

REVIEW ARTICLE

Combined or sequential DMEK in cases of cataract and Fuchs endothelial corneal dystrophy—A systematic review and meta-analysis

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Abstract

To compare the outcomes of Descemet membrane endothelial keratoplasty (DMEK) performed after phacoemulsification and intraocular lens (IOL) implantation (sequential DMEK) and DMEK combined with phacoemulsification and IOL implantation (combined DMEK) in patients with Fuchs endothelial corneal dystrophy (FECD) and cataract. Systematic literature review and meta-analysis performed according to the PRISMA guidelines and registered in PROSPERO. Literature searches were conducted in Medline and Scopus. Comparative studies reporting sequential DMEK and combined DMEK in FECD patients were included. The main outcome measure of the study was the corrected distance visual acuity (CDVA) improvement. Secondary outcomes were postoperative endothelial cell density (ECD), rebubbling rate and primary graft failure rate. Bias risk was assessed and a quality appraisal of the body of evidence was completed using the Cochrane Robin-I tool. A total of 667 eyes (5 studies) were included in this review, 292 eyes (43.77%) underwent a combined DMEK, while 375 (56.22%) eyes underwent a sequential DMEK surgery. We found no evidence of a difference between the two groups (mean difference, 95% CI) regarding: (1) CDVA improvement (−0.06; −0.14, 0.03 LogMAR; 3 studies, I^2 : 0%; $p=0.86$); (2) postoperative ECD (−62; −190, 67 cells/mm²; 4

Vito Romano and Maria Laura Passaro equal contribution.

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studies, I^2 : 67%; $p=0.35$); (3) rebubbling (risks ratio: 1.04; 0.59, 1.85; 4 studies, I^2 : 48%; $p=0.89$); and primary graft failure rate (risks ratio: 0.91; 0.32, 2.57; 3 studies, I^2 : 0%; $p=0.86$). Of all the 5 non-randomized studies, all (100%) were graded as low quality. The overall quality of the analysed studies was low. Randomized controlled trials are needed to confirm no difference or superiority of one approach in terms of CDVA, endothelial cell count and postoperative complication rate between the two arms.

KEYWORDS

cataract, combined, DMEK, Fuch's dystrophy, keratoplasty, phacoemulsification, sequential

1 | INTRODUCTION

Posterior lamellar keratoplasty (PLK) has become the primary surgical procedure for the treatment of corneal endothelial dysfunction as it introduces the replacement of only the affected layer (Price & Price, 2010), reducing allograft rejection rate post transplantation, allowing a faster visual recovery and minimizing eye structure compromise (Cochrane Library Cochrane Database of Systematic Reviews Descemet's membrane endothelial keratoplasty (DMEK) versus Descemet's stripping automated endothelial keratoplasty (DSAEK) for corneal endothelial failure (Review) Descemet's membrane endothelial keratoplasty (DMEK) versus Descemet's stripping automated endothelial keratoplasty (DSAEK) for corneal endothelial failure (Review), 2018).

Fuchs endothelial corneal dystrophy (FECD) represents the leading cause of corneal endothelial dysfunction and the main indication for corneal transplantation (Gain et al., 2016). In recent years, Descemet membrane endothelial keratoplasty (DMEK), the latest PLK technique, has become the treatment of choice for FECD, (Marques et al., 2019; Moshirfar et al., 2022) demonstrating better results in terms of visual recovery time, visual acuity level achieved at 1 year and patient satisfaction compared with its predecessor Descemet's stripping automated endothelial keratoplasty (DSAEK) (Marques et al., 2019).

Many patients suffer symptoms from coexisting corneal endothelial dysfunction and cataract and among ophthalmic surgeons there is still a debate whether to perform cataract surgery and DMEK independently in stages (sequential DMEK) or in the same operation (combined DMEK).

The aim of this systematic review is to evaluate and compare the outcomes of both sequential DMEK and combined DMEK in patients affected by FECD and cataract to address surgical strategies and to guide future clinical practice.

2 | METHODS

The protocol for this systematic review was registered before starting with the PROSPERO International prospective register of systematic reviews, with registration number CRD42022362437.

