Penetrating keratoplasty versus deep anterior lamellar keratoplasty for treating keratoconus (Protocol)

Keane M, Williams K, Coster D

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[Intervention Protocol]

Penetrating keratoplasty versus deep anterior lamellar keratoplasty for treating keratoconus

Miriam Keane[1], Keryn Williams[1], Douglas Coster[1]

[1]Department of Ophthalmology, Flinders University, Adelaide, Australia

Contact address: Miriam Keane, Department of Ophthalmology, Flinders University, Level 3 Flinders Medical Centre, Bedford Park, Adelaide, SA 5042, Australia. miriam.keane@flinders.edu.au.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare visual outcomes after penetrating keratoplasty and DALK for keratoconus and identify the factors contributing to poor outcomes.

BACKGROUND

Description of the condition

Keratoconus is an ectatic (weakening) disease of the cornea, which is the clear surface at the very front of the eye (Coster 2002). Weakness in the tensile strength of the cornea results in distortion of the anterior refractive surface of the eye. The weakened cornea is unable to stand the intraocular pressure and protrudes in a conical shape (Ertan 2008a). The increased curvature of the conical cornea results in myopia (short-sightedness) and irregularities of the cone produce astigmatism, which causes blurred vision.

Keratoconus is common. It is usually bilateral and manifests early, in the first two decades of life (Ertan 2008a; Espandar 2010). Progression is uncommon after the age of 35 years (Romero-Jimenez 2010). For most people, progression is slow. Early onset of the condition is often associated with more rapid progression.

Corneal curvature is used to assess the severity and progression of keratoconus. Central corneal curvature is adequately measured by keratometry. More extensive assessment of corneal shape requires videokeratography (Gobbe 2005; Jafri 2007).

Various systems have been developed to classify the progression of keratoconus into different stages of the disease (Romero-Jimenez 2010). One such system which is widely accepted and utilised is the Amsler-Krumeich classification system, separating the disease into four stages based on level of myopia and astigmatism, central keratometric readings, scarring and corneal thickness (Ertan 2008b). A variation on this system has been developed more recently by Alió and Shabayek (Alió 2006) to incorporate diagnostic information relating to the severity of higher order corneal aberrations, the visual distortion created by a wavefront of light passing through an irregular eye.

Advanced keratoconus is also accompanied by an increased incidence of hydrops. This is an acute stromal oedema caused by breaks in Descemet's membrane through which aqueous humour, the substance filling the space between the lens and cornea, enters and swells the stroma, the major component of the cornea. Hydrops generally results in scarring of the cornea, which can have a continued impact on visual potential (Rabinowitz 1998; Romero-Jimenez 2010), however it is a rare complication (Bilgin 2009).

Keratoconus has been reported to affect approximately one person in 2000 in the North American population (Rabinowitz 1998). Although some suggest that the prevalence could actually be as high as one per 500 people (Ertan 2008a; Espandar 2010), other studies have found lower prevalence rates, sometimes as small as one per 70,000 people. These studies were conducted in a number of different countries and though the disease affects all ethnic groups findings suggest that people of various ethnic backgrounds, particularly those of Asian descent, may be more prone to the disease than Caucasian populations (Georgiou 2004). The inconsistency in reported prevalence across studies is probably also due to the wide range of definitions and diagnostic criteria utilised by practitioners and researchers (Rabinowitz 1998; Romero-Jimenez 2010).

The disease affects both men and women however some studies have found variations in prevalence across the sexes. Genetics have been found to play a role in the disease, with a family history reported in approximately 6% to 10% of cases and an increased risk in first degree relatives also documented. The definitive cause of keratoconus is still unknown (Rabinowitz 1998; Wang 2000).

Description of the intervention

The treatment of keratoconus relies on the use of a hard or semi-rigid contact lens to cover the irregular cornea and provide a new, appropriately curved anterior refractive surface (Bilgin 2009; Rabinowitz 1998). If the surface of the conical cornea is too steep or too irregular to bear a contact lens, or if the eye is too sensitive to tolerate a lens, surgery becomes necessary. Approximately 10% to 15% of patients diagnosed with keratoconus require surgery (Rabinowitz 1998; Romero-Jimenez 2010). Corneal transplantation is the procedure employed. The purpose of corneal transplantation for keratoconus is to replace the abnormal anterior refracting surface of the eye with a donor cornea that has a normal anterior surface shape. Corneal transplantation for keratoconus may be full-thickness (penetrating) or partial-thickness (lamellar).

