

Endothelium-in hydrodissection (Maurine) versus endothelium-out stripping graft preparation for Descemet Membrane Endothelial Keratoplasty: a prospective two-centre cohort study

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Abstract

Purpose: To compare the Muraine hydrodissection (endothelium-in) and the standard (endothelium-out) techniques for Descemet membrane endothelial keratoplasty (DMEK) in routine practice.

Methods: Prospective two-centre cohort study (NCT02470793) of pseudophakic eyes undergoing DMEK with the standard (27 eyes) or the Muraine technique (42 eyes, after 10 learning-curve cases). Primary outcomes were central endothelial cell density (ECD), endothelial cell loss (ECL) from donor ECD and best-corrected visual acuity (BCVA) over 6 months; secondary outcomes were surgical times, tissue loss, complications and rebubbling.

Results: ECD and ECL at 1 month were equivalent (standard versus Muraine: 1523 versus 1560 cells/mm²; -38.9% versus -39.3%; $P = 0.76$); ECL then stabilized in the standard but rose in the Muraine group (6 months: -41.7% versus -57.4%, $P = 0.02$; ECD 1488 versus 1170, $P = 0.10$). Six-month median BCVA was 0.05 versus 0.10 logMAR ($P = 0.19$). Dissection took 12.5 min longer with the Muraine technique ($P < 0.001$), whereas, excluding eyes with a previous complicated phacoemulsification, unfolding was 1.5 min faster and less variable ($P = 0.04$). No graft was lost; partial tissue loss occurred only in the Muraine group (26.2%). Rebubbling was required in 0% versus 45.2% ($P < 0.001$), associated with air-only tamponade. Cystoid macular oedema and primary failure did not differ.

Conclusion: The Muraine technique provides visual and early endothelial outcomes equivalent to the standard technique, with faster unfolding but slower dissection, more partial tissue loss, higher 6-month ECL and more rebubbling, the latter largely due to air tamponade. Standardized tamponade and pupillary-block prophylaxis are advisable for endothelium-in DMEK.

Key message

What is known

- Descemet membrane endothelial keratoplasty (DMEK) grafts can be prepared and inserted with the endothelium facing outward (standard scroll) or inward (tri-folded or hydrodissected "burrito" rolls). The Muraine hydrodissection technique yields endothelium-in grafts that unfold spontaneously, but its clinical results have never been compared with the standard technique.

What is new

- In routine practice, the Muraine technique achieved visual acuity and 1-month endothelial cell density equivalent to the standard technique, every graft could be implanted despite partial tissue loss during dissection in 26% of cases, and graft unfolding was faster and more predictable in eyes without a previous complicated phacoemulsification.
- Endothelial cell loss continued to increase up to 6 months in the Muraine group (57% versus 42%), and rebubbling was needed in 45% of eyes versus none in the standard group.

- Air-only tamponade and pharmacological mydriasis, rather than sulfur hexafluoride 20% and an inferior iridectomy, were the main drivers of rebubbling and pupillary block; tamponade and prophylaxis protocols should be standardized when an endothelium-in technique is adopted.

Introduction

Descemet membrane endothelial keratoplasty (DMEK) [1] has become the reference procedure for irreversible corneal oedema secondary to endothelial dysfunction, offering better visual outcomes and less rejection than Descemet stripping automated endothelial keratoplasty (DSAEK) [2–5]. Graft preparation and insertion remain the most demanding steps: tearing of the Descemet membrane (DM) during dissection may cause tissue loss, and unfolding a tightly scrolled graft prolongs surgery and exposes the endothelium to trauma [6, 7].

In the standard technique, DM is peeled manually and the graft spontaneously scrolls with the endothelium on the outer surface. In 2013, Muraine et al. described an alternative in which the donor button is partially trephined, mounted on an artificial anterior chamber with inverted curvature and hydrodissected; the graft is then folded with the endothelium inside ("burrito") and injected into the anterior chamber, and because the DM is folded against its natural curvature it tends to unfold spontaneously inside the eye [8]. Laboratory studies confirmed low tissue loss and good endothelial preservation with this preparation [9, 10], and endothelium-in delivery, as tri-folded grafts [11, 12] or with pull-through devices [13], has since been widely adopted, mainly with eye-bank preloaded tissue [14]. Comparative data on endothelial cell loss (ECL), rebubbling and graft tears between the two orientations are conflicting [15–18], and the clinical results of the Muraine technique have never been compared with those of the standard technique.

This study tested the hypothesis that the Muraine technique is equivalent to the standard technique in efficacy (endothelial cell density [ECD] and visual acuity) and safety (tissue loss and complications) in routine practice. Surgery was performed in 2014–2015, before preloaded tissue became available; the results are discussed in the light of the evidence published since.

Methods

Study design and participants

This prospective observational cohort study was conducted in routine clinical practice at two tertiary corneal transplantation centres in Spain: a public university hospital (Hospital Universitari MútuaTerrassa, HUMT, Terrassa, Barcelona), where the Muraine technique was used, and a private institute (Institut de Microcirurgia Ocular, IMO, Barcelona), where the standard technique was used. Each centre used its technique of choice with two experienced surgeons in each centre (AS and IS at HUMT, and JLG and OG at IMO). The protocol was approved by the Clinical Research Ethics Committee of HUMT, registered at ClinicalTrials.gov (NCT02470793) and conducted in accordance with the Declaration

of Helsinki (2013). All participants gave written informed consent. Recruitment lasted 18 months (2014–2015).