A systematic literature search was performed according to the Preferred Reporting Items for Systematic

Reviews and Meta-Analysis (PRISMA) 2020 guidelines (Page et al., 2021). We planned to include all studies comparing sequential phacoemulsification and DMEK (first surgery phacoemulsification, second surgery DMEK) with combined phacoemulsification and DMEK that met our inclusion criteria. We expected only a few, if any, randomized controlled trials (RCTs). We, therefore, also included non-randomized studies (NRSs) comparing the two procedures in different groups of patients. We did not include data from any other study designs as they may be more susceptible to confounding factors.

Inclusion criteria comprised articles reporting observational or interventional studies and case series; reviews, case reports or abstracts were excluded. According to the Patients, Intervention, Comparator, Outcomes (PICO) approach, (Higgins et al., 2022) patients affected by FECD who underwent sequential phacoemulsification and DMEK or combined phacoemulsification and DMEK were included. Reports of patients with different causes of endothelial decompensation or studies with mixed pseudophakic and phakic DMEK surgeries where the groups were not analysed separately were excluded. There were no restrictions on gender or ethnic group. Paediatric patients were excluded. Review articles summarizing previous results and technical notes were excluded. Reports republished by the same centre were excluded.

The main outcome measure of the study was the corrected distance visual acuity (CDVA) improvement considered in LogMAR. Secondary outcomes were post-operative ECD measured by specular microscopy, graft detachment with rebubbling rate and primary graft failure rate.

A literature search was conducted in Medline and Scopus. We did not undertake manual hand searching of conference proceedings or journals. No restrictions on the date, language, or publication status were set in this phase. The final search was updated on the 5th September 2022.

Studies were sought with the following terms alone or in combination: DMEK, DMEK AND cataract, DMEK combined, DMEK sequential, cataract AND Fuchs endothelial dystrophy.

A total of 2802 records were identified from the databases; Medline ($n=1368$); SCOPUS ($n=1434$).

At first, titles and abstracts of the studies were screened by two researchers (M.L.P. and V.R.). We then obtained full-text reports for full-text screening of all relevant studies that met inclusion criteria or if

the abstracts did not clearly identify the characteristics of the study. A total of 58 reports were sought for retrieval. Only four reports were not retrieved. Reviewers then screened the 54 full-text reports; discrepancies were verbally discussed and resolved. Only five papers met the inclusion criteria, and 49 papers were excluded. Reports were excluded for one or more of the following reasons: not written in English and not possible to clearly extract or separate data regarding surgical indications other than FECD. If a centre published multiple studies on the same group of patients, the most comprehensive study was used, and the others were excluded (Figure 1).

The following variables were extracted and reported in a table: number of eyes analysed, follow-up, preoperative and postoperative CDVA, CDVA improvement, preoperative and postoperative endothelial cell density (ECD), graft detachment with rebubbling rate and primary graft failure rate. Visual outcomes reported in Snellen visual acuity and decimal visual acuity were converted in LogMAR (Moussa et al., 2021; Matafatsi et al., 2019).

Risk of bias of all eligible studies was assessed using the Cochrane ROBINS-I tool (Risk of Bias in Non-randomized Studies—of Interventions) and the associated detailed guidance document (Sterne et al., 2016). Studies were considered for bias due to confounding factors, bias due to selection of participants into the study, bias due to classification of interventions, bias due to deviation from interventions, bias due to missing data, bias in measurement of outcome and bias in selection of the reported results. An overall risk of bias was assigned to each study based on the lowest assessment across all bias domains applying the proposed levels (low, moderate, serious or critical risk of bias or no information). Any disagreements were discussed between the authors.

We treated CDVA improvement and postoperative ECD as continuous data and used the mean difference (MD). Rebubbling and primary graft failure rate were treated as dichotomous data and the risk ratio (RR) was used to measure the effect size.

Quality of evidence of each study was assessed by two authors (M.L.P. and V.R.) using the Grading of Recommendations Assessment, Development and

