम्मिलित किया जायेगा। ऐसे अध्ययन को सम्मिलित करेंगे जिनमें किसी भी खुराक, प्रकार, अनुसूची, दवा के रूप में आयुर्वेदिक उपचार (शमन, शोधन या/और नेत्र क्रिया), और चिकित्सा या नियंत्रण के रूप में पथ्यापथ्य (जीवन शैली में बदलाव) की सलाह दी गयी थी। उपचार की प्रतिक्रिया और गंभीर प्रतिकूल घटनाओं को प्राथमिक परिणाम माना जायेगा।

**नैतिकता और प्रसार:** सिस्टेमेटिक रिव्यू के परिणामों को पियर रिव्यूड् जर्नल्स में प्रकाशित कर प्रसारित किया जाएगा।

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