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Descemet's membrane endothelial keratoplasty (DMEK) versus Descemet's stripping automated endothelial keratoplasty (DSAEK) for corneal endothelial failure (Review)

Stuart AJ, Romano V, Virgili G, Shortt AJ

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[Intervention Review]

Descemet's membrane endothelial keratoplasty (DMEK) versus Descemet's stripping automated endothelial keratoplasty (DSAEK) for corneal endothelial failure

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ABSTRACT

Background

Corneal endothelial transplantation has become the gold standard for the treatment of corneal endothelial dysfunctions, replacing full thickness transplantation, known as penetrating keratoplasty. Corneal endothelial transplantation has been described using two different techniques: Descemet's membrane endothelial keratoplasty (DMEK) and Descemet's stripping automated endothelial keratoplasty (DSAEK). Both are still performed worldwide.

Objectives

To compare the effectiveness and safety of Descemet's membrane endothelial keratoplasty (DMEK) versus Descemet's stripping automated endothelial keratoplasty (DSAEK) for the treatment of corneal endothelial failure in people with Fuch's endothelial dystropy (FED) and pseudophakic bullous keratopathy (PBK).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2017, Issue 7); MEDLINE Ovid; Embase Ovid; LILACS BIREME; the ISRCTN registry; ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). The date of the search was 11 August 2017.

Selection criteria

We included randomised controlled trials (RCTs) and non-randomised paired, contralateral-eye studies in any setting where DMEK was compared with DSAEK to treat people with corneal endothelial failure.

Data collection and analysis

Two review authors independently screened the search results, assessed trial quality and extracted data using the standard methodological procedures expected by Cochrane. Our primary outcome was best corrected visual acuity (BCVA) measured in logarithm of the Minimum Angle of Resolution (logMAR). Secondary outcomes were endothelial cell count, graft rejection, primary graft failure and graft dislocation. We graded the risk of bias of non-randomised studies (NRSs) using ROBINS-I.

Main results

We did not identify any RCTs but found four non-randomised studies (NRSs) including 72 participants (144 eyes), who had received DSAEK in the first eye followed by DMEK in the fellow eye. All the studies included adult participants where there was evidence of FED and endothelial failure requiring a corneal transplant for the treatment of visual impairment. We did not find any studies that included PBK. The trials were published between 2011 and 2015, and we assessed them as high risk of bias due to potential unknown confounding factors since DSAEK preceded DMEK in all participants. Two studies reported results at 12 months, one at 6 months, and one between 6 and 24 months. At one year, using DMEK in cases of endothelial failure may result in better BCVA compared with DSAEK (mean difference (MD) -0.14, 95% confidence interval (CI) -0.18 to -0.10 logMAR, 4 studies, 140 eyes, low-certainty evidence). None of the participants had severe visual loss (BCVA of 1.0 logMAR or more; very low-certainty evidence). Regarding endothelial cell count data (4 studies, 134 eyes) it is hard to draw any conclusions since two studies suggested no difference and the other two reported that DMEK provides a higher cell density at one year (very low-certainty evidence). No primary graft failure and only one graft rejection were recorded over four studies (144 eyes) (very low-certainty evidence). The most common complications reported were graft dislocations, which were recorded in one or two out of 100 participants with DSAEK but were more common using DMEK, although this difference could not be precisely estimated (risk ratio (RR) 5.40, 95% CI 1.51 to 19.3; 4 studies, 144 eyes, very low-certainty evidence).

Authors' conclusions

This review included studies conducted on people with corneal endothelium failure due to FED for whom both DMEK and DSAEK can be considered, and found low-certainty evidence that DMEK provides some advantage in terms of final BCVA, at the cost of more graft dislocations needing 're-bubbling' (very low-certainty of evidence).

PLAIN LANGUAGE SUMMARY

Two surgical techniques for corneal transplant (replacing the clear part of the eye with donor tissue)

What is the aim of this review?
The aim of this Cochrane Review was to compare two different ways of doing corneal transplant surgery: Descemet's membrane endothelial keratoplasty (DMEK) and Descemet's stripping automated endothelial keratoplasty (DSAEK). Cochrane Review authors collected and analysed all relevant studies to answer this question and found four studies.

Key messages
DMEK may result in better vision compared with DSAEK. DMEK may be associated with more complications but these complications do not occur often and can be managed without further surgery.

What was studied in the review?
The cornea is the clear (transparent) front part of the eye. In some conditions, for example, Fuch's endothelial dystrophy, the cells that line the inside of the cornea (endothelium) stop working so well. This can lead to cloudy vision. Doctors can restore vision by doing a corneal transplant which means replacing the corneal tissue with donor tissue. When the endothelium only is replaced this is known as 'Descemet's membrane endothelial keratoplasty' or DMEK. An alternative corneal transplant is to replace the endothelium and the next layer of tissue in the cornea as well. This is known as 'Descemet's stripping automated endothelial keratoplasty' or DSAEK.

Cochrane Review authors aimed to find out whether vision is better after DMEK or DSAEK, and how the techniques compare with respect to surgical complications.

What are the main results of the review?
The Cochrane Review authors found four studies. These studies included people who had DSAEK in their first eye to receive a corneal transplant followed by DMEK in their second eye to have a transplant. The studies were from Canada, Germany, India and the USA. None of the studies were supported by sponsors with a commercial interest.

The Cochrane Review authors judged the evidence to be low- or very low-certainty because there may be differences between the first eye and second eye surgeries (other than DMEK or DSAEK) and, in some cases, the data were limited or inconsistent.

The results were:

• DMEK may result in better vision compared with DSAEK (low-certainty evidence). This difference is equivalent to reading one or two lines more on a vision chart.

• None of the people taking part in these studies had severe vision loss after surgery. Severe vision loss was defined as vision worse than 6/60 or 20/200. There were not enough people enrolled in these studies to measure reliably this infrequent outcome (very low-certainty evidence)..

• The studies measured how many cells there were in the endothelium after surgery but found inconsistent results (very low-certainty evidence).

• Almost everyone taking part in the studies had good graft survival, with very few graft rejections and no graft failures. There were not enough people enrolled in these studies to measure reliably these infrequent outcomes (very low-certainty evidence)..

• DMEK may be associated with more early surgical complications. Graft dislocation may happen in one or two out of 100 people with DSAEK and about five times more often with DMEK. This difference was not measured reliably and could be smaller or much larger (very low-certainty evidence). Graft dislocation occurs within days or weeks after surgery and is usually treated with an injection of air into the eye ('re-bubbling').

How up-to-date is this review?
Cochrane Review authors searched for studies that had been published up to August 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Descemet's membrane endothelial keratoplasty (DMEK) compared with Descemet's stripping automated endothelial keratoplasty (DSAEK) for corneal endothelial failure

DMEK compared with DSAEK for corneal endothelial failure

Patient or population: participants/eyes with corneal endothelial failure

Settings: secondary or tertiary ophthalmic care

Intervention: DMEK

Comparison: DSAEK

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of eyes (studies)	Certainty of the evidence (GRADE)	Justification for GRADE assessment
	Assumed risk	Corresponding risk				
	DSAEK	DMEK				
BCVA logMAR, 12 months' follow-up[a] (smaller values of logMAR represent better vision)	The mean visual acuity was 0.35 logMAR (range 0.2 to 0.45)	On average, best corrected visual acuity with DMEK was -0.14 (95% CI -0.18 to -0.10) logMAR better,		140 (4 studies)	⊕⊕⊖⊖ **low**	Paired, contralateral-eye studies in which DSAEK in one eye preceded DMEK in the fellow eye (-2 for potential confounding)
Severe visual loss (LogMAR BCVA of 1.0 or more) within 12 months' follow-up[a]	No studies reported any participants who experienced such loss.			140 (4 studies)	⊕⊖⊖⊖ **very low**	Paired, contralateral-eye studies in which DSAEK in one eye preceded DMEK in the fellow eye (-2 for potential confounding) sparse data (-2 for imprecision)
Endothelial cell count cells/mm^2,	2 studies showed no difference between DSAEK and DMEK. 2 studies found better final ECC for DMEK vs DSAEK			134 eyes (4 studies)	⊕⊖⊖⊖ **very low**	Paired, contralateral-eye studies in which DSAEK in one eye preceded DMEK in the fellow eye (-2 for potential confounding)

12 months' follow-up[a]						We did not conduct meta-analysis due to inconsistency (-2).
Corneal graft rejection any time point[a]	There was 1 event in 72 eyes in the DSAEK group and 0 events in 72 eyes in the DMEK group			144 (4 studies)	⊕⊖⊖⊖ **very low**	Graft rejection was very rare in both groups and a relative risk could not be estimated (-2 for imprecision), but data suggest very low rejection rate at one year for both techniques.
Primary graft failure any time point[a]	There were no events in either group (72 eyes each)			144 (4 studies)	⊕⊖⊖⊖ **very low**	Paired, contralateral-eye studies in which DSAEK in one eye preceded DMEK in the fellow eye (-1 for potential confounding) Primary graft failure was very rare in both groups and a relative risk could not be estimated (-2 for imprecision), but data suggest complete early success for both techniques.
Corneal graft dislocation any time point[a]	**14 per 1000**	**79 per 1000** (15 to 420)	RR: 5.40 (1.51 to 19.27)	144 eyes (4 studies)	⊕⊕⊖⊖ **low**	Paired, contralateral-eye studies in which DSAEK in one eye preceded DMEK in the fellow eye (-2 for potential confounding)
Primary graft failure any time point[a]	There were no events in either group (72 eyes each)			144 (4 studies)	⊕⊖⊖⊖ **very low**	Paired, contralateral-eye studies in which DSAEK in one eye preceded DMEK in the fellow eye (-1 for potential confounding) Primary graft failure was very rare in both groups and a relative risk could not be estimated (-2 for imprecision), but data suggest complete early success for both techniques.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCVA: best corrected visual acuity; **CI:** confidence interval; **RR:** risk ratio; **DMEK:** Descemet's membrane endothelial keratoplasty **DSAEK:** Descemet's stripping automated endothelial keratoplasty

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Two studies reported results at 12 months, one at 6 months, and one between 6 and 24 months.