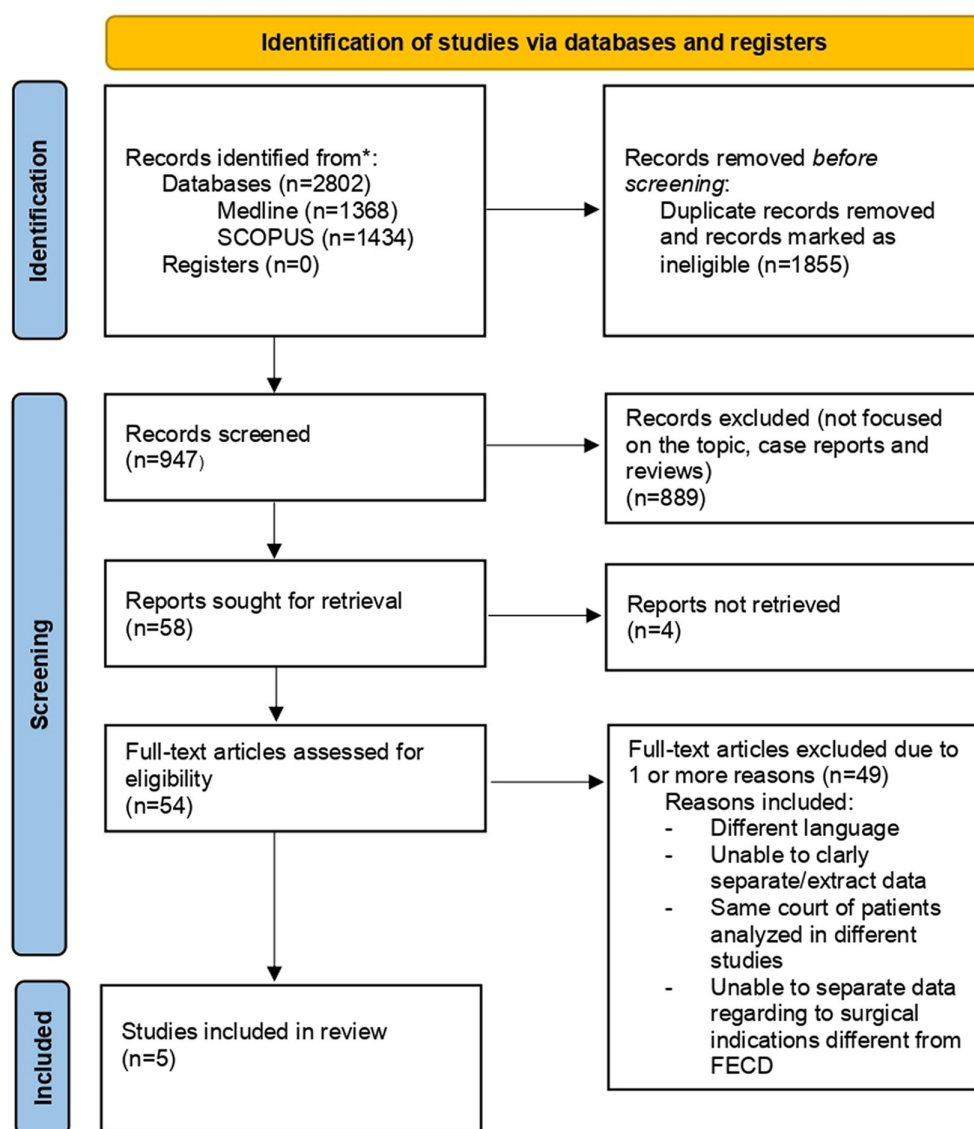


FIGURE 1 Results of the literature search strategy.

Evaluation (GRADE) tool (Cumpston et al., 2019). Each study was graded as high, moderate, low or very low based on study design, risk of bias, consistency, directness, precision, publication bias, magnitude of effect, dose response and confounding factors.

The raw data were entered into Microsoft Excel (Version 10.14 for Windows). Statistical analyses were conducted using the ‘meta’ commands in STATA 17.1 software (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). A *p*-value <0.05 was considered significant. Heterogeneity was assessed using *I*² and *τ*² statistics and by visual inspection of the overlapping of 95% confidence intervals in forest plots.

3 | RESULTS

After screening 947 articles, 5 articles satisfied our inclusion criteria and were included in our meta-analysis (Arslan et al., 2019; Fajardo-Sanchez & de Benito-Llopis, 2021; Hussien et al., 2021; Semler-Collery et al., 2022; Shahnazaryan et al., 2020). All studies were NRSs comparing outcomes in eyes that underwent combined DMEK or sequential DMEK. The studies were conducted in the United Kingdom, France, Egypt and Turkey in academic or hospital settings. The follow-up range was between 6 months and 12 months. In

particular, three studies reported results at 12 months, two at 6 months.