Eligible patients were adults with irreversible corneal oedema secondary to endothelial dysfunction requiring DMEK, pseudophakic with a posterior-chamber intraocular lens (IOL) implanted at least 1 month earlier. Exclusion criteria were combined surgery, previous intraocular surgery other than phacoemulsification, phakic IOL implantation or explantation, or IOL suture or exchange, advanced retinal or optic nerve disease limiting the visual prognosis, and learning-curve eyes of the Muraine technique. The IMO surgeons had performed more than 200 DMEK procedures with the standard technique [19], so no learning-curve exclusion applied there. The learning curve of the Muraine technique at HUMT was monitored prospectively in blocks of 10 cases: the first 10 included one total tissue loss and two early primary failures, none occurred in cases 11–20, and unfolding time stabilised below 10 min from case 11, so the first 10 cases were excluded [20]. All consecutive eligible eyes were included, targeting at least 20 standard and 40 Muraine eyes.

Surgical technique

In the standard group, grafts were prepared following the stepwise technique of Kruse et al. [6]: after marking with an 8-mm trephine and trypan blue staining, the peripheral DM was scored and stripped manually under culture medium, and the graft was trephined, stained again and loaded into a plastic IOL-cartridge injector; the endothelium-out scroll was injected by advancing the plunger and unfolded with the bimanual no-touch technique [21].

In the Muraine group, the donor button was partially trephined from the endothelial side with the Muraine punch (Moria, Antony, France), leaving two unperforated 30° bridges, mounted on an artificial anterior chamber with the endothelium up and pressurised with air until the corneal curvature inverted [8]. After trypan blue staining, the DM was hydrodissected through the bridges with a 27-gauge cannula and balanced salt solution (BSS), the bridges were cut, the graft was folded with the endothelium inside around a strip of methylcellulose (like a "burrito") and its stromal side marked with gentian violet. The graft was loaded into a plastic IOL cartridge and injected with a BSS-filled syringe connected to the cartridge. Both techniques are shown in the surgical video (Online Resource 1) and in frames taken from it (Online Resource 2, Fig. S1).

In both groups, an 8-mm descemetorhexis was performed and the anterior chamber was filled at the end of surgery with air alone or with 20% sulfur hexafluoride (SF₆) at the surgeon's discretion. Pupillary block was prevented with a surgical inferior peripheral iridectomy, a previous Nd:YAG iridotomy or postoperative pharmacological mydriasis, also at the surgeon's discretion. Postoperative treatment consisted of tobramycin–dexamethasone drops every 4 h for 1 week, followed by tapering prednisolone acetate 1% over the following months.

Follow-up and outcome measures

Patients were examined on day 1, week 1 and months 1, 3 and 6, and whenever necessary. Preoperative data included demographics, aetiology, ocular comorbidity, time since diagnosis of corneal oedema, previous phacoemulsification, best-corrected visual acuity (BCVA; Snellen decimal, converted to logMAR), intraocular pressure (IOP), axial length measurement (Lenstar, Haag-Streit, at HUMT; IOLMaster 500, Carl Zeiss Meditec, at IMO) and macular optical coherence tomography (Cirrus, Carl Zeiss Meditec). Donor age, ECD and storage method (organ culture or hypothermic) were recorded from eye-bank documentation (BST, Banc de Sang i Teixits, Barcelona).

All surgeries were video-recorded. Dissection time was measured from the first incision on the donor tissue to completion of loading into the injector, and unfolding time from injection of the graft into the anterior chamber to final pressurisation with air or gas. Tissue loss during dissection was graded as minimal (fragment < 1 mm in diameter), < 25% or 50% of graft area.

The primary outcomes were central ECD, measured by specular microscopy (SP-3000P, Topcon, Tokyo, Japan) at months 1, 3 and 6, expressed as absolute values and as percentage ECL relative to donor ECD, and BCVA. Secondary outcomes were surgical times, postoperative complications and need for rebubbling, which was decided by the treating surgeon on clinical grounds. Masking to the technique was not possible.

Statistical analysis

Analyses were performed with Stata/IC 13.1 (StataCorp, College Station, TX, USA). Normality was assessed with the Shapiro–Wilk test. Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range, IQR) and were compared with Student's t test, analysis of variance or the Wilcoxon rank-sum test; categorical variables with the chi-square test; correlations with Pearson's coefficient. Multivariable linear or logistic regression was used to estimate the effect of clinically relevant covariates on surgical times, 6-month ECL, cystoid macular oedema (CMO) and rebubbling, reporting coefficients or odds ratios (OR) and R^2 or pseudo- R^2 . The likelihood-ratio test assessed whether retinal comorbidity predicted 6-month BCVA. $P < 0.05$ (two-sided) was considered significant.