Penetrating keratoplasty

Penetrating keratoplasty has been performed as a treatment for keratoconus for over 70 years (Castroviejo 1948) and remains the leading treatment for those sufferers with contact lens intolerance (Jhanji 2010; Rabinowitz 1998). Existing longitudinal data show that keratoconus is one of the most common indications for penetrating keratoplasty and that these recipients have higher graft survival rates (Jaycock 2008; Williams 2007). An analysis conducted in 2006 concluded that it was a cost-effective treatment for severe cases of keratoconus (Roe 2008).

Penetrating keratoplasty involves the replacement of a full-thickness portion of the cornea (Coster 2002; Romero-Jimenez 2010). There are many variations in technique, however a recent review of the published evidence concluded that there was "no evidence for the superiority of any specific technique" (Frost 2006).

Deep anterior lamellar keratoplasty

More recently, lamellar transplantation, in which only a partial-thickness of the cornea is replaced, has been reintroduced as a surgical treatment for keratoconus (Romero-Jimenez 2010). This form of transplantation has been used for decades, however poor visual outcomes resulted in a decline in its use (Trimarchi 2001). Newer techniques in which the interface of the donor and host is at the level of Descemet's membrane have reinvigorated the use of this form of surgery (Karimian 2010; Sugita 1997).

Deep anterior lamellar keratoplasty (DALK) is frequently used for keratoconus. Advocates claim that this procedure is preferable to penetrating keratoplasty for eyes that are free from corneal scarring or hydrops (Jhanji 2010). The premise is that, because the endothelial cell layer of the recipient is left intact during DALK, the prospect of endothelial rejection is precluded (Romero-Jimenez 2010; Tan 2010).

Various techniques have been used to dissect the stroma from the underlying Descemet's membrane (Jhanji 2010; Tan 2010). Common approaches include manual dissection (Anwar 2002; Karimian 2010), which may be enhanced by injection of air into the anterior chamber and stroma (Archila 1984); dissection with a visco-elastic substance, as advocated by Melles (Melles 2000); or the big-bubble dissection technique advocated by Anwar et al (Anwar 2002). Each approach has its proponents.

How the intervention might work

To reiterate, the purpose of corneal transplantation for keratoconus is to replace the abnormal anterior refractive surface of the eye with a cornea that has a normal shape. In penetrating keratoplasty the full-thickness of the cornea is replaced, while in DALK the corneal stroma is replaced down to the Descemet's membrane. The benefit and risk profile of the two procedures may be different, however the desired therapeutic outcomes are identical.

Why it is important to do this review

Although the aim of the procedures is the same, the risk profiles may be different and disparate outcomes have been reported. It is important that outcomes from the newer treatment, DALK, be compared to those achieved using the traditional penetrating technique in terms of visual outcome and graft survival. The results will help to inform corneal surgeons and keratoconus sufferers of the appropriateness of each treatment for this condition. This will aid in the clinical decision making process with regard to the selection of treatment for individuals with this condition.

OBJECTIVES

To compare visual outcomes after penetrating keratoplasty and DALK for keratoconus and identify the factors contributing to poor outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) that meet the stated inclusion criteria. The review will include all RCTs in which one arm received treatment with penetrating keratoplasty and the other with DALK. Details of the randomisation procedure must be available. Where a study is defined as being randomised but the details are not included in the published literature, we will attempt to gain this information from the authors. If details of the method of randomisation cannot be obtained we will retain the study in the review, acknowledging its unclear risk of bias, but exclude it from any meta-analyses.

Types of participants

Participants of any age may be included in selected trials. We will exclude studies that included participants with other confounding related disorders, such as pellucid marginal degeneration (PMD) (the thinning of the periphery rather than the central area of the cornea) or keratoglobus in which the entire corneal surface is involved. We will only include in the review studies which specify a reliable method of diagnosis of the keratoconus (slit lamp examination, corneal topography, wave front analysis). Participants may be at any stage of the disease and there may be a mixture of stages of progression amongst participants as long as this is specified. Participants must not have a history of corneal scarring or hydrops as this would prevent DALK from being a suitable treatment for their condition. With regards to keratoconus prevalence or progression, no significant differences across cultural and racial backgrounds have been confirmed in the scientific literature. Thus, studies from anywhere in the world will be eligible for inclusion.