Overall risk of bias was assessed, and we rated three (60%) studies at moderate risk and two (40%) studies as serious risk of bias (Figures 2 and 3). The domains due to which the overall risk of bias was considered serious were bias due to missing data and bias in selection of the reported results. Specifically, Semler-Collery et al. excluded patients from statistical analysis who had persistent corneal oedema 3 months after transplantation (Semler-Collery et al., 2022) and Hussien et al. excluded primary graft failure cases from postoperative corneal thickness as well as from postoperative ECD statistical analysis (Hussien et al., 2021).

The baseline characteristics for 667 eyes are summarized in Table 1. 292 eyes (43.77%) underwent combined DMEK, while 375 (56.22%) eyes underwent sequential DMEK surgery. All features were analysed with a random effect model. CDVA improvement, postoperative ECD, re-bubbling rate and primary graft failure rate had no statistically significant difference between the two groups.

Three studies (261 eyes) provided data on CDVA improvement after 6 or 12 months. The meta-analysis evidenced a comparable improvement in both groups, with a mean difference (MD) of −0.06 LogMAR, 95% confidence interval (CI) −0.14 to 0.03, with a *p*-value=0.19 (Figure 4). Test for heterogeneity revealed low heterogeneity for CDVA improvement with *I*² statistics of 0% and

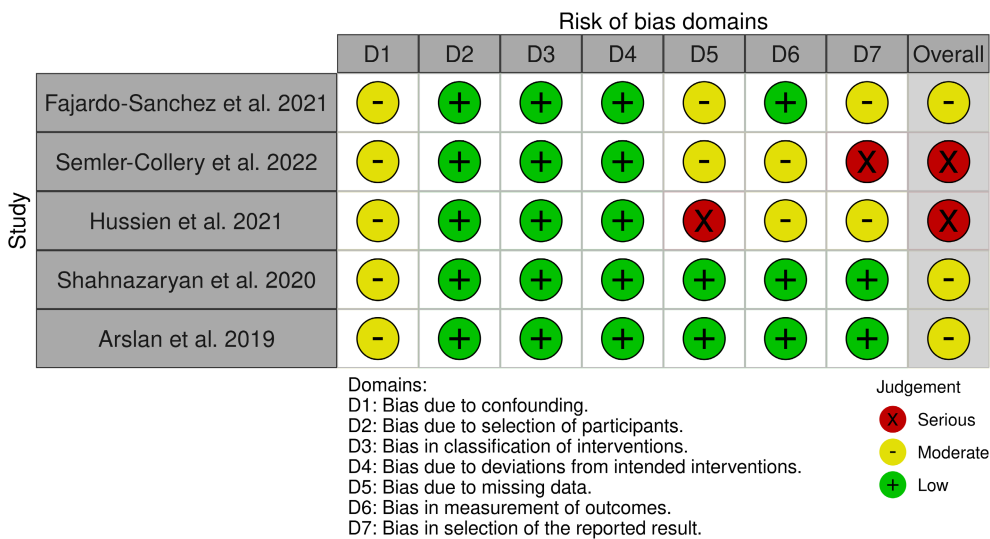


FIGURE 2 Authors' judgements of each risk of bias item for each included study.

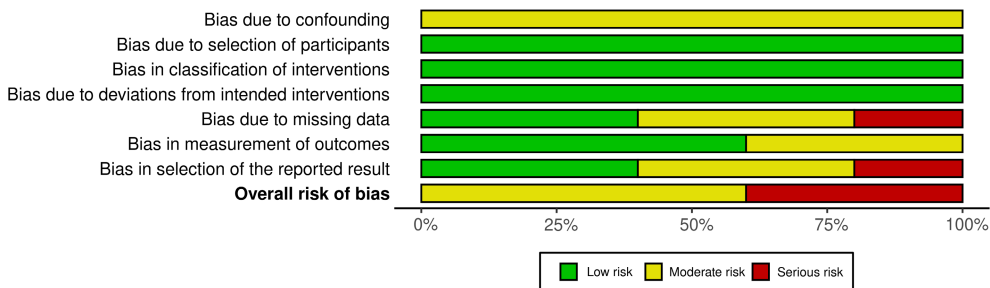


FIGURE 3 Summary of the judgements of each risk of bias domain presented as percentages.

TABLE 1 Characteristics of included studies.