Use of artificial intelligence

A large language model (Claude, Anthropic) was used to assist with journal formatting, and language and figure editing. All AI-assisted content was reviewed, verified against source data, and approved by the authors, who take full responsibility for the manuscript's accuracy.

Results

Baseline characteristics

Twenty-seven eyes of 20 patients (standard) and 42 eyes of 40 patients (Muraire) were included (Table 1). Patients in the standard group were a median of 10 years younger and had a longer recorded interval between diagnosis and surgery; preoperative BCVA, aetiology, comorbidity and previous phacoemulsification were comparable. Fuchs endothelial corneal dystrophy (FECD) was the leading indication in both groups; pseudophakic bullous keratopathy (PBK) was more frequent in the Muraire group (16.7% versus 3.7%). Three eyes in the Muraire group (7.1%) had suffered a complicated phacoemulsification (one DM detachment, two posterior capsule ruptures with vitreous loss) versus none ($P = 0.16$).

Table 1
Baseline characteristics of patients and eyes

Patients, n	Standard (n = 27)	Muraine (n = 42)	P
	20	40	
Age, years, median (IQR)	65.8 (56–70.4)	76.2 (68.7–80.4)	< 0.001
Female, n (%)	14 (51.9)	26 (61.9)	0.41
Right eye, n (%)	18 (66.7)	23 (54.8)	0.33
Time since diagnosis of oedema, months, median (IQR)	18.4 (6.5–43.5)	3.5 (1.6–7.9)	< 0.001
Preoperative BCVA, logMAR, median (IQR)	0.40 (0.30–0.52)	0.46 (0.26–0.70)	0.87
Aetiology, n (%)			0.08
Fuchs endothelial corneal dystrophy	23 (85.2)	33 (79.0)	
Pseudophakic bullous keratopathy	1 (3.7)	7 (16.7)	
Anterior chamber phakic IOL	3 (11.1)	0 (0)	
Iatrogenic Descemet membrane detachment	0 (0)	1 (2.4)	
Herpetic keratitis	0 (0)	1 (2.4)	
Ocular comorbidity, n (%)			
Pseudoexfoliation	1 (3.7)	2 (4.8)	0.83
Glaucoma	0 (0)	1 (2.4)	0.42
Retinal disease ^a	2 (7.4)	6 (14.3)	0.38
Amblyopia	1 (3.7)	1 (2.4)	0.75
IOL exchange or suture	1 (3.7)	1 (2.4)	0.75
Previous phacoemulsification			
Interval to DMEK, months, median (IQR)	3 (1–8)	8 (3–48)	0.32
IOL in the bag, n (%)	27 (100)	39 (92.9)	0.16
Complicated phacoemulsification, n (%)	0 (0)	3 (7.1)	0.16
BCVA best-corrected visual acuity, IOL intraocular lens, IQR interquartile range, DMEK Descemet membrane endothelial keratoplasty. ^a Age-related macular degeneration, epiretinal membrane, branch retinal vein occlusion, previous cystoid macular oedema or diabetic retinopathy.			

Donor tissue, surgical times and tissue loss

Donor age, donor ECD and storage method did not differ between groups (Table 2).

Table 2
Donor tissue, surgical times, tissue loss and intraoperative complications

Donor age, years, mean $\pm$ SD	Standard (n = 27)	Muraine (n = 42)	P
	69.5 $\pm$ 9.5	68.9 $\pm$ 10.1	0.79
Donor ECD, cells/mm ² , median (IQR)	2500 (2400–2700)	2600 (2500–2700)	0.06
Organ-cultured tissue, n (%) ^a	24 (88.9)	34 (81.0)	0.38
Positive donor rim culture, n (%)	0 (0)	1 (2.4)	0.41
Dissection time, min, median (IQR)	10 (7–10)	22.5 (20.75–27.5)	< 0.001
Unfolding time, min, median (IQR)	7 (5–12)	5.7 (3.5–9.5)	0.11
Unfolding time, uncomplicated phacoemulsification only, min, median (IQR)	7 (5–12)	5.5 (3.5–8.4)	0.04
Tissue loss during dissection, n (%)	0 (0)	11 (26.2)	0.04
Minimal (< 1 mm diameter)	0 (0)	6 (14.3)	
< 25% of graft area	0 (0)	4 (9.5)	
50% of graft area	0 (0)	1 (2.4)	
Intraoperative complications, eyes, n (%)	1 (3.7)	8 (19.0)	0.07
Incomplete descemetorhexis	0 (0)	1 (2.4)	0.42
Anterior chamber haemorrhage	0 (0)	6 (14.3)	0.04
Graft expelled from anterior chamber	0 (0)	2 (4.8)	0.25
Incomplete unfolding	1 (3.7)	0 (0)	0.21
Positive vitreous pressure	0 (0)	1 (2.4)	0.42
ECD endothelial cell density, SD standard deviation, IQR interquartile range. ^a Remaining corneas were cold-stored.			

Dissection was a median of 12.5 min longer with the Muraine technique (22.5 versus 10 min, $P < 0.001$) and more variable (IQR 6.75 versus 3 min). In the standard group, dissection time correlated inversely with donor age ($r = -0.58$, $P = 0.002$), unlike the Muraine group. Adjusted for storage method, donor age and donor ECD, the Muraine technique prolonged dissection by 14.7 min ($P < 0.001$).

