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Iso-osmolar 5% mannitol for post-cataract corneal edema: efficacy and tolerability

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ABSTRACT

Aims: To compare the efficacy and tolerability of topical iso-osmolar 5% mannitol with 10% mannitol and 5% sodium chloride (NaCl) for post-phacoemulsification corneal edema.

Methods: This prospective controlled study enrolled 81 patients with corneal edema after uncomplicated phacoemulsification. Patients received one of the three agents or control three times daily for 30 days. Central corneal thickness (CCT) was measured by Scheimpflug topography on postoperative days 5, 10, and 30. Day-30 tolerability was assessed on a 10-point Visual Analog Scale. Repeated-measures analysis of variance (ANOVA) and linear mixed-effects models (LMEMs) were used.

Results: CCT decreased significantly in all groups ($p<0.001$). ANOVA showed no overall treatment effect ($p=0.731$) or treatment×time interaction ($p=0.275$). In the LMEM, 5% mannitol was associated with lower postoperative CCT than control [$\beta=-5.83$ micrometers (μm); $p=0.001$] and 5% NaCl ($\beta=-4.15$ μm; $p=0.017$), but did not differ significantly from 10% mannitol ($p=0.463$). Comfort scores were higher with 5% mannitol than with 10% mannitol and 5% NaCl but did not differ significantly from control ($p=0.234$). Preoperative CCT predicted postoperative CCT ($\beta=0.94$; $p<0.001$); age and gender did not.

Conclusion: Iso-osmolar 5% mannitol was associated with lower postoperative CCT than control and 5% NaCl and greater comfort than the hyperosmotic comparators. However, nonsignificant overall treatment and interaction effects and no difference from 10% mannitol preclude superiority claims. Confirmation in larger studies including baseline endothelial cell density is required.

Keywords: Corneal edema, mannitol, sodium chloride, phacoemulsification, corneal pachymetry

INTRODUCTION

Rapid visual recovery following cataract surgery depends not only on surgical precision but also on the cornea's ability to quickly restore transparency. Corneal edema-most often related to endothelial stress and acoustic cavitation during phacoemulsification-is a common, usually self-limited complication.[1,2] While free radical development during surgery contributes to cellular injury,[3] the magnitude of this intraoperative endothelial insult is also modulated by surgical variables such as the ophthalmic viscosurgical device (OVD) employed; with contemporary dispersive agents, mean endothelial cell loss at one postoperative month remains in the range of 12-15%, without significant differences between formulations.[4] The resulting edema typically peaks within the first few days and subsides over 1-2 weeks.[5-7] However, the critical therapeutic window remains the first postoperative week, particularly in eyes with compromised endothelial function, where persistent swelling can delay visual rehabilitation.[8]

Traditionally, clinicians manage postoperative corneal edema with hyperosmotic topical agents such as 5% sodium chloride (NaCl; osmolality ~1700-1800 mOsm/kg) or 10% mannitol (~550 mOsm/kg).[5,9-11] These solutions aim to reduce stromal hydration by establishing a strong transepithelial osmotic gradient. However, such supraphysiologic osmolality has been associated with significant ocular surface discomfort, epithelial stress and pro-inflammatory signaling.[12,13] The literature suggests that hyperosmolar exposure can trigger a pro-inflammatory response [including cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α and IL-1β] and induce morphological changes in the corneal epithelium, which may inadvertently hinder the physiological recovery process and limit patient adherence.[13-16]

These clinical and tolerability challenges have prompted interest in the potential of iso-osmolar 5% mannitol (osmolality ~300 mOsm/kg). Unlike traditional agents that rely primarily on a dehydration-driven gradient, 5% mannitol

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operates at near-physiologic osmolality. Beyond its osmotic properties, mannitol is a known hydroxyl radical scavenger that may exert antioxidant, anti-fibrotic and membrane-stabilizing effects.[17-19] Experimental and clinical models have suggested that mannitol can protect the endothelium from free-radical damage and support epithelial wound healing through specific signaling pathways.[20,21]

The primary aim of this study was to investigate whether clinical corneal recovery can be effectively managed-and potentially accelerated-by leveraging the proposed non-osmotic, cytoprotective properties of 5% mannitol. By comparing it with 10% mannitol and 5% NaCl using advanced statistical modeling, we sought to determine whether maintaining an iso-osmolar environment offers a favorable balance between CCT reduction and treatment tolerability.