Authors/year	Follow-up (months)	Surgical technique	N eyes	Mean age	CDVA pre	CDVA improvement	ECD donor	Postoperative ECD	Rebubbling rate	Primary graft failure rate
Fajardo-Sanchez et al. (2021)	12	Combined	111	73.2±10.2	NA	NA	NA	NA	17.6%	9.3%
Semler-Collery et al. (2022)	NA	Combined	40	70	0.5	NA	2545	1180	40%	NA
Hussien et al. (2021)	6	Combined	37	60.05±8.19	NA	NA	2701.2	NA	13.5%	2.7%
Shahnazaryan et al. (2020)	12	Combined	80	66.6±10.2	0.33	0.33	2643	1511	2.5%	8.75%
Arslan et al. (2019)	6	Combined	24	67.5±5.1	1.09	NA	2427.3	1739	NA	NA
Fajardo-Sanchez et al. (2021)	12	Sequential	218	72.3±10.1	NA	NA	NA	NA	25.5%	12.1%
Semler-Collery et al. (2022)		Sequential	55	72	0.5	NA	2540	1300	24%	NA
Hussien et al. (2021)	6	Sequential	40	63.38±8.62	NA	NA	2671.8	NA	12.5%	5%
Shahnazaryan et al. (2020)	12	Sequential	34	76.8±8.2	0.47	NA	2630	1748	2.9%	8.8%
Arslan et al. (2019)	6	Sequential	28	67.5±5.1	1.17	NA	2427.3	1702	NA	NA

Abbreviations: CDVA, corrected distance visual acuity; ECD, endothelial cell density.

t^2 of 0. This evidence was low certainty due to risk of bias (−1) and imprecision (−1), since the lower limit of the 95% CI did not rule out clinically important differences above 0.1 LogMAR.

Regarding ECD, no significant difference was found in donor ECD, with a mean difference between combined and sequential DMEK groups of 5.94 cells/mm² [−6.73;18.60] (p -value 0.36) (Figure 5). Four studies (338 eyes) provided data on postoperative ECD after 6 or 12 months. No evidence of a difference was found for postoperative ECD (−61.79 cells/mm², 95% CI −190.33 to 66.74, p =0.35) (Figure 6); however, our meta-analytic estimate of postoperative ECD should be considered with caution due to substantial heterogeneity between studies, with an I^2 statistics of 67%, t^2 of 11 211. Specifically, two studies suggested a higher ECD loss after combined surgery and two others suggested no difference, indicating clinical or methodological differences across studies. Therefore, this evidence was scored with very low certainty due to risk of bias (−1) and large heterogeneity (−2).

Four studies (615 eyes) provided information on rebubbling events, showing a comparable rebubbling rate in the two groups with a RR of 1.04, 95% CI 0.59–1.85, p -value 0.89 (Figure 7). Heterogeneity was rated as moderate with I^2 of 47.51%, t^2 of 0.15 and H^2 of 1.91. This evidence was low certainty due to risk of bias (−1) and imprecision (−1).

Finally, four studies (520 eyes) reported primary graft failure cases, and a meta-analysis showed a comparable primary graft failure rate between eyes receiving combined DMEK and those receiving sequential DMEK, with a RR of 0.91, 95% CI 0.32–2.57, p -value 0.86 (Figure 8). Heterogeneity was low, with I^2 of 0%, t^2 of 0 and H^2 of 1.00. This evidence was low certainty due to risk of bias (−1) and imprecision (−1).

4 | DISCUSSION

Although surgeons frequently face the challenge of how to choose a strategy regarding approaching and counselling patients with symptomatic FECD and cataract, there is still no consensus regarding the best possible management of these patients.

Currently, the surgeon can choose between two different approaches, depending on patient age, lens opacity, endothelial dysfunction grade and their own expertise: 1. The combined DMEK technique, in which endothelial keratoplasty and cataract surgery are performed in a single surgical session, and 2. The staged (or sequential) DMEK technique, in which the two surgeries are performed at different times.

Our analysis shows that there is no evidence of a difference between the combined and the sequential technique, particularly regarding CDVA improvement, with comparable pre and postoperative values. However, the certainty of evidence was low, mainly due to the high risk of bias in the analysed retrospective studies, and high heterogeneity of the results for postoperative ECD, for which two studies suggested no difference, and two others found a higher ECD loss with combined surgery. These differences may have clinical and methodological explanations.