Unfolding time did not differ significantly between groups (7 versus 5.7 min, $P = 0.11$), but was longer in eyes with a previous complicated phacoemulsification (14 versus 6 min, $P = 0.03$). Excluding these eyes, unfolding was 1.5 min faster and less variable in the Muraine group (5.5 versus 7 min, $P = 0.04$; IQR 4.9 versus 7 min). No covariate had a significant effect on unfolding time in multivariable analysis.

No total tissue loss occurred, and all grafts were implanted. Partial tissue loss during dissection occurred only in the Muraine group (11 eyes, 26.2%, $P = 0.04$): minimal in six, < 25% of the graft area in four and 50% in one, which still achieved a BCVA of 0.8 at 6 months with an ECD of 397 cells/mm². Within the Muraine group, mean donor age was higher for grafts with < 25% loss (83.8 years) than with minimal (68.3 years) or no loss (66.7 years; $P = 0.01$).

Intraoperative complications

Intraoperative complications other than tissue loss occurred in one eye (3.7%) in the standard group (incomplete unfolding) and in eight (19.0%) in the Muraine group (OR 6.0, 95% confidence interval 0.72–52, $P = 0.07$; Table 2). Anterior chamber haemorrhage from the iris or angle was the most frequent (14.3%, $P = 0.04$). In two eyes the graft was expelled from the anterior chamber, one after haemorrhage and one because of positive vitreous pressure requiring pars plana vitrectomy before implantation. Eyes with a complicated phacoemulsification had more complications during DMEK ($P = 0.005$); among the others, incidence did not differ (15.4% versus 3.7%, $P = 0.13$).

Visual acuity and endothelial cell density

Preoperative BCVA was similar in both groups (0.40 versus 0.46 logMAR, $P = 0.87$). BCVA improved in both groups at every visit; at 6 months, median BCVA was 0.05 logMAR (decimal 0.89) in the standard group and 0.10 logMAR (decimal 0.79) in the Muraine group ($P = 0.19$), and the distribution of eyes by BCVA category did not differ ($P = 0.36$; Table 3). Retinal comorbidity was not a predictor of 6-month BCVA (likelihood-ratio test, $P = 0.40$).

Table 3
Visual acuity and central endothelial cell density during follow-up

BCVA, logMAR, median (IQR)	Standard	Muraine	P
Preoperative	0.40 (0.30–0.52)	0.46 (0.26–0.70)	0.87
1 month	0.22 (0.15–0.40)	0.28 (0.13–0.45)	0.54
3 months	0.10 (0.10–0.15)	0.19 (0.10–0.35)	0.10
6 months	0.05 (0–0.15)	0.10 (0–0.30)	0.19
BCVA category at 6 months, n (%) ^a	n = 26	n = 39	0.36
< 0.2	0 (0)	3 (7.7)	
0.2 to < 0.5	3 (11.5)	5 (12.8)	
0.5 to < 0.8	4 (15.4)	11 (28.2)	
0.8 to < 1.0	10 (38.5)	10 (25.6)	
≥ 1.0	9 (34.6)	10 (25.6)	
ECD, cells/mm ² , median (IQR)			
Donor	2500 (2400–2700)	2600 (2500–2700)	0.06
1 month	1523 (1260–1752)	1560 (1136–2023)	0.78
3 months	1595 (1253–1724)	1250 (917–1680)	0.48
6 months	1488 (1337–1679)	1170 (734–1614)	0.10
ECL relative to donor ECD, %, median (IQR)			
1 month	–38.9 (29.4–44.2)	–39.3 (25.8–51.7)	0.76
3 months	–38.7 (28.2–56.4)	–51.9 (41.0–64.7)	0.16
6 months	–41.7 (31.6–45.4)	–57.4 (38.6–71.8)	0.02
BCVA best-corrected visual acuity, ECD endothelial cell density, ECL endothelial cell loss, IQR interquartile range. ^a Snellen decimal categories; eyes with 6-month BCVA available.			

Donor ECD, ECD at 1 month (1523 versus 1560 cells/mm², P = 0.78) and 1-month ECL (– 38.9% versus – 39.3%, P = 0.76) were equivalent (Table 3, Fig. 1). Thereafter, ECD remained stable in the standard group but continued to decline in the Muraine group: at 6 months, median ECD was 1488 (IQR 1337–1679) versus 1170 (734–1614) cells/mm² (P = 0.10) and median ECL – 41.7% versus – 57.4% (P = 0.02), with greater dispersion in the Muraine group (IQR 880 versus 342). In a multivariable linear model including

technique, unfolding time, intraoperative complications, tissue loss, pupillary block and rebubbling ($R^2 = 32.7\%$), no covariate was an independent predictor of 6-month ECL; the largest effect was that of tissue loss (coefficient 9.0, 16.7 and 38.2 for minimal, < 25% and 50% loss; $P = 0.33, 0.26$ and 0.05), whereas the effect of unfolding time was significant but negligible ($-0.03\%/min$, $P = 0.04$).