BACKGROUND

Over the last two decades, significant advances have been made in corneal transplantation techniques. The treatment of corneal endothelial dysfunction has evolved from the replacement of a full-thickness cornea to replacing only the affected layer. This shift from penetrating to posterior lamellar surgery has improved allograft rejection rate post-keratoplasty and preserved the structural integrity of the eye (Lee 2009). Two surgical techniques are described for posterior lamellar keratoplasty or corneal endothelial transplantation; Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK). Both techniques give improved functional results compared to penetrating keratoplasty (PK), but it is still not clear which of these two techniques is the best. This meta-analysis compared DMEK and DSAEK.

Description of the condition

The cornea is the transparent tissue at the front of the eye. It is a critical component of the eye for vision as the cornea not only constitutes a clear window for the light rays to reach the retina but also provides most of the refractive power of the eye (Ayres 2006). It consists of five layers, the epithelium, the Bowman's membrane, the corneal stroma, the Descemet's membrane and the corneal endothelium (from the outer layer towards the inner surface). The clarity of the cornea is of utmost importance to provide a clear visual image; the endothelial cells of the cornea play a vital role in maintaining corneal transparency. They continuously pump fluid out of the cornea and hence keep it in a dehydrated and transparent state. The average healthy adult cornea has approximately 2500 to 2700 endothelial cells per mm^2 lining the inner surface of the cornea. This number falls slowly with age but rarely does this physiological loss of cells result in corneal endothelial failure (Smolin 1994). When, as a result of disease or damage, the number of cells is reduced more markedly below a critical level of around 300 to 500 cells/mm^2, corneal endothelial failure occurs resulting in corneal oedema and loss of vision (Borboli 2002; Smolin 1994).

The leading causes of corneal endothelial dysfunction or failure are Fuch's endothelial dystropy (FED) and pseudophakic bullous keratopathy (PBK). These conditions are also the two most common indications for endothelial corneal transplantation (Boimer 2011; Frigo 2015). In FED (a condition first described by Ernst Fuchs in 1910) there is premature degeneration of corneal endothelial cells. FED commonly affects individuals in the fifth and sixth decade of life (Afshari 2006). It affects both eyes although at its onset it is typically asymmetrical. FED occurs more commonly in women compared to men and can be inherited in an autosomal dominant fashion, although not all cases are familial (Cross 1971; Magovern 1979; Rosenblum 1980). The condition is progressive and irreversible. PBK refers to the loss of endothelial cells during cataract surgery. This may occur because of direct trauma to endothelial cells during the cataract procedure or indirectly due to the effects of inflammation or high intraocular pressure that occur following cataract surgery (Claesson 2009).

Description of the intervention

Treatment for corneal endothelial failure varies according to the severity of the disease and may range from hypertonic saline drops to surgical intervention. In moderate or severe disease, corneal grafting may be required for visual rehabilitation. Previously, the gold standard corneal grafting technique for endothelial failure was penetrating keratoplasty (PK). However, over the last 15 years endothelial keratoplasty (EK) has become the treatment of choice (Boimer 2011; Frigo 2015). In EK only the innermost layer of the cornea is replaced during surgery. A variety of EK techniques exist.

The expected benefits of EK techniques over PK are faster visual recovery, less astigmatism and stronger wound integrity (Terry 2001). Graft rejection is an important reason for failure in PK patients (Pineros 1996). Theoretically, there is also less risk of immune rejection of the transplanted corneal tissue with EK because a smaller amount of tissue is transplanted and because the endothelium is located in what is normally an immune privileged location. Finally, with EK there is the potential to make more efficient use of transplant tissue, using the posterior layer of the donor cornea for EK in one patient and the anterior layers for an anterior lamellar graft in another patient (Melles 2003). EK (Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK)) now accounts for over 50% of corneal transplants performed in the USA with over 25,000 surgeries performed in 2015, a significant increment over the last five years (Eye Bank Association of America 2015). DSAEK is much more commonly performed than DMEK. Of the 27,208 EKs performed in the USA in 2015, 22,514 were DSAEK whilst 4694 were DMEK (Eye Bank Association of America 2015).

Various subtypes of EK have been described but the most commonly performed are DSAEK and DMEK transplant. DSAEK was first described in 2006 by Mark Gorovoy (Gorovoy 2006) whilst DMEK was pioneered by Gerrit Melles in the same year (Melles 2006).

In DSAEK the surgeon uses an automated machine called a microkeratome to separate a thin layer (50 to 150 microns thick) from the back of the donor cornea containing corneal stroma, Descemet's membrane and endothelial cells. This thin layer of posterior cornea is then transplanted into the recipient eye and attached to the posterior cornea of the recipient. By contrast, in DMEK the surgeon carefully peels Descemet's membrane and endothelial cells from the back of the donor cornea and transplants this thin sheet (around 15 um) into the recipient's eye (Dapena 2011). The relative advantages and disadvantages of these procedures are discussed below.

How the intervention might work

Endothelial cells cannot regenerate in vivo (though they have been shown to do so in vitro (Joyce 2004)), so endothelial failure results in corneal swelling, that is corneal oedema, which causes blurring of vision. The fluid in the cornea causes bullae (small blisters on the surface of the cornea) which may rupture, causing pain. Medical management of the corneal oedema is limited to regular use of lubrication, hyperosmolar agents (such as sodium chloride 5% ointment) and bandage contact lenses that reduce the pain due to rupturing of surface bullae (Costagliola 2013). When the condition becomes intolerable for the patient then corneal transplantation is the treatment of choice. This surgical procedure can restore the vision or alleviate the symptoms, or both.

The aim of both DMEK and DSAEK is to transplant a healthy endothelial cell layer that will pump the fluid out of the cornea and result in restoration of corneal clarity and improvement in vision. It has been suggested that the visual rehabilitation and final visual acuity of DMEK may be better than DSAEK (Guerra

2011). This is thought to be due to the stromal layers, which cause optical irregularities, not being transplanted in the DMEK procedure (Maier 2013). Indeed, there are data to suggest that the thickness of DSAEK grafts influences the outcomes of the procedure. Thinner grafts have been associated with quicker visual rehabilitation and better overall visual outcomes (Busin 2013; Romano 2017). It is not clear which method is associated with higher rates of idiopathic primary graft failure (IPGF). Maier suggested this was lower in DMEK compared to DSAEK (Maier 2013), whilst another retrospective comparison of 100 DSAEK cases with 100 DMEK cases found the IPGF rate to be higher in the DMEK group (Hamzaoglu 2015). As DSAEK is a more established surgical procedure, most corneal surgeons have already overcome the technical learning curve whereas DMEK is still a relatively new technique. It is generally accepted that DMEK is a more technically difficult and challenging procedure (Parekh 2013). In DMEK, the graft thickness is not variable, as by definition it is just one layer of cells with their underlying Descemet's basement membrane. The main difficulty is during the preparation of the donor tissue as it is so thin and fragile. It is reported that between 4.2% and 8% of DMEK grafts cannot be prepared successfully (Parekh 2017a; Price 2009). Moreover, postoperative graft dislocation is a more common complication associated with DMEK (33% to 81%) than DSAEK (7% to 20%) (Guerra 2011; Tourtas 2012). Endothelial cell loss after DSAEK procedures has been quoted to range from 13.5% at six months (Khor 2013) to over 50% at 12 months (Dooren 2011). There are several different types of injector systems for insertion of DSAEK grafts and each is associated with different rates of endothelial cell loss. Endothelial cell loss associated with DMEK has been described to range between 24.7% (Maier 2015), and 41% (Tourtas 2012) at six months. Clearly any comparison of endothelial cell counts must take into account the post-operative time point at which the counts are assessed.

Why it is important to do this review

FED is the indication for up to 47% and PBK the indication for up to 17% of all corneal transplants (Afshari 2006; Eye Bank Association of America 2015; Frigo 2015). Both conditions commonly affect patients in the fifth and sixth decades of life. Population demographics are changing in high-income countries, with an aging population. It is possible that many cases of subclinical FED will become clinically apparent as people live longer; therefore, the incidence and prevalence of corneal endothelial failure due to FED may rise. Similarly, PBK is inherently more common in elderly patients, as it is this population that most commonly undergoes intraocular surgery, primarily for cataract. It is, therefore, possible that the incidence of PBK may rise with an aging population.

At present there are several different EK techniques. DMEK and DSAEK are the most commonly used and each has its advantages and disadvantages. In this review we aim to determine the effectiveness and safety of DMEK compared to DSAEK.

OBJECTIVES

To compare the effectiveness and safety of Descemet's membrane endothelial keratoplasty (DMEK) versus Descemet's stripping automated endothelial keratoplasty (DSAEK) for the treatment of corneal endothelial failure in people with Fuch's endothelial dystropy (FED) and pseudophakic bullous keratopathy (PBK).

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all randomised controlled trials (RCTs) of DMEK versus DSAEK that met our inclusion criteria.