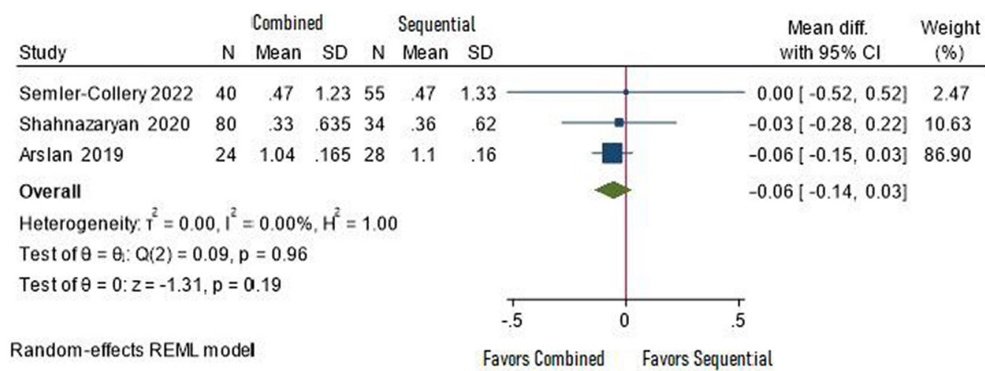


FIGURE 4 Forest plot of comparison combined DMEK versus sequential DMEK: CDVA improvement (LogMAR).

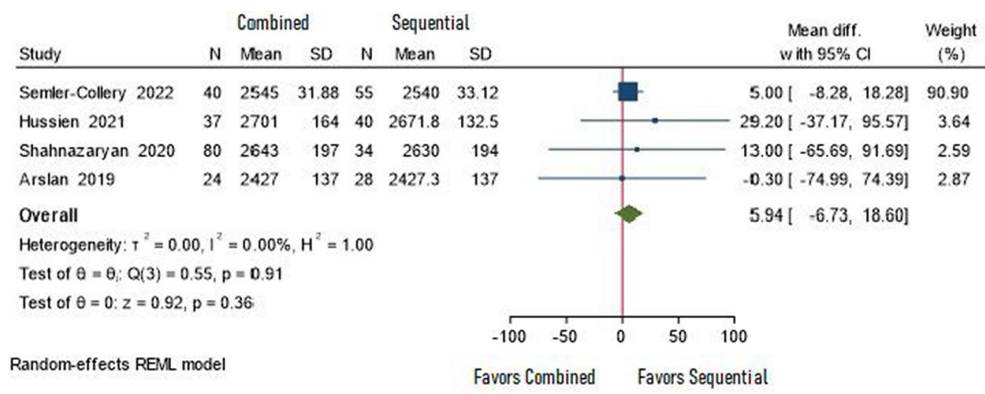


FIGURE 5 Forest plot of comparison combined DMEK versus sequential DMEK: ECD donor (cells/mm²).

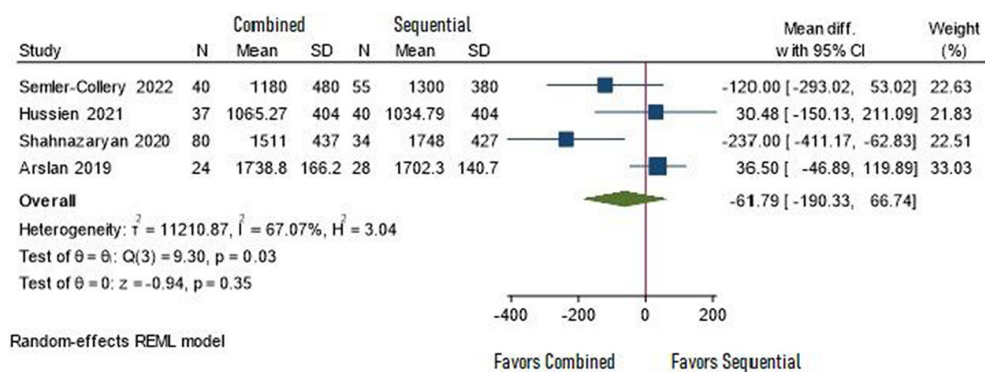


FIGURE 6 Forest plot of comparison combined DMEK versus sequential DMEK: postoperative ECD (cells/mm²).

With regard to comorbidities that could impact on visual outcomes, there is a high heterogeneity in exclusion criteria: eyes with coexisting visually significant ocular damage or previous surgeries other than cataract surgery were excluded in three studies (Arslan et al., 2019; Hussien et al., 2021; Semler-Collery et al., 2022), whereas Fajardo-Sanchez et al. only excluded eyes with previously failed penetrating keratoplasty, congenital glaucoma, post-glaucoma surgeries and infectious cases (Fajardo-Sanchez & de Benito-Llopis, 2021) and in the Shahnazaryan et al. case series no exclusion criteria were used (Shahnazaryan et al., 2020). This high variability highlights the difficulty in achieving an unambiguous conclusion.