Postoperative complications, tamponade and rebubbling

All eyes in the standard group received air with 20% SF6 and an intraoperative inferior iridectomy. In the Muraine group, 15 eyes (35.7%) received air with 20% SF6 and 27 (64.3%) air alone; pupillary block was prevented with an iridectomy or iridotomy in 13 eyes (31.0%) and with mydriasis in 29 (69.0%) (Table 4). Residual gas on day 1 was comparable in SF6 eyes of both groups (62.5% versus 59.1%, $P = 0.50$) but lower at week 1 in the Muraine group (20% versus 0%, $P = 0.002$).

Table 4
Tamponade, pupillary-block prophylaxis, postoperative complications and rebubbling

Air + 20% SF6 tamponade, n (%)	Standard (n = 27)	Muraine (n = 42)	P
	27 (100)	15 (35.7)	< 0.001
Peripheral iridectomy/iridotomy (others: mydriasis), n (%)	27 (100)	13 (31.0)	< 0.001
Residual gas, day 1, %, mean $\pm$ SD (SF6 eyes)	62.5 $\pm$ 8.6	59.1 $\pm$ 23.7	0.50
Residual gas, week 1, %, median (IQR) (SF6 eyes) ^a	20 (0–33)	0 (0–10)	0.002
Postoperative complications, n (%)			
Pupillary block (first 24 h)	1 (3.7)	4 (9.5)	0.35
Anterior chamber fibrin	0 (0)	4 (9.5)	
Filamentary keratitis	0 (0)	2 (4.8)	0.25
Persistent epithelial defect	0 (0)	1 (2.4)	0.44
Cystoid macular oedema	3 (11.1)	5 (11.9)	
Epiretinal membrane	0 (0)	1 (2.4)	0.42
Primary graft failure	0 (0)	2 (5.0)	0.25
Allograft rejection	0 (0)	0 (0)	–
Any complication, n (%) ^b	4 (18.2)	18 (46.2)	0.03
Rebubbling, n (%)	0 (0)	19 (45.2)	< 0.001
1 rebubbling	0 (0)	15 (35.7)	
2 rebubbings	0 (0)	3 (7.1)	
3 rebubbings	0 (0)	1 (2.4)	
Rebubbling with air-only tamponade (Muraine, n = 27)	–	13 (48.2)	0.61 ^c
Rebubbling with air + SF6 tamponade (Muraine, n = 15)	–	6 (40.0)	
First rebubbling, days, mean $\pm$ SD (air / SF6)	–	8.4 $\pm$ 5.1 / 14.5 $\pm$ 7.0	0.05

SF6 sulfur hexafluoride, SD standard deviation, IQR interquartile range. ^a Excluding rebubbled eyes. ^b Eyes with at least one complication among those with complete follow-up. ^c Air versus SF6 within the Muraine group.

More eyes in the Muraine group had at least one postoperative complication (46.2% versus 18.2%, $P = 0.03$), but no individual complication differed significantly (Table 4). Pupillary block occurred within 24 h in one (3.7%) and four eyes (9.5%, $P = 0.35$); no eye with an iridectomy or iridotomy developed pupillary block, and three of the four cases in the Muraine group had received SF6 with mydriasis. Anterior chamber fibrin, filamentary keratitis and one persistent epithelial defect occurred only in the Muraine group and resolved with topical treatment. IOP did not differ between groups at any visit.

CMO was the most frequent postoperative complication (three eyes, 11.1%, versus five, 11.9%), mostly diagnosed at 1 month; all but one resolved with topical corticosteroids and/or non-steroidal anti-inflammatory drugs within 2.5–5 months. No covariate significantly predicted CMO.

No graft rejection or early primary failure occurred. Two primary failures (5.0%) occurred at 6 months in the Muraine group ($P = 0.25$): one graft with < 25% tissue loss, pupillary block and two rebubbings, and one with an otherwise uneventful course. No graft was upside down.

No eye in the standard group required rebubbling, whereas 19 (45.2%) in the Muraine group did ($P < 0.001$): once in 15, twice in 3 and three times in 1, always with air and within the first 30 days (Fig. 2). Within the Muraine group, rebubbling did not differ between air-only and SF6 tamponade (48.2% versus 40.0%, $P = 0.61$), but was performed later with SF6 (14.5 ± 7 versus 8.4 ± 5.1 days, $P = 0.05$). In a logistic model including donor age, axial length, tamponade, residual gas and tissue loss (pseudo- $R^2 = 33.4\%$), air-only tamponade showed a 16-fold higher odds of rebubbling (OR 16.03, $P = 0.07$), longer axial length tended to be protective (OR 0.25 per mm, $P = 0.09$) and minimal tissue loss increased the odds of rebubbling (OR 99.1, $P = 0.03$). Rebubbled eyes did not have less residual gas on day 1 or at week 1 ($P = 0.41$ and 0.12).

Discussion

This study is, to our best knowledge, the first clinical comparison of the Muraine hydrodissection technique with the standard technique for DMEK. Both achieved comparable visual results and equivalent ECD and ECL at 1 month, no graft was lost during preparation, and 6-month graft survival was high. Excluding eyes with a previous complicated phacoemulsification, the endothelium-in graft unfolded 1.5 min faster and more predictably. The Muraine technique, however, required a longer dissection and was associated with partial tissue loss in one in four grafts, progressive ECL up to 6 months and a much higher rebubbling rate.