Types of interventions

We will include trials in which the outcomes of penetrating keratoplasty and DALK, as treatments for keratoconus, were directly compared to one another. We will also include studies in which both treatments were compared to one another as well as a third treatment or a control group. We will exclude studies comparing either one of these treatments alone to a third treatment or a control group.

Types of outcome measures

Studies which report at least one clinical outcome will be eligible for inclusion.

Primary outcomes

The vast majority of keratoconus patients who undergo corneal graft surgery do so in order to gain improved vision (Williams 2007). In some cases, uncorrected post-graft vision may improve to a functional level but for others, approximately half of recipients, correction with contact lenses or spectacles will still be necessary in

order to achieve optimal, useful vision. Therefore, we will use post-graft best corrected visual acuity (BCVA) as the primary outcome measure.

BCVA should be provided (mean and range) in terms of either Snellen or LogMAR measurements (measurements given in either of these two forms can be easily converted into the other for the relevant analyses). Where necessary, Snellen measurements will be converted into LogMAR, not LogMAR as measured on an ETDRS chart. Post-graft BCVA should be measured at three months after surgery. Post-graft BCVA will be considered in two ways, firstly in terms of the level of BCVA achieved (6/12 or better versus 6/15 or worse) and also in terms of change from pre-graft BCVA (difference in lines of Snellen acuity), where recorded.

Secondary outcomes

BCVA at six months, 12 months and 24 months will be analysed as secondary outcomes. Further measures of refraction will be analysed. Uncorrected visual acuity (UCVA) will be a secondary outcome measure. Again, this will be analysed for measurements at three, six, 12 and 24 months post-surgery and should be provided (mean and range) in terms of either Snellen or LogMAR measurements. As with BCVA, these data will be considered both in terms of the final UCVA achieved and with regards to the change in UCVA pre to post-graft. We will also consider method of visual correction (in order to be able to achieve a desirable BCVA) and keratometry readings (to determine level of astigmatism) as secondary outcome measures.

Other secondary outcome measures will be the frequency of rejection episodes and graft failure.

Timing of outcome assessment

As visual recovery from corneal grafting can continue for a long time, outcome measures will be analysed primarily at three months post-graft; as well as in the context of secondary outcome measures at the following periods of time post-graft, where possible: six, 12 and 24 months. In addition, the removal of sutures has been shown to impact on final visual acuity and so, if practical, comparisons will be made between both BCVA and UCVA before and after suture removal.

Adverse outcomes

Other adverse effects may be reported, including intraoperative complications like perforation or need for rebubbling, and post-operative events such as scarring, infection, cataract or pain. We will also compare these across treatment groups.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register), the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library)*, MEDLINE, PubMed, EMBASE, Latin American and Caribbean Health Sciences Literature Database (LILACS), Cumulative Index to Nursing and Allied Health Literature (CINAHL), OpenGrey, Web of Science - Science Citation Index (SCI), Health Collection - Informit, the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There will be no date or language restrictions in the electronic searches for trials.

See: Appendices for details of search strategies for CENTRAL and DARE (Appendix 1), MEDLINE (Appendix 2), PubMed (Appendix 3), EMBASE (Appendix 4), LILACS (Appendix 5), CINAHL (Appendix 5), OpenGrey (Appendix 7), SCI (Appendix 8), Informit (Appendix 9), *m*RCT (Appendix 10), ClinicalTrials.gov (Appendix 11) and the ICTRP (Appendix 12).

Searching other resources

We will handsearch the following international conference proceedings from 1999 onwards in order to identify further, unpublished studies.

1. American Society of Cataract and Refractive Surgery Symposium and Congress
2. Asia Pacific Academy of Ophthalmology Congress
3. Cambridge Ophthalmological Society Meeting
4. European Society of Cataract and Refractive Surgeons Congress
5. International Congress of Eye Research
6. Royal Australian and New Zealand College of Ophthalmology Congress
7. Royal College of Ophthalmologists Congress
8. World Cornea Congress
9. World Ophthalmology Congress

We will contact the authors of any studies identified in this way to gain further information where this is required. We will also handsearch the reference lists of selected studies in order to identify other relevant articles, conference presentations or book chapters.