METHODS

Ethics

This prospective, single-center trial adhered to the tenets of the Declaration of Helsinki (1975, revised in 2000) and was approved by the Van Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 29.11.2024, Decision No: 60KAEK-2024-070). All participants provided written informed consent prior to inclusion.

Study Population

This study included 81 eyes of 81 patients who underwent phacoemulsification surgery. The inclusion criterion was the development of corneal edema following uncomplicated phacoemulsification. Patients were systematically assigned to one of four groups:

- 5% mannitol [prepared by 1:1 dilution of 10% mannitol (Terso; DMG, İstanbul, Turkiye) with sterile distilled water], administered three times daily (n=20). The diluted 5% mannitol was compounded by hospital pharmacy personnel under a sterile laminar-flow hood. The diluted formulation was stored at room temperature, with the bottle tightly closed and protected from heat sources, following the storage conditions specified for the commercial Terso product. Each prepared bottle was used for no longer than the 30-day study treatment period and was discarded at treatment completion.
- 10% mannitol (Terso; DMG, İstanbul, Turkiye), administered three times daily (n=21).
- 5% NaCl (Coredem; Deva Holding, İstanbul, Turkiye), administered three times daily (n=20).
- **Control:** Standard treatment consisting of topical antibiotics and steroids administered three times daily without any osmotic agent (n=20).

The treatments were administered for four weeks. Patients with preexisting corneal pathologies (e.g., corneal dystrophies or glaucoma) or a history of intraocular surgery were excluded. Additionally, individuals who experienced intraoperative or postoperative complications-such as Descemet membrane detachment, posterior capsule rupture, postoperative intraocular pressure elevation, toxic anterior segment syndrome, hypotony or wound leakage-were not included.

Surgical Technique

All surgeries were performed by a single experienced surgeon using the Stellaris Vision Enhancement System (Bausch & Lomb, Rochester, NY, USA). Procedures were standardized under topical anesthesia (0.5% proparacaine) and intracameral 1% lidocaine. A uniform superior clear-corneal main incision and two limbal paracenteses were used. Sodium hyaluronate (1.6 mg/ml) served as the OVD. Standard institutional preset parameters for vacuum, ultrasound and aspiration were maintained across all cases. Techniques included hydrodissection and hydrodelamination followed by nucleus emulsification.

Outcomes and Assessments

Treatment began on postoperative day 1 and continued for 30 days. The 30-day window was chosen to (i) capture the critical early recovery phase (days 1-10), when between-group differences are most likely; (ii) monitor the slower resolution observed in approximately 15-20% of cases;[8,22] and (iii) provide a uniform endpoint beyond the typical 2-week resolution to verify sustained normalization and safety.

- **Primary outcome:** The change in CCT from baseline to postoperative days 5, 10 and 30, measured with the Sirius Scheimpflug-Placido topographer (CSO, Florence, Italy).
- **Secondary outcome (treatment tolerability):** To assess the parallel impact of treatment on patient comfort, a VAS was used at postoperative day 30. Patients quantified their overall ocular comfort (considering stinging, burning or foreign body sensation) on a 10-point scale, where 0 indicated severe discomfort and 10 indicated complete comfort. To ensure objective data collection and minimize bias, the VAS assessment was performed by independent ophthalmology residents who were not members of the surgical team, had no involvement in treatment assignments and were not among the authors of this study. These evaluators remained completely masked to the study groups throughout the assessment period.
- **Other assessments:** Best-corrected visual acuity and intraocular pressure were also recorded.

Data Collection

The primary outcome of the study was the reduction in CCT over time, with the aim of identifying the treatment regimen that facilitated the most rapid resolution of corneal edema. Preoperative specular microscopy was not available; therefore, baseline endothelial cell density (ECD) was not captured.

Statistical Analysis

All data analyses (descriptive statistics, repeated-measures analysis of variance (ANOVA) and Bonferroni-corrected post-hoc tests) were conducted using JASP (version 0.19.1; JASP Team, University of Amsterdam, Amsterdam, The Netherlands). In addition, the LMEM was implemented in both Python (Statsmodels library, version 0.13.5; Python Software Foundation, Beaverton, OR, USA) and JASP to validate the robustness of the results across platforms. Post-hoc analyses were adjusted for preoperative CCT to account for baseline differences, providing conditional comparisons. Bonferroni correction was applied to control for multiple comparisons, and p-values less than 0.05 were considered statistically significant.