Visual outcomes in both cohorts were within the range of large series (50–100% of eyes at 0.5 or better and 22–66% at 0.8 or better at 6 months) [22–25], and the proportion reaching 1.0 or better (35% and 26%) matched the 19–40% reported elsewhere [21–23]; the higher figures of the original Muraine series [8] reflect the inclusion of FECD eyes without comorbidity.

ECL at 1 month (about 39% in both groups) was similar to that reported with the standard technique by Kruse et al. [6] and Schlögl et al. [24]. Most ECL after DMEK occurs during the first month and stabilises

thereafter [24, 26–28]. This pattern was reproduced in the standard group, but in the Muraine group ECL continued to increase to 57% at 6 months, above the 25–47% reported in large series [2, 22–24, 27, 29] and above the 1658 cells/mm² reported by Muraine et al. [8]. Because the 1-month values, which most directly reflect preparation and insertion trauma, were identical, the later divergence is unlikely to be explained by the dissection technique itself; several factors specific to the Muraine cohort may have contributed. First, PBK was more frequent; in PBK the recipient endothelium is diffusely depleted, so donor cells migrating towards the periphery affect central ECD measurement [30], and ECL is higher and graft survival lower than in FECD [29, 31, 32]. Second, rebubbling was far more frequent; air reinjection has been associated with additional ECL [26, 33] and, in a large registry, with graft failure [34]. Third, partial tissue loss had the largest effect on 6-month ECL in our model, as smaller grafts deliver fewer cells. Our sample size did not allow these effects to be separated from that of the technique, and the difference in absolute 6-month ECD was not significant.

The endothelium-in versus endothelium-out question has received considerable attention since our cohorts were recruited: Parekh et al. showed in the laboratory that endothelium-in grafts unfold faster [12], Busin et al. reported short surgical times with tri-folded pull-through grafts [11], and Price et al. found similar unfolding times, rebubbling and ECL with both orientations in 754 procedures [15], whereas the meta-analysis favoured endothelium-in insertion for ECL [16] and recent preloaded series reported more rebubbling [17] or more graft tears [18] with endothelium-in techniques. Our findings mirror this heterogeneity: unfolding was slightly faster and more predictable with endothelium-in grafts, consistent with the laboratory data and the narrower range of unfolding times published for endothelium-in grafts (0.8–17 min) than for scrolls (4–30 min) [11, 12, 21, 35], but ECL beyond the first month, tissue loss and rebubbling were all at or beyond the upper end of the endothelium-in literature. Most endothelium-in surgery now uses eye-bank preloaded tissue [14, 36–38]; the Muraine technique has also been validated for eye-bank pre-stripping without measurable additional cell loss [10], and hydrodissection-based preparation continues to evolve [39]. The dissection plane is the same with both techniques [8, 40], so lower adhesiveness of hydrodissected grafts is unsupported.

Dissection took 12 min longer with the Muraine technique and was already approximately 20 min throughout the learning curve [20], so the additional time is inherent to the technique (mounting on the artificial anterior chamber, hydrodissection and folding) rather than to inexperience. Partial tissue loss in the Muraine group (26%, minimal in 14%) matches the 25% of tears found by Brissette et al. in the laboratory with the Muraine technique, versus none with manual peeling [9], and lies within the 4.7–32.5% reported for manual peeling [6]; it is higher than the 4% of unusable preparations in the original Muraine series [8], the 6.7% of tissues discarded after stripping in a large eye-bank endothelium-in programme [14] and the 6.5% of intraoperative tears with surgeon-prepared tri-folded grafts [18], although those studies did not record small losses compatible with implantation. Losses were absent in our standard group, whose surgeons had performed more than two hundred procedures; the only total tissue loss with the Muraine technique at our centre (1 of 66 grafts, 1.5%) occurred during the learning curve, below the 4% of Muraine et al. [8]. Older donor age was associated with larger tissue losses in the Muraine group but facilitated manual peeling in the standard group [35, 41]. Learning-curve effects are

well documented for surgeons [7, 42] and eye banks [14] and may partly explain the difference between our cohorts.

The most striking difference was the need for rebubbling (45% versus 0%). Reported rebubbling rates range from 3% to 67% with air [8, 22, 23] and from 2% to 24% with SF6 20% [19, 43, 44]; in the original Muraine series it was 28% [8]. Our standard group was entirely tamponated with SF6 20% and had an inferior iridectomy, whereas two thirds of the Muraine group received air alone and two thirds were managed with mydriasis. A fellow-eye comparison [45], a 1-year cohort [44] and a meta-analysis [46] have since confirmed that SF6 20% substantially reduces graft detachment and rebubbling compared with air without increasing ECL, and SF6 also changes the pattern of detachment [47]. In our model, air tamponade carried a 16-fold higher odds of rebubbling, although the Vienna comparison still found more rebubbling with endothelium-in than endothelium-out preloaded tissue [17]. Rebubbling is also partly a matter of surgical culture: the threshold for reinjecting air rather than observing small peripheral detachments varies among surgeons, and rebubbled eyes did not have less residual gas. Because rebubbling carries additional ECL [26, 33] and a risk of graft failure [34], we recommend SF6 20% and a standardised rebubbling policy when adopting an endothelium-in technique. Minimal tissue loss also increased the odds of rebubbling, possibly because peripheral defects let aqueous reach the interface.