Moreover, another limitation is the lack of information on FECD and cataract grade. In particular, no study

refers to the FECD or cataract grade, only two studies refer to clinical features related to FECD (Hussien et al., 2021; Shahnazaryan et al., 2020). Also, the duration of corneal decompensation is not reported, although a correlation has indeed been demonstrated between pre-operative duration of corneal oedema and postoperative visual acuity after endothelial keratoplasty (Amano et al., 2017; Morishige et al., 2012). Finally, the follow-up periods vary from 6 to 12 months, which makes it difficult to make a definitive conclusion.

With regard to ECD decrease, it is one of the primary factors related to graft survival (Vasiliauskaite et al., 2021). As evidenced in the literature, intense graft manipulation during surgery, postoperative inflammation, pronounced anterior chamber depth fluctuation and prolonged surgical time are factors associated with

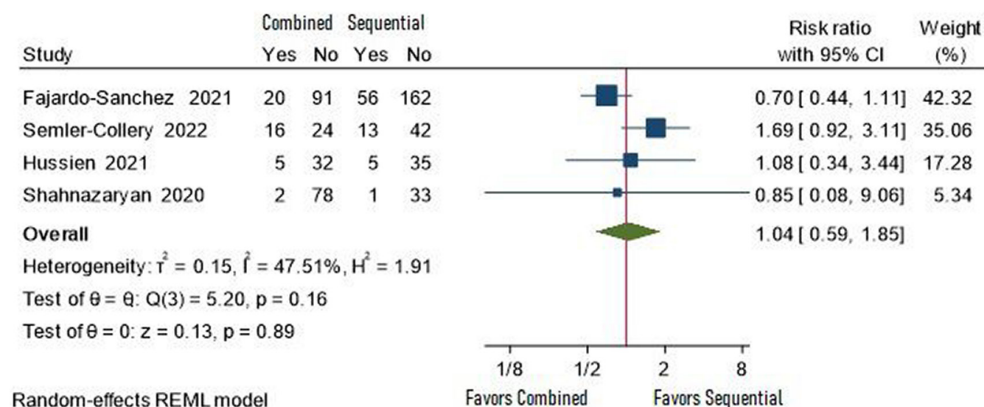


FIGURE 7 Forest plot of comparison combined DMEK versus sequential DMEK: rebubbling rate.

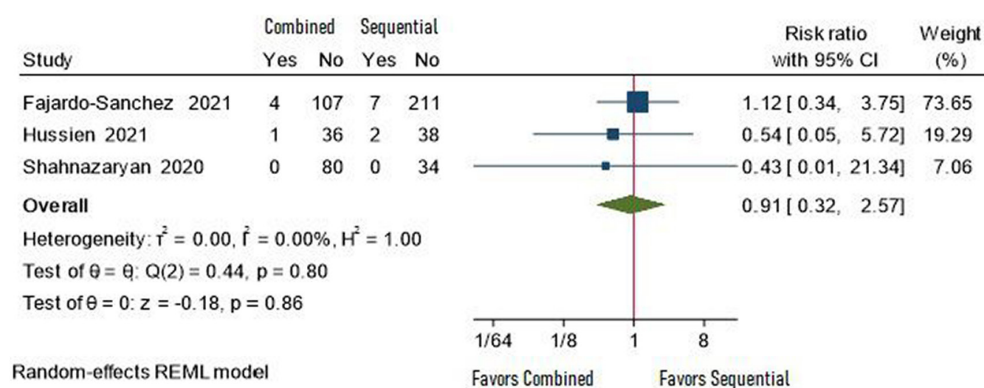


FIGURE 8 Forest plot of comparison combined DMEK versus sequential DMEK: primary graft failure rate.

elevated risk of a decrease in ECD, (Chaurasia et al., 2014; Hayashi et al., 2020) so it may seem intuitive that the combined procedure would lead to more endothelial cell loss. In our meta-analysis, only the Shahnazaryan et al. case series study observed a higher ECD loss with combined DMEK and higher ECD decrease (41% vs. 33%, $p=0.034$) in patients with FECD at 1-month and 1-year follow-up, without influencing graft survival rates (Shahnazaryan et al., 2020). The other four studies did not find a difference in ECD between the two arms. The reason for this discrepancy remains unclear; we can only hypothesize that it could be related to the above-mentioned surgical factors or acute inflammation during the combined procedure (Claesson et al., 2009; Stuart et al., 2018). Based on current evidence, the two procedures should be considered comparable in terms of clinical outcomes.