RESULTS

A total of 81 patients (81 eyes; mean age: 65.9±8.1 years; 44 males and 37 females) were evaluated across four treatment

groups: 5% mannitol (20 eyes), 10% mannitol (21 eyes), 5% NaCl (20 eyes) and control (20 eyes). CCT was measured on postoperative days 5, 10 and 30. Gender distribution did not differ significantly among the groups (p=0.890, Chi-square test). Age and preoperative CCT also did not differ significantly among groups (p>0.05, ANOVA). Visual acuity and intraocular pressure were recorded preoperatively and postoperatively, with no significant between-group differences (Table 1).

Table 1. Baseline demographic and preoperative characteristics of the study groups

Parameter	5% mannitol (n=20)	10% mannitol (n=21)	5% NaCl (n=20)	Control (n=20)	p-value
Age (years)	64.15±8.2	67.62±8.9	64.40±7.5	67.48±7.4	0.34¥
Gender (M/F)	10/10	12/9	10/10	12/9	0.90*
Preoperative CCT (µm)	533.35±22.3	537.43±36.3	537.15±36.0	540.38±26.9	0.82¥

Values are presented as mean±standard deviation unless otherwise stated. ¥One-way analysis of variance; *Chi-square test. Statistical significance was set at p<0.05. NaCl: Sodium chloride, M: Male, F: Female, CCT: Central corneal thickness, µm: Micrometers

Mixed-Effects Model: JASP Versus Python Comparison

A LMEM was applied via both JASP and Python to assess the effects of treatment and time on postoperative CCT. This analysis aimed to evaluate the consistency of findings across different statistical software programs and to ensure the reliability of the results.[22,23]

Preoperative CCT was identified as a strong and statistically significant predictor of postoperative CCT in both models. In the JASP analysis, the estimated effect of preoperative CCT was β=0.94±0.022 (p<0.001), whereas in Python the estimate was β=0.92±0.027 (p<0.001). These findings indicate that greater preoperative corneal thickness is associated with higher postoperative CCT values. The close agreement between both models underscores the robustness of this effect and highlights the critical role of preoperative CCT as a key determinant of postoperative corneal recovery.

The effect of postoperative time on CCT reduction was statistically significant in both models. In JASP, the mean difference in CCT between day 10 and day 5 was -14.528±0.683 micrometers (µm) (p<0.001), whereas the difference between day 30 and day 5 was -4.569±0.683 µm (p<0.001). In Python, the estimated mean difference in CCT between day 10 and day 5 was -18.33±1.447 µm (p<0.001), and between day 30 and day 5 it was -23.46±1.447 µm (p<0.001). Although both models confirmed a statistically significant reduction in CCT over time, Python's estimates suggested a greater decrease in CCT between days 10 and 30, whereas JASP's model indicated that CCT stabilized after day 10.

Treatment coefficient estimates differed slightly between the two models. In JASP, the 5% mannitol group had the largest numerical CCT estimate attributable to treatment (48.287±12.567 µm), followed by the 10% mannitol, 5% NaCl and control groups. In Python, with control as the reference, both mannitol concentrations were associated with lower postoperative CCT: 5% mannitol (β=-5.83 µm; p=0.001) and 10% mannitol (β=-4.55 µm; p=0.007). The 5% NaCl coefficient did not differ significantly from control (β=-1.68 µm; p=0.332).

Pairwise LMEM comparisons showed no statistically significant difference between 5% and 10% mannitol (β=-1.27 µm; p=0.463). The 5% mannitol group had lower postoperative CCT than the 5% NaCl group (β=-4.15 µm; p=0.017), whereas the 10% mannitol versus 5% NaCl comparison did not reach statistical significance (β=-2.88 µm; p=0.097). Thus, the LMEM indicates a modest association between 5% mannitol and lower postoperative CCT, but does not establish superiority, particularly in view of the nonsignificant overall treatment and treatment×time effects in the repeated-measures ANOVA.

Neither model identified age as a significant predictor of postoperative CCT. The p-value for age was 0.824 for JASP and 0.935 for Python, indicating that age does not significantly influence corneal thickness recovery. Gender showed a borderline effect in Python (p=0.075), suggesting a possible trend toward lower postoperative CCT values in males, although this finding was not statistically significant.

Overall, the findings from both JASP and Python confirm that preoperative CCT and postoperative time significantly influence corneal thickness recovery. While the general trends in treatment effectiveness were consistent, Python's model suggested a greater reduction in CCT over time, whereas JASP indicated a stabilization effect after day 10 (Figure 1).