Data collection and analysis

Selection of studies

The two authors will independently assess all citations gathered using the outlined parameters. The authors will classify each citation as either 'definitely not relevant' or 'potentially relevant'. Where a study is judged by both authors at this time to be 'definitely not relevant', it will be excluded from further analysis. In cases where one author believes a study to be 'definitely not relevant' while the

other classifies it as 'potentially relevant' the final classification of the study will be determined by consensus or, if the two authors cannot reach an agreement, by reference to a third author.
Where citations were classified as 'potentially relevant', full copies of related studies will be obtained and assigned an identification number (ID). Where a study published in a language other than English is identified as being potentially relevant, we will initially arrange translation of the methods and results sections of the study. If they appear to meet the selection criteria, we will then seek a full English translation of the study. Where the published data are felt by at least one author to be insufficient to determine the relevance of the study, trial investigators will be contacted to request the necessary information.
Having read the full articles and considered any further information gathered from trial investigators, the two authors will classify them as either 'relevant' or 'not relevant'. The lists of both authors will be compared. Those that are classified as 'not relevant' by both authors will be excluded at this point from the review. We will record the reasons for their exclusion and these will be documented in the review. Those that are classified as 'relevant' by both authors will be included in the review. Those that are classified as 'relevant' by one author and 'not relevant' by the other will be further discussed by the two authors and a decision made regarding their inclusion. If, for any studies requiring further discussion, the two authors cannot reach agreement on classification, consensus will be obtained by reference to a third author. The reasons for any further exclusions will be recorded and documented in the review.
The data will be entered into RevMan (Review Manager 2011) at each step in the review process.

Data extraction and management

The two authors will independently extract the data using a form developed by the Cochrane Eyes and Vision Group. This will include information on the following.
1. The age, gender, race, geographical location and grade of keratoconus of the participants, as well as the number in each treatment group and the comparability of the two groups on the aforementioned parameters at baseline.
2. The methods used in each intervention group.
3. Information on missing data and participants who did not complete the trial.
4. The outcomes of the treatments. Dichotomous data will be collected in terms of number at risk and number of events, while means and standard deviations will be used for continuous data, or medians and interquartile ranges for skewed continuous data. Data will be extracted for the outcome measures outlined for this review.
One of the authors will enter the data into RevMan (Review Manager 2011), with the second author checking the entered data for inconsistencies or errors. Any disagreement will be resolved by discussion amongst the two authors, or with reference to a third author if no consensus can be reached. Where there is missing data, this will be identified, along with any reasons given, and analysis will be conducted utilising the available data.

Assessment of risk of bias in included studies

The two authors will independently assess the risk of bias for the included studies as per the methods given in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Methodological quality will be assessed for the following parameters.

Potential issues relating to selection bias

1. Inclusion and exclusion criteria.
2. Method of keratoconus grading (slit lamp examination, corneal topography, wave front analysis or combination).
3. Randomisation technique: randomisation via a random number generator, random number table, shuffled cards or shuffled envelopes, where the assignment of treatment groups is conducted and confirmed prior to specific patient allocation and cannot be changed after this point, will be considered appropriate. Inadequate techniques will include alternation, assignment based on variables such as record numbers, dates of birth or days of the week, or any form of randomisation in which participant assignment could be altered or affected by the treating surgeon after the initial assignment. Studies with inadequate randomisation techniques will be excluded and the reasons for this recorded.
4. Equality of comparison groups.

Potential issues relating to performance bias

5. Allocation concealment: as the two techniques differ, the providers cannot be masked however the recipients and those administering the assessments of outcomes should ideally be.

Potential issues relating to detection bias

6. Outcome measurements: despite differences in the techniques, outcomes of the interventions should be measured in the same way for both.

Potential issues relating to attrition bias

7. Completion of follow-up: was this equal across treatment groups, what were the reasons for this and were there adequate numbers remaining for the results to be meaningful?
Each author will grade the studies on each of these six parameters, providing a determination of A (low risk of bias), B (unclear risk of bias), or C (high risk of bias). The review authors will discuss any disagreements in classification. If necessary, the authors of the trials in question will be contacted to clarify any unclear information.