We anticipated that there would be few, if any, RCTs. The way in which these surgical procedures have evolved means that there are more likely to be studies in which people underwent DSAEK in the past, as the procedure of choice, before undergoing DMEK in their fellow eye. Such non-randomised contralateral-eye studies have obvious limitations, but nonetheless the data from these studies may be of value because they are at lower risk of confounding bias than that from cohort studies. We, therefore, also included data from non-randomised studies (NRSs) with paired design in which patients undergo DSAEK in one eye and DMEK in the other eye.

We did not include data from any other study designs, such as matched, unpaired studies, since they may be even more prone to unknown confounding factors than within-person studies.

Types of participants

Inclusion criteria

- We included people with a clinical diagnosis of FED or PBK requiring a corneal transplant for the treatment of corneal endothelial failure. We included people undergoing combined cataract surgery and corneal transplant (phaco-DMEK/DSAEK).

Exclusion criteria

- We excluded trials that included participants with visually significant co-morbidities (e.g. glaucoma, glaucoma filtration surgeries, aphakia, anterior chamber intraocular lenses, scleral fixated intraocular lenses).

There were no age or gender restrictions.

Types of interventions

We included studies in which participants or eyes underwent a DMEK or DSAEK procedure, with or without simultaneous cataract surgery as a primary procedure.

Types of outcome measures

We originally planned to collect data on the following outcomes.

Primary outcomes

- Mean logarithm of the Minimum Angle of Resolution (LogMAR) best corrected visual acuity (BCVA) at 12 months postoperatively

Secondary outcomes

- Mean logMAR BCVA at 1 month and 3 months post-treatment (to indicate speed of visual recovery)
- Mean unaided LogMAR visual acuity at six months post-treatment (to evaluate effect of treatment on unaided vision)
- Mean endothelial cell count as measured by specular microscopy at 6 months, 12 months, 24 months and 5 years post-treatment

- Mean spherical equivalent refraction in dioptres at 24 months post-treatment
- Mean regular refractive astigmatism in dioptres at 24 months post-treatment
- Mean irregular astigmatism in dioptres at 24 months post-treatment, measured by corneal topography

Harms

Information was collected on all harms but we specifically analysed the following:

- Corneal graft rejection at any time up to five years post surgery. Corneal graft rejection is defined as clinical evidence of endothelial dysfunction (increase in corneal thickness) in the presence of cells in the anterior chamber with or without the presence of keratic precipitates
- Primary graft failure (defined as failure of postoperative corneal oedema to resolve within three months of surgery)
- Graft dislocation within one week of surgery
- Endophthalmitis within one month of surgery
- Severe visual loss as (LogMAR) BCVA of 1.0 or less within 12 months (see Differences between protocol and review)

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 11 August 2017.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 7) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 11 August 2017) (Appendix 1).
- MEDLINE Ovid (1946 to 11 August 2017) (Appendix 2).
- Embase Ovid (1980 to 11 August 2017) (Appendix 3).
- LILACS BIREME(1982 to 11 August 2017) (Appendix 4).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 11 August 2017) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 11 August 2017) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 11 August 2017) (Appendix 7).

Searching other resources

We searched the reference lists of includable studies to identify any other potentially relevant studies. We did not undertake manual handsearching of conference proceedings or journals for this review.

Data collection and analysis

Selection of studies

Two review authors (AJS, VR) worked independently to assess the titles and abstracts resulting from the searches. We then obtained full-text reports of all possibly or definitely relevant studies for further assessment. The two review authors assessed these full-text copies to see whether they met the inclusion criteria. We resolved discrepancies through discussion. We documented excluded trials which were thought to be possibly relevant on the basis of the abstract but not eligible based on the assessment of the full-text copy, and recorded the reasons for exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (AJS, VR) extracted the data independently using pre-piloted forms and web-based software Covidence (Covidence 2015).

We collected the following information on study characteristics and summarise these in Table 1.

- Study design: parallel-group RCT/non-randomised within-person studies/one or both eyes reported
- Unit of randomisation: (participants or eyes)
- Participants: country, total number of participants, total number of eyes, age, sex, inclusion and exclusion criteria
- Intervention and comparator details: including number of people (eyes) randomised to each group
- Primary and secondary outcomes as measured and reported in the trials, adverse events
- Length of follow-up
- Date study conducted
- Funding and conflicts of interest

We extracted data on all of the outcomes pre-specified in our Methods (Types of outcome measures) section. We resolved discrepancies through discussion amongst all review authors. One review author entered the data into Review Manager 5 (RevMan 5) (RevMan 2014), and a second review author checked the entered data for errors and inconsistencies.

Assessment of risk of bias in included studies

Two review authors (AJS, VR) assessed studies meeting the inclusion criteria for risk of bias. For eligible RCTs we planned to use the principles described in Cochrane's 'Risk of bias' tool in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We considered the following domains: random sequence generation (selection bias) and allocation concealment (selection bias), masking of participants, masking of outcome assessment (performance bias and detection bias), completeness of follow-up (attrition bias) and selective reporting (reporting bias). Masking of surgeons performing the procedure is clearly not possible. However, we considered studies where the participants and the assessors had been masked to be at low risk of performance bias and detection bias. Studies where participants or assessors had not been masked to the intervention were deemed as having high risk of performance bias and detection bias. For RCTs, we planned to grade each parameter as: low risk of bias, high risk of bias and unclear. However, no RCTs were included in the current version of this review.

To assess the risk of bias in non-randomised contralateral eye studies (NRSs) meeting our inclusion criteria we planned to use the ACROBAT-NRSI ("A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies") tool (Sterne 2014), which has been renamed to ROBINS-I (Sterne 2016) with minimal

changes at the time this review was published. This tool requires us to define a hypothetical generic target randomised trial addressing the population, intervention, comparator and outcomes of interest. The conceptualisation of this hypothetical generic target trial allows the research question to be clearly specified, and complexities that may arise with respect to the tools used to measure an outcome domain or the timing of measurements to be identified. Based on the inclusion and exclusion criteria for this review as a whole, we have defined our generic target trial as DMEK versus DSAEK for the treatment of corneal decompensation and visual acuity of 6/12 or less.

When using the ROBINS-I tool, we defined DMEK as the experimental intervention and DSAEK as the control intervention. In our hypothetical generic target trial, our effect of interest would be the effect of assigning participants to one treatment or other (DMEK or DSAEK) at baseline. This effect would be measured using an intention-to-treat analysis in our generic target trial. We therefore used the ROBINS-I analogue of starting experimental intervention versus starting control intervention to evaluate risk of bias.

NRSs meeting inclusion criteria may have confounding domains that predict whether a participant receives the experimental or control intervention. The most likely confounding domain is the differing follow-up periods between eyes. DSAEK is an older procedure and therefore many participants in non-randomised contralateral eye studies had undergone DSAEK many months or years previously and DMEK (the newer intervention) more recently. It is possible that there could be a difference of many months or even years between the procedures, which could confound the results, particularly regarding long-term outcomes. The second confounding domain is ocular co-morbidity. DSAEK is perceived as technically more straight forward than DMEK and, therefore, may be used more commonly in more complicated cases where the patient has a shallow anterior chamber or anterior chamber lens inserted or has undergone previous glaucoma surgery. Our inclusion and exclusion criteria for this review excluded such patients. All studies included were single intervention studies, and subsequently there were no co-interventions that would have an effect on the outcome of interest.

For NRSs, we assigned an overall risk of bias to each study based on the worst assessment across all bias domains using the recommended levels (low, moderate, serious or critical risk of bias or no information). We resolved any disagreements between the review authors by discussion.

Measures of treatment effect

We planned to treat the following outcomes as continuous data and used the mean difference (MD).

- BCVA (LogMAR)
- Unaided visual acuity (LogMAR)
- Severe visual loss (BCVA 1.0 logMAr or less, see Differences between protocol and review)
- Degree of irregular astigmatism
- Refractive error (spherical equivalent in dioptres and amount of regular astigmatism in dioptres)
- Endothelial cell density

We planned to treat these outcomes as dichotomous data and used the risk ratio (RR) to measure the effect size.

- Graft dislocation
- Primary graft failure
- Corneal graft rejection (dichotomous)
- Endophthalmitis

If we suspected or found that the values for these outcomes were not normally distributed then we would have reported the median and interquartile ranges.

Unit of analysis issues

Trials may randomise one or both eyes to the intervention or comparator. Should we find RCTs in the updates of this review, we will consider the following approach to unit of analysis issues.

If people are randomised and allocated to treatment but only one eye per person is included in the trial, then there will not be a unit of analysis issue. In these cases, we will document how and when the eye was selected in order to determine whether the selection was data driven.

If people are randomly allocated to treatment but both eyes are included and reported, we will analyse as 'clustered data', that is, adjust for within-person correlation as appropriate. We may have to contact the trial investigators for further information to do this.

We analysed non-randomised trials included in the review (within-person study) as paired data (Deeks 2011). Therefore, for BCVA and endothelial cell count (ECC) we have used inverse variance meta-analysis methods and computed standard errors of paired difference from t-values or P values when these were not available. We did not account for paired analysis of dichotomous data given limitations in their reporting in the included studies.

Dealing with missing data

We evaluated all studies for missing outcome data, missing summary data, missing individuals (e.g. lost to follow-up) and missing study-level characteristics such as subgroup analyses.

In the event of missing data we documented the cause and assessed whether the data were missing at random (where the fact that the data are missing is not related to the actual values of the data) or whether the data were not missing at random (where the missing data may be related to the treatment administered) such as losses to follow-up.

