Review title

Effectiveness of adjunctive photoactivated chromophore–corneal collagen cross-linking versus standard antimicrobial treatment on corneal healing in adults with infectious keratitis: a systematic review protocol.

Review question(s)

The question of this review is: what is the effectiveness of adjunctive photoactivated chromophore–corneal collagen cross-linking (PACK-CXL) versus standard topical antimicrobial treatment (SAT) on corneal healing in adults with infectious keratitis (IK)?

Additional specific review sub-questions are:

i) What are the effects of the intervention on time to complete healing, size of epithelial defect, size of infiltrate and visual acuity?

ii) What are the effects of the intervention on adverse events

Introduction

Infectious keratitis (IK) represents the leading cause for corneal blindness in the world.[1, 2] It is a common, yet potentially sight-threatening, ophthalmic emergency that often warrants hospital admission for intensive antibiotic treatment and monitoring.[3, 4] It can be caused by a wide array of microorganisms, including bacteria, fungi, viruses and parasites. Broad-spectrum antimicrobial therapy is currently the mainstay of treatment for IK; however there is a decline in efficacy of antibiotic treatment due to an emerging trend of antimicrobial resistance in ocular infection.[5-7] Furthermore complications such as corneal melt, perforation and endophthalmitis, may ensue despite timely and intensive topical antibiotic treatment, necessitating further surgical interventions such as tectonic or therapeutic keratoplasty in a trial to preserve the eye and vision.[3, 4, 8, 9] However performing tectonic / therapeutic keratoplasty in a "hot eye" is associated with an increased incidence of recurrence of the disease, uncontrolled intraocular pressure, and graft rejection / failure.[3, 10] These issues highlight the need for alternative or adjuvant antimicrobial treatment to supplement the current therapeutic armamentarium for IK.

Corneal collagen cross-linking (CXL) was first introduced in 2003 by Wollensak et al.[11] to stabilize the progression of keratoconus. It utilizes a combination of ultraviolet-A (UVA) light of 370 nm and photosensitizing agent "riboflavin" to increase the corneal biomechanical stability and rigidity. The long-term efficacy and safety of CXL for corneal ectatic disorders have been well established by many long-term studies.[12-14] In addition to the stiffening effect on the cornea, CXL has been increasingly used for IK in the recent years. The rationale for using CXL for infection is based on the strong

inherent antimicrobial activity of the UV light, which can directly damage the DNA and RNA of various types of microorganisms. Furthermore, the reactive oxygen species released from photoactivated riboflavin can directly affect the DNA and cell membranes of the microorganisms, culminating in a powerful synergistic antimicrobial action.[15-17] These effects together with the increased corneal rigidity and hence resistance to proteolytic enzymatic digestion of stromal collagen has made CXL an attractive adjuvant in the management of IK.[18]

In view of the emerging evidence of CXL for infectious keratitis, a new terminology – Photo-Activated Chromophore for Keratitis – Corneal Cross-Linking (PACK-CXL) – was coined in 2013 at the ninth CXL congress in Dublin, Ireland, to help distinguish its use from CXL for corneal ectasia and to avoid scientific confusion.[19] However PACK-CXL is not routinely used in clinical practice due to the uncertainty of its efficacy and safety. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and no comprehensive review on the effect of the intervention on adverse effects that include randomized controlled trials and nonrandomized trials were identified. Since the last two exiting reviews[20-21] on PACK-CXL further studies have been conducted including two randomized controlled trials. The objective of this review is to evaluate the effectiveness of adjunctive PACK-CXL versus standard antimicrobial treatment alone on corneal healing in adults with infectious keratitis.

Keywords

Antibiotic; Antimicrobial; Corneal infection; Corneal ulcer; Cross-linking; CXL; Microbial keratitis; Infectious keratitis; PACK-CXL.

Inclusion criteria

Participants
This review will consider studies that include adults with infectious keratitis. This is inclusive participants with bacterial, fungal, acanthamoeba, viral, mixed or culture-negative presumed infectious keratitis.