Measures of treatment effect

Outcome measures will comprise two types of data: continuous and dichotomous. Weighted mean differences will be used to analyze continuous data (BCVA and UCVA measured in LogMAR, as well as change in BCVA and UCVA LogMAR results) where the data is normally distributed. Where BCVA and UCVA are provided in terms of Snellen acuity, these figures will be transformed into LogMAR measurements for the purposes of these analyses. Where continuous data are not normally distributed, they will be dichotomised for analysis. For outcomes with dichotomous data (functional level of BCVA or UCVA, contact lens tolerance, rejection episodes, graft failure, occurrence of other adverse events) we will measure the effect size using the odds ratio (OR).

Unit of analysis issues

All unit of analysis issues will be dealt with in the manner specified in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). As keratoconus is a bilateral condition, it is possible that some trials will involve one eye of each patient to be assigned to one treatment group (penetrating keratoplasty or DALK) and the other to the other treatment group and then the overall outcomes compared. Providing that adequate randomisation occurred in terms of which eye was assigned to which treatment group, the analysis allowed for clustering by patient and all patients had both eyes included in the study, such studies would still meet the criteria for the review as these surgeries will be performed at different times. These trials will still be included in the analysis, with attention paid to this issue during sensitivity analysis.

It is also possible that some studies may enter all eyes meeting the inclusion criteria into the study (including multiple eyes of one patient) and then randomise all of the eyes to a treatment group. This would mean that the same treatment may be received in both eyes of the same patient, or that some patients may have both eyes included in the trial while others have just one. Because of the potential inconsistent within-person clustering inherent in this design, such trials will be excluded from meta-analyses.

Dealing with missing data

Should any studies have missing data, the cases lost to follow-up will be documented and available case analysis reported. No missing data will be imputed. We will consider the potential impact of any missing data. Where large amounts of data are missing, we will conduct intention-to-treat (ITT) analyses, where possible, to determine if this has had a significant impact on the results. If it is determined that it did have, the study will be excluded from further analyses.

Assessment of heterogeneity

The heterogeneity of the included studies will be assessed in order to determine whether it is appropriate to carry out a meta-analysis on the data. This will be done by examining the characteristics of the studies and the forest plot of study results, and by conducting a Chi^2 test of statistical heterogeneity and using this to determine the I^2 statistic. If the I^2 statistic indicates under 30% variability due to heterogeneity, this will be considered to be non-significant, while over 50% will be considered to indicate significant heterogeneity. For cases in which 30% to 50% heterogeneity is estimated, the magnitude and direction of the effect as well as the P value of the Chi^2 test and confidence interval of the I^2 statistic will be considered when making a final decision about the significance. If heterogeneity of the studies is determined to be significant, the results will not be combined in a meta-analysis but rather reported in a descriptive summary. If significant heterogeneity is not present, a meta-analysis will be conducted using the random-effects model or, if only a small number of studies are included, the fixed-effect model.

Assessment of reporting biases

In order to assess reporting bias the intended outcome measures for each included trial, as recorded in either the trial protocol or the methods sections of resulting articles, will be compared to those reported in the results sections of subsequent reports and articles. In addition, a funnel plot and sensitivity analysis will be used to assess reporting bias.

Data synthesis

Where meta-analyses are deemed appropriate, summary measures will be calculated using the random-effects model if four or more RCTs are identified, or using the fixed-effect model if two or three studies are identified. If meta-analyses are not judged to be appropriate, results will be provided in a descriptive summary form.

Subgroup analysis and investigation of heterogeneity

If heterogeneity of the studies is determined to be significant, the results may not be combined in a meta-analysis but rather reported in a descriptive summary. Where reported in the same trials, subgroup analyses will be conducted for the two main DALK surgical techniques: the big-bubble and the Malles. These analyses will determine whether the heterogeneity of the overall review is affected by the differences between these two techniques.