Whenever possible, we contacted the original investigators to request missing data. In this review, we included only paired studies in which missing data are less of an issue since each participant is exposed to both the experimental and the control intervention.

Assessment of heterogeneity

In order to decide whether it was possible to carry out a meta-analysis on the results of the trials found, we checked for heterogeneity by examining:

- the characteristics of the studies;
- the forest plot of results of the studies;
- the results of the Chi^2 test for statistical heterogeneity;

- the I^2 statistic (Higgins 2003) computed to quantify inconsistencies between study results.

We regarded a Chi^2 P value of less than or equal to 0.10 as indicating statistically significant heterogeneity.

We used the following thresholds for the interpretation of I^2:

- 0% to 30%: unlikely to be any heterogeneity;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity

*We interpreted the I^2 statistic value in light of the magnitude and direction of intervention effects and the strength of evidence for heterogeneity (P value from the Chi^2 test, or confidence interval for I^2).

Assessment of reporting biases

We found only NRSs and followed the guidance provided for ROBINS-I to assess this issue (Sterne 2016). Our literature searches did not yield enough publications to warrant assessing for publication bias.

Data synthesis

We included only NRSs in this review and performed a meta-analysis of these. If we find RCTs in future updates of this review, we will adopt the following strategy for including studies with both designs in meta-analyses.

In the absence of heterogeneity we will perform meta-analysis of data from RCTs and non-randomised contralateral eye studies separately in the first instance. We will then pool the data from both study types and, in the absence of heterogeneity, we will perform a meta-analysis on these pooled data.

We had planned to combine parallel-arm studies with studies using paired data by means of generic inverse variance meta-analysis. However, there were insufficient data from studies and study authors for this purpose.

Subgroup analysis and investigation of heterogeneity

Due to the small number of included studies, we did not perform any subgroup analyses. In future updates, if there are enough studies included, we will perform subgroup analysis of:

- outcomes in participants with PBK and participants with FED; and
- combined phaco-DMEK/phaco-DSAEK procedures and DSAEK/DMEK alone.

Sensitivity analysis

Due to the small number of included studies, we did not perform any sensitivity analyses. In future updates, if there are enough studies included, we will evaluate the effect of excluding RCTs deemed as high risk of bias for allocation concealment. We will then examine the effect of excluding studies assessed as high risk of bias on any parameter, unpublished studies or data, and industry-funded studies, by repeating the analysis without these.

We will utilise the NRSI (Sterne 2014) tool to identify non-randomised contralateral eye studies deemed to be at high risk of bias and evaluate the effect of excluding these from the pooled and subgroup analysis.

'Summary of findings' table

We prepared a 'Summary of findings' table presenting relative and absolute risks. Two review authors graded independently the overall quality of the evidence for each outcome using the GRADE classification (GRADEpro 2015). We included the following outcomes in the 'Summary of findings' table:

- LogMAR BCVA at 12 months postoperatively in the operated eye
- Severe visual loss (LogMAR BCVA of 1.0 or more) within 12 months
- Mean endothelial cell count as measured by specular microscopy at 12 months post-treatment
- Corneal graft rejection
- Primary graft failure
- Graft dislocation

Further guidance was published by the GRADE Working Group (Schünemann 2018) on how to integrate ROBINS-I assessment with the GRADE assessment of the certainty of evidence. We decided that evidence based on NRSs should start as high-certainty, but we expected to downgrade it for risk of bias, particularly due to confounding or selection biases, which are hard to rule out in NRSs. We acknowledged that the certainty of evidence could be upgraded with large effects or if all plausible residual confounders or other biases increased our certainty in the estimated effect, generally meaning that confounding may have led us to underestimate, rather than overestimate, the observed effect. No dose-response was possible with our surgical interventions.

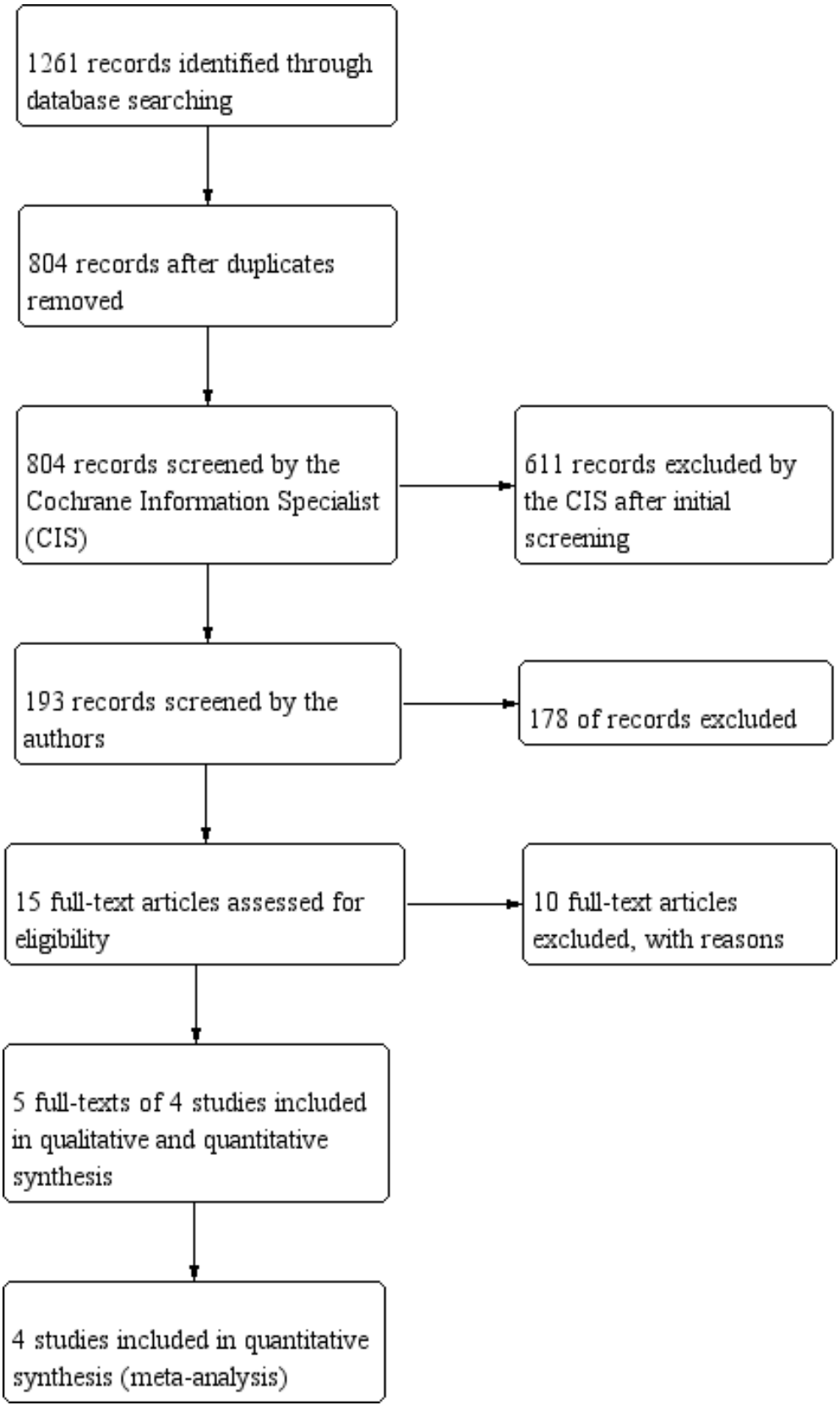
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 1261 records (Figure 1). After removing 457 duplicates, the Cochrane Information Specialist (CIS) screened the remaining 804 records and removed 611 records that were not relevant to the scope of the review. We screened the remaining 193 records and obtained 15 full-text reports for further assessment. We excluded 10 studies, see Characteristics of excluded studies for details and identified five reports for the following four studies that met the inclusion criteria: Bhandari 2015; Goldich 2015; Guerra 2011; and Maier 2015b. We did not identify any ongoing studies from our searches of the clinical trials registries.

Figure 1. Study flow diagram



Included studies

We selected four studies for inclusion (Bhandari 2015; Goldich 2015; Guerra 2011a; Maier 2015b). All studies were NRSs and, following our inclusion criteria, they adopted a paired design in which they used DSAEK in one eye and DMEK in the fellow eye of the same participant.

The overall sample size was 72 participants (144 eyes) for BCVA, corneal graft rejection, primary graft failure, graft dislocation, and ECC. The studies were conducted in Canada, Germany, India and the USA in academic or hospital settings. All the studies included adult participants where there was evidence of FED requiring a corneal transplant for the treatment of visual impairment. The follow-up range was between 6 months and 36 months. In particular, two studies reported results at 12 months, one at 6 months, and one between 6 and 24 months. In all reports DSAEK surgery was performed before DMEK with the average time between surgeries ranging from 12 to 16 months.

Excluded studies

We excluded 10 studies (Characteristics of excluded studies). Five of these were NRSs that compared DMEK with DSAEK, but we excluded them because they did not adopt a paired, contralateral-eye design.

Risk of bias in included studies

Table 2 presents the risk of bias in the included NRSs as assessed with ROBINS-I tool (Sterne 2016).

Bias due to confounding

Baseline confounders were shown to be balanced in the DSAEK and DMEK groups before surgery in all studies, particularly at least three of the following for each study: lens status, BCVA, CCT, ECT and donor ECC. Since DSAEK is an earlier technique, it preceded DMEK in all participants; according to new findings (Steger 2016), the first graft could take advantage of better graft survival, which may be due to concurrent systemic immunosuppressive treatment or unknown confounders. Moreover, there may have been an imbalance regarding unknown confounders and we scored all studies at serious risk of bias for this domain for all outcomes. We have provided a discussion of the potential implications of performing DMEK as the second intervention in the Quality of the evidence section.

