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Item type

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Effect of Intravenous Mannitol on Intraocular Pressure Changes in Vitrectomized and Non-Vitrectomized Eyes: A Systematic Review and Meta-Analysis



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- **PURPOSE:** Intraocular pressure (IOP) control is paramount during ophthalmic surgeries to ensure successful outcomes and prevent complications. Intravenous mannitol has been explored for its ability to manage IOP fluctuations in both vitrectomized and non-vitrectomized eyes. This meta-analysis aimed to assess the efficacy of mannitol in controlling IOP across these patient groups.
- **DESIGN:** Systematic review and meta-analysis.
- **METHODS:** A literature search was conducted across PubMed, EMBASE, Scopus, and Web of Science from inception up to March 1, 2024, focusing on studies investigating mannitol's impact on IOP in vitrectomized and non-vitrectomized eyes. Randomized controlled trials, cohort studies, and case-control studies were included, while case reports and review articles were excluded. The primary outcome was the change in IOP following mannitol administration. Meta-analysis was per-

formed using a random-effects model. R software (V 4.3) was used for statistical analysis.

- **RESULTS:** Our search included five studies of both vitrectomized (145 eyes) and non-vitrectomized eyes (91 eyes). The meta-analysis demonstrated significant IOP reductions following mannitol administration across multiple time points. Three studies were included at 30 min and 2 studies at all other time points in the analysis. In vitrectomized eyes, notable decreases were observed: at 30 min, the Ratio of Means (ROM) was 0.81 (95% CI: 0.53; 1.24), indicating a 19% reduction; at 60 min, the ROM of 0.833 (95% CI: 0.77; 0.89) showed a 16.7% reduction; at 90 min, the ROM of 0.757 (95% CI: 0.755; 0.758) corresponded to a 24.3% reduction; at 2 h, the ROM of 0.726 (95% CI: 0.642; 0.820) reflected a 27.4% reduction; at 3 h, the ROM of 0.692 (95% CI: 0.600; 0.797) resulted in a 30.8% reduction; and at 4 h, the ROM of 0.700 (95% CI: 0.363; 1.350) indicated a 30% reduction. No significant changes were observed on IOP with mannitol administration when comparing vitrectomized versus non-vitrectomized eyes.

- **CONCLUSION:** Intravenous mannitol effectively reduces IOP in both vitrectomized and non-vitrectomized eyes, demonstrating its utility in the acute management of elevated IOP during and after ophthalmic surgeries. These findings support the integration of mannitol into perioperative care protocols. However, further research, particularly randomized controlled trials and studies with broader demographic representation, is needed to optimize mannitol's usage and fully understand its long-term safety and efficacy. (Am J Ophthalmol 2024;268: 45–53. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>))

Supplemental Material available at AJO.com.
Accepted for publication July 15, 2024.

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INTRODUCTION

THE MAINTENANCE OF INTRAOCULAR PRESSURE (IOP) is crucial for ocular health, serving as an essential marker in diagnosing and managing various eye con-

ditions.^{1,2} Vitrectomy, which involves the removal of the vitreous humor to treat eye disorders, can induce IOP changes that impact postoperative recovery.³⁻⁵ Against this backdrop, intravenous mannitol, an osmotic diuretic, has been explored as a method to control IOP fluctuations during and after ophthalmic procedures.⁶ Despite its widespread use, debates continue regarding its effectiveness and safety, particularly in differentiating between vitrectomized and non-vitrectomized eyes.

Mannitol operates by increasing plasma osmolality, facilitating the transfer of water from the vitreous body into the bloodstream, thereby causing vitreous dehydration and reducing IOP.⁶⁻⁸ Its action not only involves physical osmotic effects but also encompasses central mechanisms through osmoreceptors in the hypothalamus, which contribute to decreased aqueous humor production.⁶⁻⁸ Studies have highlighted mannitol's capability to lower IOP equivalently in both vitrectomized and non-vitrectomized eyes.⁹ In non-vitrectomized eyes, specifically, mannitol has been observed to decrease vitreous cavity depth (VCD) and increase anterior chamber depth (ACD), reinforcing the premise that vitreous dehydration is a key mechanism in IOP reduction.⁹ Beyond its ophthalmic applications, mannitol's osmotic properties are leveraged in various medical fields to alleviate intracranial pressure and manage renal failure.¹⁰⁻¹² Within ophthalmology, mannitol's capacity to establish an osmotic gradient across the blood-ocular barrier, prompting fluid egress from the eye, makes it an attractive option for IOP management.¹⁰ This is particularly relevant in surgical contexts, where maintaining IOP within optimal ranges is imperative to avert complications like retinal detachment, hemorrhage, and optic nerve damage. Proactively administering mannitol intravenously before or during eye surgeries is a strategic approach to mitigate these risks, potentially improving patient outcomes and recovery.¹³