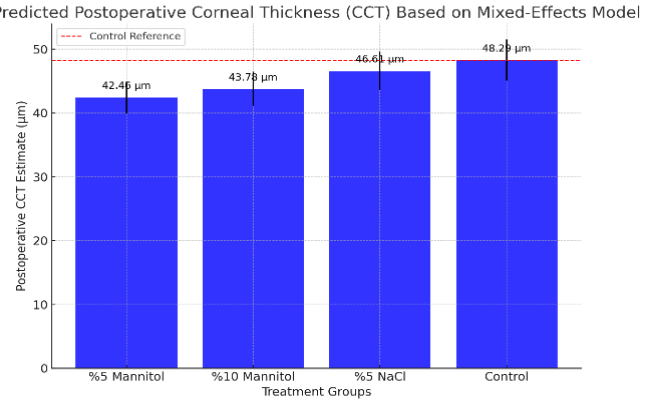

Figure 1. Postoperative CCT values according to the mixed-effects model estimates

CCT: Central corneal thickness; NaCl: Sodium chloride

Minor numeric discrepancies between JASP and Python primarily reflect implementation choices (e.g., optimizer algorithms, scaling methods and covariance structure specification) and differences in the coding of time contrasts. Both implementations yielded directionally consistent time effects and a similar numerical ranking of treatment estimates, with 5% mannitol showing the largest estimated reduction. This numerical ranking should not be interpreted as evidence of superiority.

Repeated-Measures ANOVA

Repeated-measures ANOVA revealed no significant difference between the treatment groups [F (3; 77)=0.432; p=0.731]. A significant reduction in corneal thickness was observed over time, particularly between day 5 and subsequent time points (p<0.001). The interaction effect between treatment and time

was not significant [F (3.25; 83.43)=1.314; p=0.275], indicating a similar recovery pattern across all groups.

Bonferroni-corrected post-hoc comparisons (time effect) were as follows. Day 5 vs. day 10; the mean difference in CCT was 19.117 µm (p<0.001), indicating a significant reduction in corneal thickness across all treatment groups during this period. Day 5 vs. day 30: the mean difference was 28.023 µm (p<0.001), indicating a further significant reduction in CCT by day 30. Day 10 vs. day 30; the mean CCT difference was 8.906 µm (p=0.077), suggesting that corneal thickness stabilized between these time points (Table 2). Between days 10 and 30, the overall recovery pattern remained consistent across all treatment groups, with no significant differences observed, indicating a plateau in corneal recovery after day 10 (Table 3, Figure 2).

Table 2. Estimated marginal means of postoperative CCT (µm) by treatment group and time point, derived from the linear mixed-effects model

Group	Postoperative day 5	Postoperative day 10	Postoperative day 30
5% mannitol	563.1 (SE=1.95)	542.6 (SE=0.67)	537.46 (SE=7.8)
10% mannitol	564.9 (SE=1.89)	543.6 (SE=0.65)	537.48 (SE=7.6)
5% NaCl	564.8 (SE=1.94)	545.6 (SE=0.67)	544.61 (SE=7.8)
Control	566.5 (SE=1.90)	551.0 (SE=0.66)	527.63 (SE=7.6)

All values are expressed in micrometers (µm). CCT: Central corneal thickness, NaCl: Sodium chloride, SE: Standard error

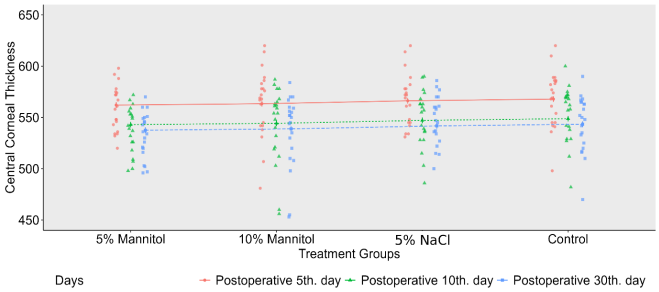

Figure 2. Changes in central corneal thickness across postoperative time points

NaCl: Sodium chloride

Patient Tolerability: VAS Comfort Scores

Parallel to the clinical recovery data, treatment tolerability was assessed at day 30 via a 10-point VAS. Significant differences in ocular comfort were observed between the groups (p<0.001, ANOVA).

- **5% mannitol vs. comparators:** The 5% mannitol group reported significantly higher comfort scores (7.13±0.79) than the 10% mannitol group (6.44±0.81; p=0.008) and the 5% NaCl group (5.78±1.07; p<0.001).
- **5% mannitol vs. control:** The comfort score in the 5% mannitol group (7.13±0.79) was not significantly different from that in the control group (6.85±0.70; p=0.234).
- **NaCl group:** The 5% NaCl group exhibited the lowest comfort scores among all groups, reflecting the irritation typically associated with high-osmolarity topical agents.