What clearly emerges from our meta-analysis on postoperative ECD is a remarkable variability among different studies. In our opinion, and as confirmed in literature, it could be related to surgeon factors but could also be related to preoperative issues, such as type of graft preparation, graft storage (Garzin et al., 2020; Romano et al., 2018) and eye bank ECD counting technique (Miron et al., 2018). In particular, it has been hypothesized that the variability in ECD loss between centres could be related to an overestimation in preoperative ECD, resulting in grafts that appear to be less stress tolerant (Miron et al., 2021; Patel et al., 2019).

While graft detachment is the most common postoperative complication after DMEK, (Parekh et al., 2018)

the rebubbling rate was also investigated in our meta-analysis and no evidence of a difference between the two groups was found. The only study with which these results are not perfectly matched is the retrospective cohort study by (Semler-Collery et al., 2022), in which in 95 eyes with FECD that underwent combined or sequential DMEK, eyes that received combined DMEK tended to be associated with higher rebubbling rates than sequential DMEK (40% vs. 24%; $p=0.09$). According to the authors (Semler-Collery et al., 2022), one possible explanation could be related to the use of viscoelastic substances (OVD), as the sequential procedure is generally performed under air without the use of viscoelastic, which is usually only utilized in combined DMEK procedures. There is evidence that graft detachment and consequently the rebubbling rate can be influenced by the use of OVD in combined DMEK (Anshu et al., 2012; Chaurasia et al., 2014; Woo et al., 2019). As a confirmation of this, Semler-Collery et al. noted persisting OVD in the central zone between the graft and the recipient stroma in one case with graft detachment following combined DMEK (Semler-Collery et al., 2022). A scrupulous wash out of viscoelastic from the anterior chamber before inserting the graft and the choice of a cohesive viscoelastic that is easier to remove (Arslan et al., 2019; Fajardo-Sanchez & de Benito-Llopis, 2021; Hussien et al., 2021) should minimize these issues.

Another factor we intended to compare was the injected tamponade to promote primary graft attachment at

the end of the DMEK procedure, that is sulphur hexafluoride 20% (SF₆20%) and conventionally used, 100% air, as the different tamponades have been reported as a possible crucial factor in graft detachment (Parekh et al., 2018). In the published literature there is evidence of a significantly lower incidence of graft detachments with SF₆20% anterior chamber tamponade compared with 100% air, resulting in a lower rebubbling rate not negatively impacting on other surgery DMEK outcomes (Güell et al., 2015; Rickmann et al., 2018; Schaub et al., 2017). In contrast to these reports, the only study included in our meta-analysis which compared the use of 100% air and SF₆20% did not find an association between the tamponade applied and rebubbling rates (Fajardo-Sanchez & de Benito-Llopis, 2021), while in all the other studies only air was employed.

Primary donor graft failure is a rare complication defined as corneal oedema that never clears in the immediate postoperative period secondary to the inherent deficiencies in the donor graft, surgical trauma, or improperly stored tissue. The primary graft failure rate was similar in combined and sequential DMEK groups; however, the outcomes may be different in terms of complications in procedures performed by less experienced surgeons (Price et al., 2010).

With equal outcomes in terms of effectiveness and risks, patients' experience and costs are issues that could be considered. In our opinion, eliminating an additional trip to the operating theatre could alleviate patients' stress and this could be perceived as lower risk, although there is no description of patients' experience in literature. Moreover, combined DMEK rather than sequential procedures provide a reduction in the overall health care costs (Chaurasia et al., 2014; Terry et al., 2009).

In conclusion, our review suggests that the choice of performing cataract surgery and DMEK in separate stages or in the same operation in patients with FECD may not affect the expected surgical outcomes, however, the high risk of study bias and the heterogeneity of study design, populations, duration of follow-up result in designation of the available evidence as low quality. Our analysis highlights the need for a randomized clinical trial with detailed inclusion criteria. Further trials are also required to investigate which surgical techniques could minimize cellular stress on the graft and optimize the intraocular environment.

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