The efficacy of mannitol in modulating IOP may be influenced by the structural and physiological changes post-vitrectomy. The removal of the vitreous body, coupled with the potential introduction of tamponade agents or gas bubbles, alters the eye's internal dynamics, possibly impacting the drug's effectiveness.¹⁴ Many studies have evaluated the effect of mannitol on IOP reductions. However, no systematic review has been performed to date to evaluate this.¹⁵⁻¹⁷

This systematic review and meta-analysis sought to elucidate the effect of intravenous mannitol on IOP changes in both vitrectomized and non-vitrectomized eyes. Through comprehensive data collection and analysis from various studies, our objective is to provide a detailed evaluation of mannitol's efficacy across different ocular conditions and surgical interventions.

METHODS

The methodology for this systematic review and meta-analysis adhered to the Preferred Reporting Items for Sys-

tematic Reviews and Meta-Analyses (PRISMA) guidelines, as outlined in Table S1,¹⁸ and was duly registered with PROSPERO: CRD42024511865. For the screening and data extraction processes, the Nested-Knowledge web software (Nested-Knowledge, MN, USA) was employed. An Institutional Review Board is not required for this study since it is a systematic review based on published data.

- **SELECTION CRITERIA:** The population of interest comprised adult patients undergoing ophthalmic surgery, focusing on subgroups of vitrectomized and non-vitrectomized eyes. Studies were eligible if they involved administering mannitol in any dosage. The primary outcome assessed was the IOP change following mannitol administration. Our analysis included randomized controlled trials (RCTs), cohort studies, and case-control studies. No restriction was kept on the follow-up duration after mannitol administration. Exclusion criteria encompassed case reports, editorials, review articles, and studies that did not report on the specified outcomes or involve the administration of intravenous mannitol.

- **LITERATURE SEARCH:** A systematic search was conducted from inception across PubMed, EMBASE, Scopus, and Web of Science databases on February 5, 2024, and re-run on March 1, 2024. The search strategy combined terms related to "mannitol," "intraocular pressure," and "vitrectomy" using Boolean operators. The search was not limited by language or publication type, ensuring comprehensive coverage of relevant literature. No filters were applied in any database search. The search strategy is given in Table S2.

- **SCREENING:** Two independent reviewers (BKP, MNK) screened titles and abstracts for eligibility based on pre-defined inclusion criteria. Full texts of potentially eligible studies were then retrieved and assessed in detail for relevance. Nested knowledge software facilitated the screening process. Differences in opinion among reviewers were settled through discussion with a third reviewer (HAS) for a final decision.

- **DATA EXTRACTION AND QUALITY ASSESSMENT:** For each study included in the review, information was extracted on study design, sample size, participant characteristics, intervention details, outcome measures, and findings. Data extraction was carried out independently by two reviewers (BKP, MNK), with any discrepancies resolved by consensus or by involving a third reviewer (HAS), if needed. The "tagging" function of the nested knowledge software was utilized for efficient data extraction.

The risk of bias was assessed by ROBINS-I tool.^{19,20} Studies were accordingly adjudged to have a low, moderate, high, or critical risk of bias.

- **STATISTICAL ANALYSIS:** A meta-analysis was conducted to aggregate the results of IOP change from baseline after treatment. The analysis used forest plots to represent the findings graphically, showcasing individual study results and the overall combined estimate. The means and standard deviations (SDs) of IOP changes from baseline at various time points post-treatment were compiled for analysis to calculate the Ratio of means (ROM). A random-effects model was implemented to synthesize the data, premised on the notion that the study-specific effect sizes could vary and adhere to a distinct distribution.²¹ The analysis method was inverse variance. Statistical heterogeneity among the included studies was assessed using the I^2 statistic and the Chi-square test.^{22,23} The I^2 statistic quantifies the percentage of total variance across studies due to heterogeneity rather than chance, with elevated values indicating greater heterogeneity.^{24,25} The I^2 statistic is interpreted with thresholds indicating low (25%-49%), moderate (50%-74%), and high (75% and above) heterogeneity.^{26,27} A significance threshold was established at a P -value of less than .05. All statistical procedures utilized the R software, version 4.3.²⁸