DISCUSSION

This study provides new evidence regarding the efficacy of three topical agents-5% mannitol, 10% mannitol, and 5% NaCl-in the treatment of corneal edema following phacoemulsification. The 5% mannitol group showed the greatest numerical reduction in central corneal thickness (CCT) during the early postoperative period, and the linear mixed-effects model (LMEM) estimated lower postoperative CCT values in this group than in the control and 5% NaCl groups. However, repeated-measures ANOVA showed no significant overall treatment effect or treatment×time interaction, and the LMEM analysis revealed no significant difference between 5% and 10% mannitol. Accordingly, the findings regarding the rate of corneal edema resolution should be interpreted as suggestive of a possible clinical effect rather than as evidence of unequivocal superiority of 5% mannitol.

The association between 5% mannitol and lower postoperative CCT despite its lower osmotic strength suggests that mechanisms beyond dehydration may contribute to this effect. Mannitol is a hydroxyl radical scavenger and can attenuate oxidative stress-related lipid peroxidation and cell

Table 3. Bonferroni-corrected pairwise comparisons of central corneal thickness between treatment groups at each postoperative time point

Time point	Group 1	Group 2	Mean difference (µm)	95% CI (lower-upper)	SE	pBonf	Significance
Postoperative day 5	5% mannitol	10% mannitol	-1.768	-9.126 to 5.590	2.717	1.000	ns
	5% mannitol	5% NaCl	-1.640	-9.112 to 5.832	2.759	1.000	ns
	5% mannitol	Control	-3.362	-10.740 to 4.015	2.724	1.000	ns
	10% mannitol	5% NaCl	0.128	-7.229 to 7.485	2.717	1.000	ns
	10% mannitol	Control	-1.594	-8.858 to 5.669	2.682	1.000	ns
	5% NaCl	Control	-1.722	-9.071 to 5.627	2.714	1.000	ns
Postoperative day 10	5% mannitol	10% mannitol	-1.032	-3.584 to 1.520	0.942	1.000	ns
	5% mannitol	5% NaCl	-3.016	-5.608 to -0.424	0.957	0.014	*
	5% mannitol	Control	-8.419	-10.978 to -5.860	0.945	<0.001	***
	10% mannitol	5% NaCl	-1.984	-4.535 to 0.568	0.942	0.231	ns
	10% mannitol	Control	-7.387	-9.906 to -4.867	0.930	<0.001	***
	5% NaCl	Control	-5.403	-7.952 to -2.854	0.941	<0.001	***
Postoperative day 30	5% mannitol	10% mannitol	-0.007	-29.504 to 29.490	10.892	1.000	ns
	5% mannitol	5% NaCl	-7.150	-37.105 to 22.805	11.061	1.000	ns
	5% mannitol	Control	9.831	-19.742 to 39.404	10.920	1.000	ns
	10% mannitol	5% NaCl	-7.143	-36.634 to 22.348	10.890	1.000	ns
	10% mannitol	Control	9.838	-19.279 to 38.956	10.752	1.000	ns
	5% NaCl	Control	16.981	-12.479 to 46.441	10.878	0.736	ns

*p<0.05, ***p<0.001. CI: Confidence interval, SE: Standard error, pBonf: Bonferroni-corrected p-value, NaCl: Sodium chloride, ns: Not significant

membrane damage. These properties support the possibility that, in addition to its osmotic activity, mannitol may exert antioxidant and cytoprotective effects on the cornea that facilitate edema resolution.[17,18] In experimental corneal models, mannitol-containing viscoelastic formulations have been shown to protect the endothelium against free radical-mediated injury,[20] while preoperative systemic mannitol administration has been associated with reduced endothelial cell loss after cataract surgery.[21] These mechanisms provide a biological rationale for the clinical trend observed in the present study. However, oxidative stress, apoptosis, and endothelial protection were not directly assessed; therefore, this explanation remains hypothesis-generating.

The tolerability findings were consistent with the near-physiological osmolality of 5% mannitol. Comfort scores were significantly higher in the 5% mannitol group than in the 10% mannitol and 5% NaCl groups, whereas no significant difference was observed compared with the control group. Because no non-inferiority margin or corresponding analysis was prespecified, the comparison with the control group indicates only the absence of a statistically significant difference and should not be interpreted as evidence of equivalence or non-inferiority. The better tolerability of 5% mannitol may be related to avoidance of the epithelial stress and stinging associated with hyperosmolar saline preparations.[12-15] Reduced ocular surface irritation may support treatment adherence during early recovery; however, adherence and epithelial integrity were not directly assessed in this study.