Pupillary block occurred only in eyes managed with mydriasis, three of four Muraine cases after SF6, consistent with the early IOP rises described with SF6 [44] and a longer-lasting bubble [48, 49]. DMEK without iridotomy has been reported without pupillary block [50], but our data support routine iridectomy when SF6, no more toxic to the endothelium than air [51], is used.

CMO was the most frequent complication in both groups (11–12%), consistent with the 7.5–13% found with OCT screening [52–54] and independent of tamponade, technique or rebubbling; intensified topical corticosteroids in the first postoperative week may reduce it [55]. No rejection was observed, and the two primary failures in the Muraine group (5%) fell within the 0.2–7.5% reported [8, 22, 23, 27, 43]. Intraoperative anterior chamber haemorrhage exceeded the 0.5–0.7% reported [22, 23], probably reflecting a preference for a hypotonous anterior chamber during unfolding; eyes with a previously complicated phacoemulsification accounted for a disproportionate share of complications, arguing for cautious case selection when starting a new technique.

The main limitation is the non-randomised, two-centre design: technique, surgeon, centre, tamponade, pupillary-block prophylaxis and rebubbling threshold were confounded, and recipients in the Muraine group were older, with more PBK. These differences do not affect the comparison of the primary outcomes. The sample size was modest, follow-up was limited to 6 months, and surgery was performed in 2014–2015, before preloaded tissue and the SF6 and rebubbling evidence summarised above; the cohorts therefore isolate the effect of surgeon-prepared graft orientation from eye-bank loading and could help tissue banks choose their preparation technique for preloaded grafts. Strengths include the prospective design in routine practice and the prospectively defined learning curve.

Conclusion

The Muraine technique for DMEK provided visual outcomes and 1-month endothelial survival equivalent to those of the standard technique, with 100% graft implantation, at the cost of a somewhat longer dissection and partial tissue loss. Endothelial cell loss continued to increase up to 6 months and rebubbling was required in almost half of the eyes, findings associated with air-only tamponade, bullous keratopathy and tissue loss rather than with graft orientation and preparation per se. Endothelium-in techniques should be combined with SF6 20% tamponade, a peripheral iridectomy and a standardised rebubbling policy; larger, preferably randomised, cohorts with longer follow-up are needed to establish whether graft orientation itself influences long-term endothelial survival.

Declarations

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Competing interests The authors declare no competing interests relevant to this work.

Ethics approval The study protocol was approved by the Clinical Research Ethics Committee (CEIC) of Hospital Universitari MútuaTerrassa and registered at ClinicalTrials.gov (NCT02470793). The study was performed in accordance with the ethical standards of the 2013 Declaration of Helsinki.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Data availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Author contributions Conceptualisation and study design: EPS, OG, JGA. Surgery: OG, JLG (standard technique), AS, IS (Muraine technique). Data collection: EPS, AS, IS, JLG, OG. Statistical analysis: EPS. Supervision: OG, JGA. Writing – original draft: EPS. Writing – review and editing: all authors. All authors read and approved the final manuscript.

Artificial intelligence A large language model (Claude, Anthropic) was used to assist with journal format, and language and figure editing. All AI-assisted content was reviewed, verified against source data, and approved by the authors, who take full responsibility for the manuscript's accuracy.