Sensitivity analysis

The initial analysis conducted will include all trials which met the inclusion criteria. Analyses will then be re-run on the data in which: 1) any trials for which the risk of allocation bias was judged to be high are removed, 2) any trials for which the risk on any parameter was judged to be high are removed, 3) any trials that were funded by industry are removed, and 4) trials which

are unpublished are removed. In this way, it will be possible to assess how strongly the results of our review are related to the decisions and assumptions that we have made throughout the review process. In addition, if any trials are included in which each patient receives each intervention (one in each eye) and the outcomes are compared, these will be removed to check that this clustering of participants does not have a significant impact on the results.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL and DARE search strategy

#1 MeSH descriptor Keratoconus
#2 keratocon*
#3 ectatic* or ectasia
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Keratoplasty, Penetrating
#6 (penetrating or perforating) near/2 (keratoplast*)
#7 full near/3 thickness near/3 cornea*
#8 (#5 OR #6 OR #7)
#9 deep anterior lamellar keratoplast*
#10 deep lamellar keratoplast*
#11 partial near/3 thickness near/3 cornea*
#12 big near/2 bubble
#13 DALK
#14 (#9 OR #10 OR #11 OR #12 OR #13)

#15 (#4 AND #8 AND #13)

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp Keratoconus/
14. keratocon$.tw.
15. (ectatic$ or ectasia).tw.
16. or/13-15
17. Keratoplasty, Penetrating/
18. ((penetrating or perforating) adj2 keratoplast$).tw.
19. (full adj3 thickness adj3 cornea$).tw.
20. or/17-19
21. deep anterior lamellar keratoplast$.tw.
22. deep lamellar keratoplast$.tw.
23. (partial adj3 thickness adj3 cornea$).tw.
24. (big adj2 bubble).tw.
25. DALK.tw.
26. or/21-25
27. 16 and 20 and 26
28. 12 and 27

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

Appendix 3. PubMed search strategy

(((randomized controlled trial[pt] OR controlled clinical trial[pt]) OR (randomized OR randomised OR randomly OR placebo[tiab]) OR (trial[ti]) OR ("Clinical Trials as Topic"[MeSH Major Topic])) NOT (("Animals"[Mesh]) NOT ("Humans"[Mesh] AND "Animals"[Mesh]))) AND (((keratoconus[MeSH Terms]) OR (keratocon*) OR (ectatic* OR ectasia)) AND ((keratoplasty, penetrating[MeSH Terms]) OR (keratoplast*) OR (DALK)))

Appendix 4. EMBASE (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp keratoconus/
34. keratocon$.tw.
35. (ectatic$ or ectasia).tw.
36. or/33-35
37. exp penetrating keratoplasty/
38. ((penetrating or perforating) adj2 keratoplast$).tw.
39. (full adj3 thickness adj3 cornea$).tw.
40. or/37-39
41. deep anterior lamellar keratoplast$.tw.
42. deep lamellar keratoplast$.tw.
43. (partial adj3 thickness adj3 cornea$).tw.
44. (big adj2 bubble).tw.
45. DALK.tw.
46. or/41-45
47. 36 and 40 and 46
48. 32 and 47

Appendix 5. LILACS search strategy

keratocon$ and keratoplast$ or DALK

Appendix 6. CINAHL (EBSCO) search strategy

S7 S3 AND S6
S6 S4 OR S5
S5 DALK
S4 keratoplasty or keratoplasties
S3 S1 OR S2
S2 ectatic or ectasia
S1 Keratoconus

Appendix 7. OpenGrey search strategy

keratoconus and keratoplasty

Appendix 8. Web of Science SCI search strategy

#9 #7 AND #8
#8 TS=random*
#7 #3 AND #6
#6 #4 OR #5
#5 TS=DALK
#4 TS=keratoplasty
#3 #1 OR #2
#2 TS=ectatic
#1 TS=keratoconus

Appendix 9. Health Collection (Informit) search strategy

SUBJECT=(keratoconus) AND SUBJECT=(keratoplasty)

Appendix 10. *meta*Register of Controlled Trials search strategy

keratoconus AND keratoplasty

Appendix 11. ClinicalTrials.gov search strategy

Keratoconus AND Keratoplasty

Appendix 12. ICTRP search strategy

keratoconus AND keratoplasty

HISTORY

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CONTRIBUTIONS OF AUTHORS

KW and DC had performed previous work that was the foundation of the current review. MK, KW and DC wrote drafts of the protocol and responded to comments from the editorial base. MK and KW responded to peer review comments.

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None known

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