In the LMEM analysis, preoperative CCT was identified as a statistically significant predictor of postoperative CCT (β=0.941; $p<0.001$). Eyes with thicker corneas preoperatively had higher postoperative CCT values across all assessed time points. Nevertheless, this association is independent only with respect to the covariates included in the model and does not establish independence from unmeasured baseline ECD.

Baseline pachymetry may therefore provide useful prognostic information regarding postoperative CCT recovery within the scope of the variables measured in this study. However, pachymetry cannot substitute for specular microscopy, and adjustment for preoperative CCT cannot eliminate potential between-group differences in endothelial reserve. The observed association with CCT should therefore be interpreted as prognostic rather than as evidence that the treatment effect is independent of baseline ECD.

Pairwise between-group differences were most pronounced on postoperative day 10 and became less apparent by day 30. This finding suggests that any treatment-related separation may be concentrated in the early postoperative period.[5,6] However, because the treatment×time interaction was not significant, this temporal interpretation remains exploratory.

A strength of this study is the combined use of repeated-measures ANOVA and LMEM, with analyses performed in both JASP and Python.[22] The LMEM accounted for repeated observations and adjusted for measured variability in baseline CCT, an approach well suited to longitudinal ophthalmic data.[23,24] However, baseline ECD was not measured. Adjustment for preoperative CCT therefore cannot statistically eliminate unobserved differences in ECD or establish that the observed between-group differences in CCT represent a true treatment effect independent of endothelial reserve.

This single-center study had a relatively modest sample size and did not include baseline ECD measurements, standardized cataract grading, or case-level records of phacoemulsification energy and duration. Consequently, residual confounding related to baseline endothelial reserve and surgical energy exposure cannot be excluded. An identical dispersive viscoelastic protocol was used in all cases, and comparative evidence indicates similar endothelial cell loss among contemporary dispersive OVDs following uncomplicated phacoemulsification.[4] All procedures were performed by the same surgeon using the same platform, device settings, and incision technique. Participants and assessors were masked, visit windows and imaging protocols were standardized, and the LMEM was adjusted for baseline CCT. Future multicenter studies should prospectively collect specular microscopy data, standardized cataract grades, and case-level phacoemulsification energy and duration records. Dedicated stability studies should also be performed when compounded formulations are evaluated.

Limitations

This single-center study had a relatively modest sample size and did not include baseline ECD measurements, standardized cataract grading, or case-level records of phacoemulsification energy and duration. Consequently, residual confounding related to baseline endothelial reserve and surgical energy exposure cannot be excluded. Although all procedures were performed by a single surgeon using the same platform, preset parameters, incision technique, and dispersive viscosurgical protocol, these measures do not replace direct assessment of baseline ECD. Participants and outcome assessors were masked, visit windows and image acquisition were standardized, and the LMEM adjusted for baseline CCT; however, adjustment for CCT cannot eliminate unmeasured differences in endothelial reserve. The diluted 5% mannitol was compounded by the hospital pharmacy under a sterile laminar-flow hood and handled according to the commercial Terso instructions, but its stability after dilution was not independently tested. The findings should therefore be confirmed in larger multicenter studies incorporating baseline specular microscopy, standardized cataract grading, case-level phacoemulsification parameters, and dedicated stability testing of compounded formulations.

CONCLUSION

Iso-osmolar 5% mannitol was associated with lower postoperative CCT than the control and 5% NaCl groups in the LMEM, as well as higher comfort scores than the two hyperosmotic comparators. Nevertheless, repeated-measures ANOVA showed no significant overall treatment effect or treatment×time interaction, and the LMEM analysis revealed no significant difference between 5% and 10% mannitol. Preoperative CCT was identified as a significant prognostic covariate within the measured model. Larger studies incorporating baseline specular microscopy measurements are needed to confirm these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Van Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 29.11.2024, Decision No: 60KAEK-2024-070).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: ÖBT, YE; Design: ÖBT, YE; Control: ÖBT, YE; Resources: ÖBT, YE; Materials: ÖBT, YE; Data Collection and/or Processing: ÖBT, YE; Analysis and/or Interpretation: ÖBT, YE; Literature Review: ÖBT, YE; Writing the Article: ÖBT, YE; Critical Review: ÖBT, YE.

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