Bias in selection of participants

The intervention and follow-up start were simultaneous as a rule for surgery. There was no evidence of selection into the studies due to variables measured after the intervention. In fact, studies were all paired NRSs and patients were included in the studies only if DSAEK was used in one eye and DMEK in the fellow eye. Therefore, all studies were at low risk of bias for this domain.

Bias in classification of interventions

DSAEK and DMEK are well defined surgical interventions. Therefore, all studies were at low risk of bias for this domain.

Bias due to departures from intended interventions

In all studies there was no mention of or reasons to presume a difference in surgeon training in either of the techniques. There was no evidence of differences in co-interventions such as concurrent cataract surgery. Therefore, all studies were at low risk of bias for this domain.

Bias due to missing data

None of the included studies reported any missing data. Maier 2015b reported a longer follow-up for DSAEK compared to DMEK (21 vs 7 months), which could have favoured DSAEK, since visual acuity continues to improve with this technique, thus we rated it at serious risk of bias for this domain. The other studies were at low risk of bias,

Bias in measurement of outcomes

All studies were retrospective and we assume no risk of bias due to differential measurement in BCVA for the DSAEK versus DMEK groups since outcome assessors were unaware of the research use of these data. Guerra 2011 and Maier 2015b used Snellen charts to measure visual acuity, which was then converted to logMAR, but we did not increase risk of bias, since differential measurement is unlikely to have taken place. Other outcomes, as well as adverse events, were objectively measured. Therefore, all studies were at low risk of bias for this domain.

Bias in selection of the reported result

The primary and secondary outcomes of our review were measured and reported in all studies. Therefore, all studies were at low risk of bias for this domain.

Overall bias

We rated all studies at serious risk for all outcomes because DSAEK preceded DMEK in each participant. In fact, although Steger 2016 found an advantage for the first eye when a graft was received in the second eye, it is unknown whether this can balance any confounding or selection effect occurring due to ordering of the interventions.

Effects of interventions

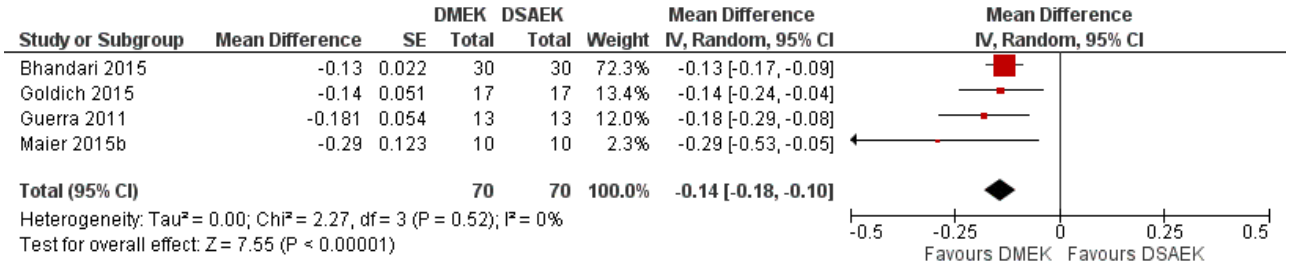
See: **Summary of findings for the main comparison** Descemet's membrane endothelial keratoplasty (DMEK) compared with Descemet's stripping automated endothelial keratoplasty (DSAEK) for corneal endothelial failure

We aimed to extract data at 12 months for our primary outcome, but Goldich 2015 provided data at six months and Maier 2015b provided data at the last follow-up time, which was longer for DSAEK as compared to DMEK (21 vs 7 months on average, which we considered a source of potential bias favouring DSAEK).

Best corrected visual acuity (BCVA)

Four studies (70 participants, 140 eyes) provided data on BCVA after six or more months (Analysis 1.1, paired data; Figure 2). The results favoured DMEK over DSAEK: mean difference (MD) -0.14 logMAR, 95% confidence interval (CI) -0.18 to -0.10 with no evidence of heterogeneity (I^2 = 0%) and consistent effects.

Figure 2. Forest plot of comparison 1. DMEK versus DSAEK, outcome: 1.1 Best corrected visual acuity (logMAR)



This evidence was of low certainty due to risk of bias (-2) related to potential confounding since DSAEK preceded DMEK in all studies.

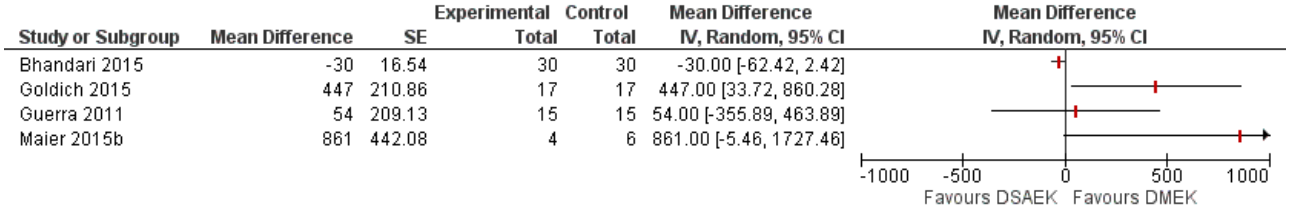
There were no data provided for BCVA at one or three months, as well as for unaided BCVA.

Among vision-related harms, no participants were reported to suffer from severe visual loss (LogMAR BCVA of 1.0 or less).

Endothelial cell count (ECC)

Four studies (68 participants, 134 eyes) provided data on this outcome after six or more months (Analysis 1.2, paired data; Figure 3). We present data as if they were independent groups for Goldich 2015, since they reported a P value from a paired t-test which was larger (less significant) than that achieved by an unpaired t-test (P = 0.049 versus 0.014) but gave no explanation for this. Final ECC in Bhandari 2015 and Guerra 2011 favoured DSAEK but the difference was small and not significant. On the contrary, Goldich 2015 and Maier 2015b found a large difference in favour of DMEK. Since there was high heterogeneity and inconsistency of effects we did not conduct a meta-analysis.

Figure 3. Forest plot of comparison 1. DMEK versus DSAEK, outcome: 1.2 Endothelial cell count (cells/mm²)

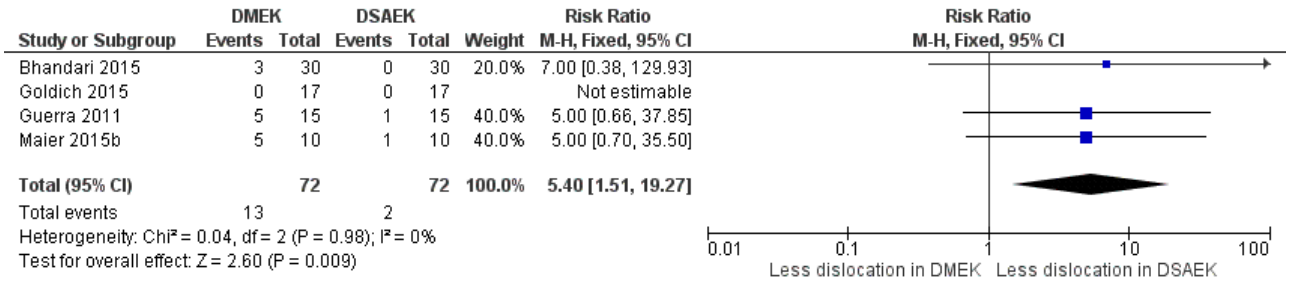


This evidence was of very low certainty for risk of bias (potential confounding, -2) and inconsistency (-2).

Harms: corneal graft complications

All studies (72 participants, 144 eyes) reported graft complications. The most common complications reported were graft dislocations, which were recorded in 1 or 2 out of 100 participants with DSAEK and were more common using DMEK, although this difference could not be precisely estimated (risk ratio (RR) 5.40, 95% CI 1.51 to 19.27; I^2 = 0%; Analysis 1.3; Figure 4). There were no primary graft failures in either group and only 1 corneal graft rejection in the DSAEK group. Thus, both DMEK and DSAEK appeared to be successful regarding these outcomes but we did not obtain any relative estimates of effect since events were very rare and the total sample size was small (Analysis 1.4; Analysis 1.5). For illustrative purposes, a binomial exact confidence interval of 0 events out of 72 eyes in each arm ranges from nil to 5% and that of 1 out of 72 events from nil to 7.5%.

Figure 4. Forest plot of comparison 1. DMEK versus DSAEK, outcome: 1.3 Graft dislocation



The evidence regarding any graft complication was of low certainty for graft dislocations (risk of bias, potential confounding, -2) and very low for graft failure or rejection due to sparse data (imprecision, -2).

Other outcomes

We did not find data on spherical equivalent, regular or irregular astigmatism in any included study. Among harms, we did not find cases of postoperative endophthalmitis.

DISCUSSION

During the last decade there has been a shift from penetrating keratoplasty to endothelial keratoplasty (EK): the anterior corneal surface is no longer compromised by corneal incisions and sutures, and the corneal refractive surface has been largely preserved. A faster visual recovery can be obtained with these improved techniques by minimising wound healing processes and suture-derived complications (Bahar 2008; Melles 1998; Terry 2005). DSAEK or DMEK have become the procedures of choice for the replacement of corneal endothelium in people with endothelial decompensation of various origins. We conducted this systematic review since there is a need to summarise the evidence on whether the preferred option to treat the endothelial dysfunction is DMEK or DSAEK. We found four studies adopting a paired, contralateral-eye design (144 eyes) in which one eye received DSAEK and the fellow eye received DMEK. Two studies reported data at 12 months, one study at 6 months and one between 6 and 24 months.