Intervention(s)
This review will consider studies that evaluate adjunctive Photo-Activated Chromophore for Keratitis – Corneal Cross-Linking (PACK-CXL).

Comparator(s)
This review will consider studies that compare the intervention to standard topical antimicrobial treatment alone.

Outcomes

This review will consider studies that include the following outcomes:

Primary outcome measure: time to complete corneal healing (defined as complete corneal re-epithelialization and clearance of infiltrate and hypopyon; days). Secondary outcome measures:

i. Size of epithelial defect (mm^2) and size of infiltrate (mm^2) at 7 days and at final follow-up.
ii. Visual acuity (LogMAR) at final follow-up.
iii. Adverse events (defined as worsening IK and/or corneal melt requiring tectonic / therapeutic keratoplasty or evisceration) at final follow-up.

Types of studies

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials (RCT), non-randomized controlled trials, before and after studies and interrupted time-series studies. Only RCTs will be included in meta-anlaysis. In addition, analytical observational studies including prospective and retrospective cohort studies and case-control studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports and descriptive cross-sectional studies for inclusion.

Methods

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence.[22] The review title was registered with with the Joanna Briggs Institute (http://joannabriggs.org/research/registered_titles.aspx)

Search strategy

The search strategy will aim to locate both published studies. An initial limited search of MEDLINE and EMBASE was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (see Appendix 1). Studies published in English language will be included. Studies published from 1950 to the present will be included. The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference list of all studies selected for critical appraisal will be screened for additional studies.

Information sources

The databases to be searched include: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ISRCTN registry (www.isrctn.com/editAdvancedSearch), US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp).

Study selection

Following the search, all identified citations will be loaded into EndNote X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the Rayyan (Qatar). The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion, or with a third reviewer. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[23]

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers at the outcome level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for experimental and quasi-experimental studies.[22] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). The results of the critical appraisal will be reported in a tabular and narrative form.

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using the standardized RevMan 5.3[24]. The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objective The extracted data included the authors and study title, year of publication, sample size, types of interventions, types of causative microorganisms, results and complications. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis

Studies will, where possible, be pooled with statistical meta-analysis using RevMan5.3. Effect sizes will be expressed as either odds ratios (for dichotomous data) or post-intervention mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi squared and I^2 tests. Statistical analyses will be performed using random effects.[25] Subgroup analyses will be conducted where there is sufficient data

to investigate bacterial and fungal keratitis cohorts. Sensitivity analyses will be conducted to test decisions made regarding studies at high risk of bias for an outcome in one or more key domains; selection, performance, detection, attrition and reporting biases[26-27]. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate. The direction of effect of PACK-CXL on adverse events will be graphically represented on albatross plots generated by the module installed on STATA 15.1 statistical software.[28] A funnel plot will be generated using RevMan 5.3 to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) will be created using GRADEPro GDT software (McMaster University, ON, Canada).[29] The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The outcomes reported in the SoF will be presented in a tabular form. Outcomes for inclusion in SoF will be: time to complete healing, size of epithelial defect, size of infiltrate, visual acuity and adverse events.

Funding

Conflicts of interest

There is no conflict of interest in this project.

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Appendix I: Search strategy for MEDLINE

#	Searches	Records
1	Cross-link*.mp	82,392
2	Crosslink*.mp	30,100
3	CXL.mp	1,107
4	KXL.mp	23
5	Cross-Linking Reagents/	24,263
6	Riboflavin*.mp	37,586
7	Vitamin B.mp	39,024
8	Photosensiti*.mp	12,848
9	Keratitis.mp	18,259
10	Corneal infect*.mp	987
11	Corneal ulcer*.mp	6,575
12	Exp Keratitis/	20,164
13	Exp Corneal Ulcer/	5,023
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	188,909
15	9 or 10 or 11 or 12 or 13	25,673
16	14 and 15	384
17	Limit 16 to humans	246
18	Limited 1 January 2003 - present	204