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Figures

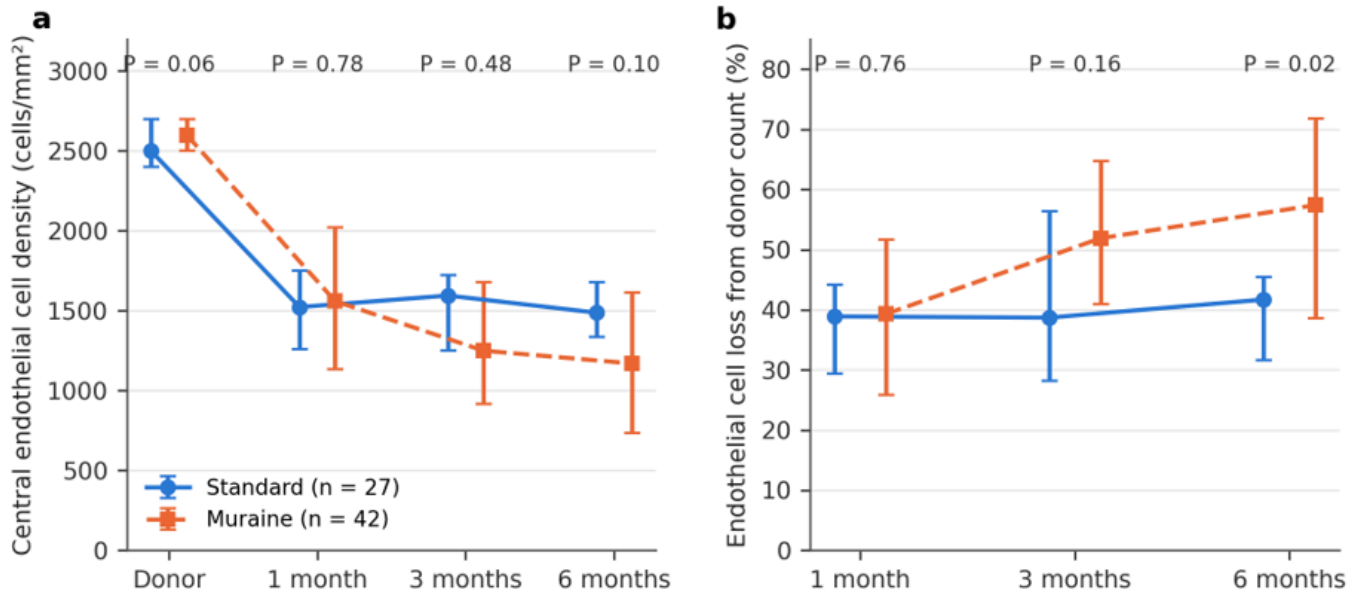


Fig. 1

Figure 1

Central endothelial cell density (a) and endothelial cell loss relative to the donor count (b) in the standard (n = 27) and Muraine (n = 42) groups. Points are medians and bars the interquartile range; P values from the Wilcoxon rank-sum test. Cell loss was equivalent at 1 month and then stabilised in the standard group but continued to increase in the Muraine group

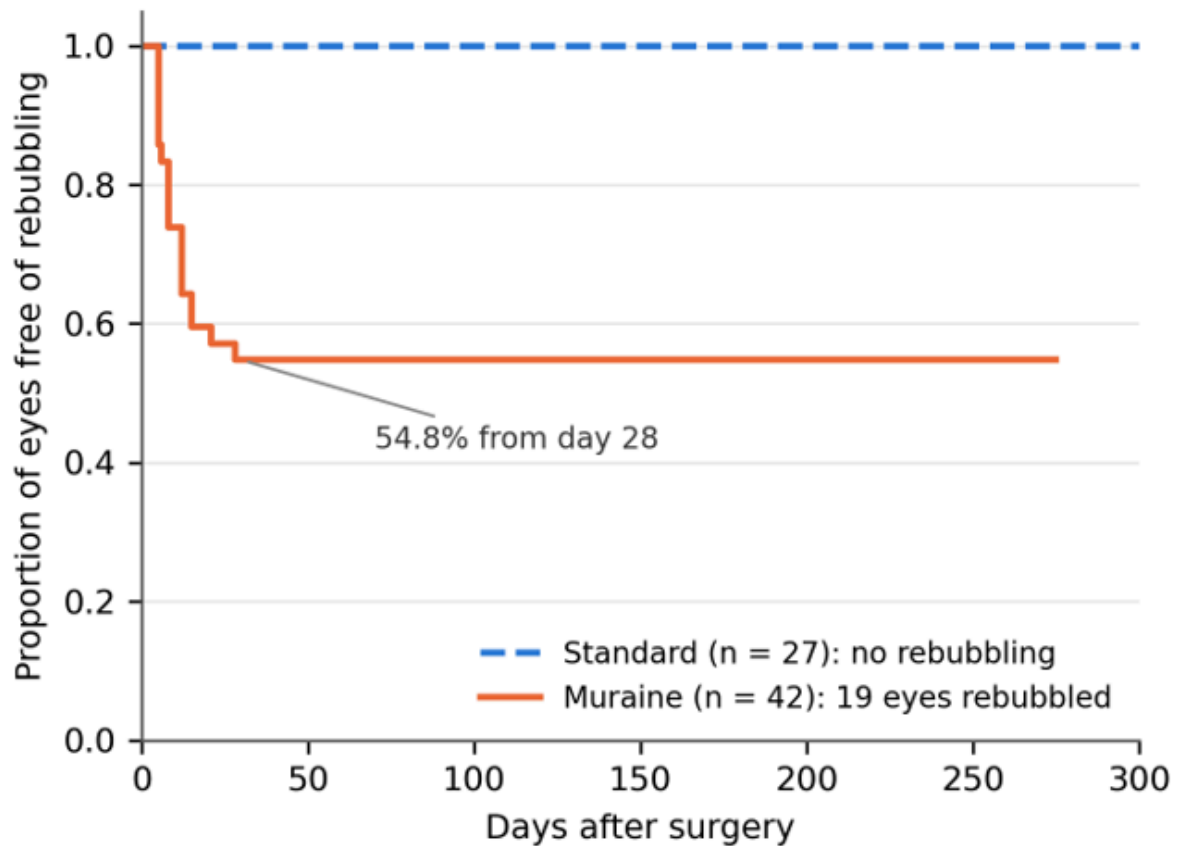


Fig. 2

Figure 2

Kaplan–Meier estimate of the time free of rebubbling. No eye in the standard group required rebubbling, whereas 19 of 42 eyes (45.2%) in the Muraine group did, all within the first 30 days (median follow-up 190 days)

Supplementary Files

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