Summary of main results

We found low-certainty evidence that DMEK is better than DSAEK in terms of final BCVA by about 1.5 lines. As expected, DMEK eyes were more commonly associated with graft dislocation compared to DSAEK, but this difference was imprecisely estimated and the evidence was of very low certainty. We could not estimate the relative effect of DMEK versus DSAEK on final ECC, since the results of the studies were heterogeneous. The occurrence of corneal graft rejection and primary graft failure was very low both for DMEK and DSAEK, but the event rate was too small to investigate any differences between them (very low-certainty evidence). Other harms, such as severe visual loss and endophthalmitis, were not recorded.

Further analyses are needed for long-term outcomes, including observational and registry-based studies.

Overall completeness and applicability of evidence

There was variability across studies related to different races of participants, the use of different characteristics of donor corneal tissue, and different lengths of follow-up; and some follow-up times were short. Moreover, it must be noted that graft endothelial cell density and primary graft failure is correlated to the surgeon's skills. It has been highlighted in the literature that DMEK has not gained popularity over DSAEK mainly because it is technically much more demanding, requiring considerable surgical skills and prolonged surgical time, leading to complications, and iatrogenic primary graft failure (Anshu 2012; Guerra 2011b; Price 2009). The learning curve of DMEK is accompanied by a high rate of tissue loss (up to 16% in some reports), and a failure rate of up to 8%, which is higher than that for other procedures (Parekh 2017b; Patel 2012). Our review found no data to investigate the effect of surgeon training on the relative effectiveness of the two techniques.

Although good visual outcomes are recorded in most cases after DSAEK, speed of vision recovery and final visual outcome may not be as good as could be expected in the DMEK group. Some reports propose ultrathin (UT) DSAEK in order to achieve better vision outcomes compared to standard DSAEK, while obtaining the same low rates of postoperative complications of standard DSAEK surgery (Busin 2012; Busin 2013; Dickman 2016; Romano 2015a; Romano 2015b). They recommended performing UT DSAEK surgery in cases where DMEK surgery may be extremely difficult such as in eyes with complicated anatomy (i.e. in the presence of anterior synechiae, anterior chamber intraocular lenses (IOLs), natural crystalline lens, or when there is no barrier between anterior chamber and vitreous cavity). However, there is still not strong evidence comparing UT DSAEK and DMEK.

Quality of the evidence

In terms of visual outcomes the certainty of the evidence, which for NRS we initially GRADE-ed as low certainty, was very low since DSAEK preceded DMEK in all individuals, which may have led to an imbalance in unknown confounders. In particular, eyes operated with DSAEK may have been selected based on known outcomes to undergo DMEK. Therefore we downgraded this domain to high risk of bias despite the fact that all studies reported balanced baseline BCVA and donor ECC. Additionally, the certainty of the evidence on all other outcomes was very low due to heterogeneity (ECC) or large imprecision of the estimates or inability to estimate any relative effect since most studies recorded no graft complications. Beyond differences in baseline ECC density, the heterogeneity in final ECC values could be related to confounders, such as simultaneous cataract extraction and, for Maier 2015b, loss to follow-up of about half of study eyes.

The risk of bias due to the fact that DSAEK preceded DMEK in all individuals is worth further discussion since this is a fundamental limitation of this type of research. As reported above, Steger 2016 found better outcomes for the first eye regarding corneal graft failure, especially in eyes with FED. A learning curve of 50 DMEK surgeries was reported in previous studies, but a recent study found that surgeons experienced in DSAEK perform DMEK with adequate functional and anatomic results (Phillips 2017). Moreover, this type of surgery is typically performed in small numbers by each surgeon, who would continue their surgical training between the two surgeries. Therefore, the small studies included in this review are likely to resemble most of the current clinical practice. Ultimately, we acknowledge that the need for graft repositioning (re-bubbling) after either technique may be lower as a surgeon becomes more fully trained.

Potential biases in the review process

We included only NRSs that used a paired, contralateral-eye design. We considered that a contralateral-eye design avoided confounding bias. However, we found that DSAEK always preceded DMEK in all individuals in the included contralateral-eye studies. This may have induced confounding, but in all studies, major known confounders were balanced in the two groups.

Agreements and disagreements with other studies or reviews

We found two recently published systematic reviews (Singh 2017; Zhu 2017).

Singh 2017 included seven NRSs, included all our studies, but reported results at six months rather than at one year. They did not mention the reason for the exclusion of Bhandari 2015. We did

not include the following studies: Hamzaoglu 2015; Rudolph 2012 and Tourtas 2012 because they were not paired, contralateral-eye studies. Singh 2017 evaluated the limitations of the studies as well as of the review methodology, but did not adopt formal methods to incorporate them in the conclusions.

Zhu 2017 included seven NRSs, of which three (Goldich 2015; Guerra 2011; Maier 2015b) were included in our review. They did not mention the reason for the exclusion of Bhandari 2015. We did not include the following studies: Droutsas 2016; Green 2015, Hamzaoglu 2015 and Tourtas 2012 because they were not paired, contralateral-eye studies. Zhu 2017 used the Newcastle–Ottawa Scale to assess study quality and found all studies were high quality (score > 6), but did not relate study quality to specific outcomes.

Despite partial overlap in study inclusion criteria, this review reached similar overall conclusions on the relative effect of DMEK and DSAEK regarding BCVA and graft dislocation.

AUTHORS' CONCLUSIONS

Implications for practice

For people in which both Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK) can be considered, we found very low-certainty evidence that DMEK provides some advantage in terms of final best corrected visual acuity (BCVA), at the cost of more graft dislocations needing 're-bubbling' (very low-certainty of evidence). These results might be considered in personalised decision making involving the patient and the surgeon.

Severe visual loss, primary graft failure and endophthalmitis were not found and only one graft rejection was recorded, which means these harms are not a concern.

Implications for research

Studies should report on surgeons' training and the usability of DMEK compared to DSAEK. In addition, since a randomised clinical trial has shown that UT-DSAEK results in faster and better recovery of BCVA with similar refractive outcomes, endothelial cell loss, and incidence of complications (Dickman 2016), an interesting comparison could be between ultra-thin (UT) DSAEK and DMEK for visual acuity, intra- and postoperative complications.

Future research should focus on higher level evidence, that is a randomised clinical trial comparing UT-DSAEK with DMEK surgery. Data from wide-scale transplant registries such as those in the United Kingdom (Greenrod 2014) or Australia, could provide a large comparative dataset, which may be valuable for real-world efficacy and safety of these surgical techniques.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bhandari 2015

Methods	Comparative, non-randomised, retrospective study to evaluate visual outcome and endothelial cell density after DMEK in comparison with DSAEK in the fellow eye for FED
Participants	Country: India Number of participants: 30 Number of eyes: 60 Number of participants followed up: 100% Average age: 55 years (range 44-71 years) % female: 40% (12 female/18 male) Inclusion criteria: people with FED, pseudophakic with a posterior chamber intraocular lens implanted previously Exclusion criteria: people with other ocular comorbidity besides FED were not included
Interventions	Intervention: DMEK

Bhandari 2015 *(Continued)*

	Comparator: DSAEK
Outcomes	List outcomes: BCVA, ECD, corneal thickness, graft thickness, graft detachment, graft rejection Follow-up: 12 months
Notes	Funding source: none Conflict of interest: none Date study conducted: not stated in trial report

Goldich 2015

Methods	Comparative, non-randomised, retrospective studies aiming to compare objective and subjective outcomes after DMEK and DSAEK in the fellow eye of the same participants.
Participants	Country: Canada Number of participants: 17 Number of eyes: 34 Number of participants followed up: 100% Average age: 73 years (range 42-87 years) % female: 55% (9 female/8 male) Inclusion criteria: People with FED and at least 6 months postoperative follow-up Exclusion criteria:
Interventions	Intervention: DMEK Comparator: DSAEK
Outcomes	List outcomes: BCVA, ECD. Subjective questionnaires were used to assess patients' satisfaction Follow-up: 36.5 ± 15.4 months (DSAEK group); 9.6 ± 2.2 months (DMEK group)
Notes	Funding source: none Conflict of interest: none Date study conducted: Toronto Western Hospital between 2012 and 2013

Guerra 2011

Methods	Comparative, non-randomised, retrospective studies aiming to compare objective and subjective outcomes after DMEK and DSAEK in the fellow eye of the same participants.
Participants	Country: USA, Indianapolis Number of participants: 15 Number of eyes: 30

Guerra 2011 *(Continued)*

	Number of participants followed up: 100% Average age: 67 years (53-83) % female: 60% (9 female/6 male) Inclusion criteria: people who underwent DSAEK in 1 eye and DMEK in their fellow eye and had completed at least 1 year of follow-up after the last procedure Exclusion criteria: people with pre-existing ocular comorbidities that could result in less than optimal visual potential were excluded from the visual acuity and visual quality analyses.
Interventions	Intervention: DMEK Comparator: DSAEK
Outcomes	List outcomes: visual outcomes and ECD, and patient satisfaction using a subjective questionnaire Follow-up: 12 months
Notes	Funding source: none Conflict of interest: none Date study conducted: not stated in trial report

Maier 2015b

Methods	Comparative, non-randomised, retrospective studies aiming to compare objective and subjective outcomes after DMEK and DSAEK in the fellow eye of the same participants.
Participants	Country: Germany, Berlin Number of participants: 10 Number of eyes: 20 Number of participants followed up: 100% Average age: 71 years (53-83) % female: 40% (4 female/6 male) Inclusion criteria: people who underwent DSAEK in 1 eye and DMEK in their fellow eye. Exclusion criteria: people with pre-existing ocular comorbidities that could result in less than optimal visual potential were excluded from the visual acuity and visual quality analyses.
Interventions	Intervention: DMEK Comparator: DSAEK
Outcomes	List outcomes: visual outcomes and ECD, and patient satisfaction using a subjective questionnaire. Follow-up: 24 months
Notes	Funding source: none Conflict of interest: none Date study conducted: not stated in trial report

BCVA: best corrected visual acuity
DMEK: Descemet's membrane endothelial keratoplasty
DSAEK: Descemet's stripping automated endothelial keratoplasty
ECD: endothelial cell density
FED: Fuchs endothelial dystrophy

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cursiefen 2010	Review article and comparisons made were against penetrating keratoplasty
Cursiefen 2013	Provided a description of surgical techniques, but not their outcomes
Droutsas 2016	Not a paired, contralateral-eye study
Green 2014	Neither a RCT nor a paired, contralateral-eye study
Green 2015	Neither a RCT nor a paired, contralateral-eye study
Hamzaoglu 2015	Neither an RCT nor a paired, contralateral-eye study
Heinzelmann 2016	Comparisons made are against penetrating keratoplasty
Rudolph 2012	Neither an RCT nor a paired, contralateral-eye study
Tourtas 2012	Neither a RCT nor a paired, contralateral-eye study

RCT: randomised controlled trial

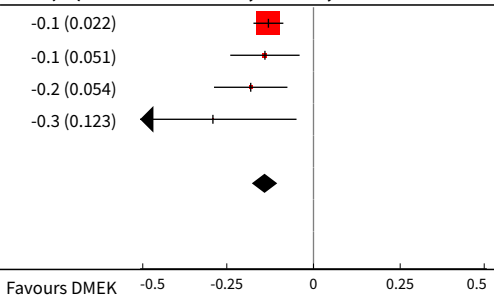
DATA AND ANALYSES

Comparison 1. DMEK versus DSAEK

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Best corrected visual acuity (logMAR)	4	140	Mean Difference (Random, 95% CI)	-0.14 [-0.18, -0.10]
2 Endothelial cell count (cells/mm^2)	4		Mean Difference (Random, 95% CI)	Totals not selected
3 Graft dislocation	4	144	Risk Ratio (M-H, Fixed, 95% CI)	5.4 [1.51, 19.27]
4 Corneal graft rejection	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Primary graft failure	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

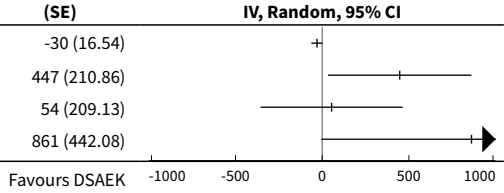
Analysis 1.1. Comparison 1 DMEK versus DSAEK, Outcome 1 Best corrected visual acuity (logMAR).

Study or subgroup	DMEK N	DSAEK N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Bhandari 2015	30	30	-0.1 (0.022)		72.25%	-0.13[-0.17,-0.09]
Goldich 2015	17	17	-0.1 (0.051)		13.44%	-0.14[-0.24,-0.04]
Guerra 2011	13	13	-0.2 (0.054)		11.99%	-0.18[-0.29,-0.08]
Maier 2015b	10	10	-0.3 (0.123)		2.31%	-0.29[-0.53,-0.05]
Total (95% CI)					**100%**	**-0.14[-0.18,-0.1]**
Heterogeneity: Tau^2=0; Chi^2=2.27, df=3(P=0.52); I^2=0%						
Test for overall effect: Z=7.55(P<0.0001)						



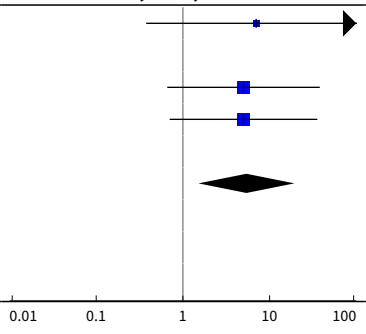
Analysis 1.2. Comparison 1 DMEK versus DSAEK, Outcome 2 Endothelial cell count (cells/mm^2).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Bhandari 2015	30	30	-30 (16.54)		-30[-62.42,2.42]
Goldich 2015	17	17	447 (210.86)		447[33.72,860.28]
Guerra 2011	15	15	54 (209.13)		54[-355.89,463.89]
Maier 2015b	4	6	861 (442.08)		861[-5.46,1727.46]



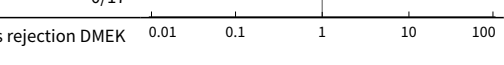
Analysis 1.3. Comparison 1 DMEK versus DSAEK, Outcome 3 Graft dislocation.

Study or subgroup	DMEK n/N	DSAEK n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhandari 2015	3/30	0/30		20%	7[0.38,129.93]
Goldich 2015	0/17	0/17			Not estimable
Guerra 2011	5/15	1/15		40%	5[0.66,37.85]
Maier 2015b	5/10	1/10		40%	5[0.7,35.5]
Total (95% CI)	**72**	**72**		**100%**	**5.4[1.51,19.27]**
Total events: 13 (DMEK), 2 (DSAEK)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=2.6(P=0.01)					



Analysis 1.4. Comparison 1 DMEK versus DSAEK, Outcome 4 Corneal graft rejection.

Study or subgroup	DMEK n/N	DSAEK n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bhandari 2015	0/30	0/30		Not estimable
Goldich 2015	0/17	0/17		Not estimable



Study or subgroup	DMEK n/N	DSAEK n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Guerra 2011	0/15	1/15		0.33[0.01,7.58]
Maier 2015b	0/10	0/10		Not estimable
		Less rejection DMEK	0.01 0.1 1 10 100	Less rejection DSAEK

Analysis 1.5. Comparison 1 DMEK versus DSAEK, Outcome 5 Primary graft failure.

Study or subgroup	DMEK n/N	DSAEK n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bhandari 2015	0/30	0/30		Not estimable
Goldich 2015	0/17	0/17		Not estimable
Guerra 2011	0/15	0/15		Not estimable
Maier 2015b	0/10	0/10		Not estimable
		More likely with DMEK	0.01 0.1 1 10 100	More likely with DSAEK

ADDITIONAL TABLES

Table 1. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	• **Parallel-group RCT** i.e. people randomised to treatment • **Within-person RCT** i.e. eyes randomised to treatment • **Non-randomised contralateral-eye studies** i.e. one eye in same participant randomised to one intervention and other eye to other intervention	Number randomised/analysed (RCT) or Number recruited/analysed (contralateral-eye studies) Reported power calculation (Y/N), *if* yes, sample size and power
Eyes or Unit of randomisation/ unit of analysis	**Unit of randomisation:** participants or eyes **One eye included in study**, specify how eye selected • **Both eyes included in study, both eyes received same treatment**, briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye • **Both eyes included in study, eyes received different treatments,** specify if correct pair-matched analysis done	
Participants		
Country		Setting Ethnic group
Total number of participants	This information will be collected for total number of study participants who received the intervention and follow-up data were reported. We collect the average age of the participants and also the age range.	
Average age and age range	If only one eye from one participant is selected we will record why and when this decision was made.	

Table 1. Data on study characteristics *(Continued)*

Inclusion criteria	• People with a clinical diagnosis of endothelial decompensation secondary to FED or PBK and who required a corneal transplant • People with co-existent cataracts undergoing combined cataract surgery and corneal transplant (phaco-DMEK/phaco-DSAEK) will be included
Exclusion criteria	• People who have corneal endothelial failure as a result of a pathology other than FED or PBK • Visually significant co-morbidities, especially glaucoma • People with visually significant cataract which is not treated prior to, or at the time of, corneal transplant
Interventions	DMEK or DSAEK with or without simultaneous phacoemulsification and lens implant
Intervention (n =) Comparator (n =) **See MECIR 65 and 70**	• Number of people randomised to DSAEK • Number of people randomised to DMEK
Outcomes	Primary outcomes • Mean logMAR BCVA at 12 months postoperatively Secondary outcomes • Mean logMAR BCVA at 1 month and 3 months post-treatment (to indicate speed of visual recovery) • Mean endothelial cell count as measured by specular microscopy at 6 months, 12 months, 24 months and 5 years post-treatment • Corneal graft rejection • Primary graft failure • Graft dislocation • Loss of 10 or more letters (logMAR) versus preoperative BCVA
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	We will collect data on adverse events A 6-, 12- and 24-month follow-up schedule will be collected
Notes	
Declaration of interest **See MECIR 69**	

BCVA: best corrected visual acuity
FED: Fuchs endothelial dystrophy
DMEK: Descemet's membrane endothelial keratoplasty
DSAEK: Descemet's stripping automated endothelial keratoplasty
logMAR: logarithm of the Minimum Angle of Resolution
PBK: pseudophakic bullous keratopathy
RCT: randomised controlled trial

Table 2. ROBINS-I assessment of risk of bias in included studies

Study: Bhandari 2015

ROBINS-I domain	Risk of Bias	Description: paired, contralateral-eye study
Bias due to confounding	Serious risk	All participants received DSAEK before DMEK. Baseline BCVA, CCT, donor ECD and lens status were similar. No previous glaucoma surgery or treatment
Bias in selection of participants	Low risk	Intervention and follow-up start were simultaneous as a rule for surgery. No evidence of selection into the study due to variables measured after the intervention since participants were included in the studies only if DSAEK was used in one eye and DMEK in the fellow eye.
Bias in classification of interventions	Low risk	Well-defined surgical interventions
Bias due to deviations from intended interventions	Low risk	There is no mention of a difference in surgeon training in both techniques. There is no evidence of differences in co-interventions such as concurrent cataract surgery.
Bias due to missing data	Low risk	No differential follow-up or missing data reported; no participant selection due to missing data reported.
Bias in measurement of outcomes	Low risk	Retrospective study. BCVA measurement done routinely and not related to study objectives. Other outcomes and adverse events: objectively measured
Bias in selection of the reported result	Low risk	No selective reporting possible for our pre-specified outcomes.
Overall bias	**All outcomes: serious risk**	

Study: Goldich 2015

ROBINS-I domain	Risk of Bias	Description: paired, contralateral-eye study
Bias due to confounding	Serious risk	All participants underwent DSAEK before DMEK. Baseline BCVA and donor ECD or lens status were similar. CCT not reported. No previous glaucoma surgery or treatment
Bias in selection of participants	Low risk	Intervention and follow-up start were simultaneous as a rule for surgery. No evidence of selection into the study due to variables measured after the intervention since participants were included in the studies only if DSAEK was used in one eye and DMEK in the fellow eye.
Bias in classification of interventions	Low risk	Well-defined surgical interventions
Bias due to deviations from intended interventions	Low risk	There is no mention of a difference in surgeon training in both techniques. There is no evidence of differences in co-interventions such as concurrent cataract surgery.
Bias due to missing data	Low risk	No differential follow-up or missing data reported; no patient selection due to missing data reported
Bias in measurement of outcomes	Low risk	Retrospective study. BCVA measurement done routinely and not related to study objectives. Other outcomes and adverse events: objectively measured

Table 2. ROBINS-I assessment of risk of bias in included studies *(Continued)*

Bias in selection of the reported result	Low risk	No selective reporting possible for our pre-specified outcomes
Overall bias	**All outcomes: serious risk**	
Study: Guerra 2011		
ROBINS-I domain	**Risk of BIas**	**Description: paired, contralateral-eye study**
Bias due to confounding	Serious risk	All participants underwent DSAEK before DMEK. Baseline confounding variables as BCVA and donor ECD are similar. CCT not reported
Bias in selection of participants	Low risk	Intervention and follow-up start were simultaneous as a rule for surgery. No evidence of selection into the study due to variables measured after the intervention since participants were included in the studies only if DSAEK was used in one eye and DMEK in the fellow eye.
Bias in classification of interventions	Low risk	Well-defined surgical interventions
Bias due to deviations from intended interventions	Low risk	There is no mention of a difference in surgeon training in both techniques. There is no evidence of differences in co-interventions such as concurrent cataract surgery.
Bias due to missing data	Low risk	No differential follow-up or missing data reported; no patient selection due to missing data reported
Bias in measurement of outcomes	Low risk	Retrospective study. BCVA measurement done routinely and not related to study objectives. Other outcomes and adverse events: objectively measured
Bias in selection of the reported result	Low risk	No selective reporting possible for our pre-specified continuous outcomes
Overall bias	**All outcomes: serious risk**	
Study: Maier 2015b		
ROBINS-I domain	**Risk of BIas**	**Description: paired, contralateral eye study**
Bias due to confounding	Serious risk	All participants underwent DSAEK before DMEK. Baseline confounding variables as BCVA and donor ECD are similar. CCT not reported
Bias in selection of participants	Low risk	Intervention and follow-up start were simultaneous as a rule for surgery. No evidence of selection into the study due to variables measured after the intervention since participants were included in the studies only if DSAEK was used in one eye and DMEK in the fellow eye.
Bias in classification of interventions	Low risk	Well defined surgical interventions
Bias due to deviations from intended interventions	Low risk	There is no mention of a difference in surgeon training in both techniques. There is no evidence of differences in co-interventions such as concurrent cataract surgery.
Bias due to missing data	Serious risk	Differential follow-up reported: 21 months for DSAEK and 7 month for DMEK; this could have favoured DSAEK since visual acuity continues to improve during follow-up with this technique.

Table 2. ROBINS-I assessment of risk of bias in included studies *(Continued)*

Bias in measurement of outcomes	Low risk	Retrospective study. BCVA measurement done routinely and not related to study objectives. Other outcomes and adverse events: objectively measured
Bias in selection of the reported result	Low risk	No selective reporting possible for our pre-specified continuous outcomes
Overall bias	**All outcomes: serious risk**	

BCVA: best corrected visual acuity
CCT: central corneal thickness
DMEK: Descemet's membrane endothelial keratoplasty
DSAEK: Descemet's stripping automated endothelial keratoplasty
ECD: endothelial cell density

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Fuchs' Endothelial Dystrophy] this term only
#2 fuchs* near/3 endothelial near/3 dystroph*
#3 fuchs* near/3 dystroph*
#4 bullous keratopath*
#5 pbk
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Descemet Membrane] this term only
#8 Descemet* near/2 strip* near/5 keratoplast*
#9 Descemet* near/2 membrane* near/5 keratoplast*
#10 DSAEK or DMEK
#11 #7 or #8 or #9 or #10
#12 #6 and #11

Appendix 2. MEDLINE Ovid search strategy

1. Fuchs' Endothelial Dystrophy/
2. (fuchs$ adj3 endothelial adj3 dystroph$).tw.
3. (fuchs$ adj3 dystroph$).tw.
4. bullous keratopath$.tw.
5. pbk.tw.
6. or/1-5
7. Descemet Membrane/
8. (Descemet$ adj2 strip$ adj5 keratoplast$).tw.
9. (Descemet$ adj2 membrane$ adj5 keratoplast$).tw.
10. (DSAEK or DMEK).tw.
11. or/7-10
12. 6 and 11

Appendix 3. Embase Ovid search strategy

1. congenital cornea dystrophy/
2. (fuchs$ adj3 endothelial adj3 dystroph$).tw.
3. (fuchs$ adj3 dystroph$).tw.
4. bullous keratopath$.tw.
5. pbk.tw.
6. or/1-5
7. Descemet Membrane/
8. (Descemet$ adj2 strip$ adj5 keratoplast$).tw.
9. (Descemet$ adj2 membrane$ adj5 keratoplast$).tw.
10. (DSAEK or DMEK).tw.
11. or/7-10

12. 6 and 11

Appendix 4. LILACS BIREME search strategy

(fuchs$ endothelial dystroph$ or fuchs$ dystroph$) and (Descemet$ strip$ keratoplast$ or Descemet$ membrane$ keratoplast$ or DSAEK or DMEK)

Appendix 5. ISRCTN search strategy

"(fuchs OR endothelial dystrophy OR bullous keratopathy OR pbk) AND (descemet OR DSAEK OR DMEK)"

Appendix 6. ClinicalTrials.gov search strategy

(fuchs OR endothelial dystrophy OR bullous keratopathy OR pbk) AND (descemet OR DSAEK OR DMEK)

Appendix 7. ICTRP search strategy

fuchs OR endothelial dystrophy OR bullous keratopathy OR pbk = Condition AND descemet OR DMEK or DSAEK = Interventions

CONTRIBUTIONS OF AUTHORS

Protocol

- Written by AJ Stuart and edited by AJ Shortt with additions by G Virgili

Review

- Search results screened by AJ Stuart and V Romano
- Included studies analysed by AJ Stuart and V Romano
- Results written by AJ Stuart, V Romano, G Virgili and A Shortt

DECLARATIONS OF INTEREST

AJ Stuart: none known
V Romano: none Known
G Virgili: none known
AJ Shortt: none known

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Additional co-author V. Romano added.

In our protocol the inclusion criteria were the clinical diagnosis of Fuch's endothelial dystropy (FED) or pseudophakic bullous keratopathy (PBK) requiring a corneal transplant for the treatment of corneal endothelial failure. In order to reduce confounding factors, we restricted the selection to paired design in which participants underwent Descemet's stripping automated endothelial keratoplasty (DSAEK) in one eye and Descemet's membrane endothelial keratoplasty (DMEK) in the other eye. We did not include data from any other study designs, such as matched, unpaired studies, since they may be even more prone to unknown confounding factors than within-person studies. However, we did not find any reports where people with PBK were recruited. Conversely FED, as is corneal dystrophy, is bilateral by definition and often these patients require corneal transplant for the treatment of corneal endothelial failure in both eyes.

We used guidance recently provided by the GRADE Working Group (Schünemann 2018) on how to integrate ROBINS-I assessment with GRADEing the certainty of evidence.

We replaced the outcome "Loss of 10 or more ETDRS letters (0.2 logMAR) or more" with "Severe visual loss of 1.0 logMAR or less".

INDEX TERMS

Medical Subject Headings (MeSH)

*Descemet Stripping Endothelial Keratoplasty [adverse effects]; Cell Count; Corneal Diseases [*surgery]; Corneal Transplantation; Descemet Membrane [*surgery]; Endothelial Cells [cytology]; Fuchs' Endothelial Dystrophy [*surgery]; Non-Randomized Controlled Trials as Topic; Postoperative Complications [etiology]; Visual Acuity

MeSH check words

Adult; Humans