RESULTS

- **LITERATURE SEARCH:** The literature search of various databases resulted in 1458 records being initially identified. Before detailed screening, 443 duplicate records were recognized and subsequently removed. This action reduced the number of records to be screened to 1015. During the title and abstract screening process, 982 records were excluded as they did not align with the specified inclusion criteria. The next phase involved a closer examination of the remaining 33 records, for which full texts were retrieved and assessed for eligibility. Out of these, 28 records were further excluded due to reasons such as case reports or not focusing on the outcomes of interest. Ultimately, the stringent selection process culminated in including 5 studies that satisfied all the criteria for the systematic review and meta-analysis^{9,15,16,29,30} (Figure 1).

- **CHARACTERISTICS OF INCLUDED STUDIES:** The characteristics of the studies are presented in Table 1. Three out of the five studies were conducted in India,^{9,15,16} one in China,²⁹ and one in Pakistan.³⁰ Four studies were prospective comparative studies,^{9,15,16,30} while only one study was a retrospective case-control study.²⁹ All studies administered 20% mannitol. Three studies included both vitrectomized and non-vitrectomized patients, while two studies only evaluated vitrectomized eyes. All studies reported a beneficial effect of mannitol for reducing IOP. The quality assessment of the studies is given in Table S3.

Ramachandra et al.¹⁵ conducted a prospective comparative study (30 samples) in India on patients with

post-vitrectomy elevated IOP (≥ 40 mm Hg) and open-angle glaucoma, using 20% mannitol IV at a dosage of 1 g/kg body weight over 30 min, and found that mannitol significantly reduces IOP in both vitrectomized and non-vitrectomized eyes. Takkar et al.¹⁶ offered a retrospective study, also in India, focusing on 31 post-vitreoretinal surgery patients treated for raised IOP, and observed that mannitol is useful for short-term IOP reduction in vitrectomized eyes, with effects that are sustained, higher, and independent of baseline IOP. Sahu et al.⁹ prospective comparative study involved phakic eyes of 25 patients with IOP ≥ 40 mm Hg and open angles, concluding that mannitol significantly reduced IOP in both groups. Feng et al.²⁹ from China conducted a retrospective case-control study on 24 patients who underwent pars plana vitrectomy (PPV) for ocular hypertension, noting that mannitol was effective for short-term IOP reduction post-vitrectomy. Ahmad et al. from Pakistan,³⁰ a prospective comparative study on patients with open angles and IOP lower than 38 mm Hg, demonstrated that mannitol dramatically lowered IOP in 36 vitrectomized eyes with silicon fillings and 36 non-vitrectomized eyes. These studies collectively demonstrate the efficacy of mannitol in managing IOP.

- **META-ANALYSIS:** We performed a meta-analysis for the effect of mannitol on vitrectomized eyes by comparing baseline and after the treatment IOP at each time point (Figure 2). The analysis included multiple time points: 30 min, 60 min, 90 min, 75 min, 2 h, 3 h, and 4 h post-treatment. Three studies were included for the 30-minute time point, and two studies were included for each of the following time points: 60 min, 75 min, 90 min, 2 h, 3 h, and 4 h in the analysis.

At 30 min, the ROM in IOP reduction was 0.81 (95% CI: 0.53; 1.24), indicating a 19% reduction from baseline. At the 60-minute mark, the ROM was 0.833 (95% CI: 0.77; 0.89), showing a substantial reduction of approximately 16.7%. At the 75-minute time point from the study by Feng, 2019, the ROM was 0.698 (95% CI: 0.667; 0.730), which translates to a 30.2% reduction. This trend continued at 90 min with a ROM of 0.757 (95% CI: 0.755; 0.758), corresponding to a 24.3% reduction in IOP. The effect remained sustained at 2 h, with an ROM of 0.726 (95% CI: 0.642; 0.820), indicating a 27.4% reduction, and at 3 h, the ROM was 0.692 (95% CI: 0.600; 0.797), reflecting a 30.8% reduction. At 4 h, the ROM was 0.700 (95% CI: 0.363; 1.350), corresponding to a 30% reduction in IOP. The meta-analysis demonstrates that mannitol effectively reduces IOP in vitrectomized eyes at various time points post-treatment. The reductions were statistically significant for most of the measured time points, and the magnitude of the effect varied.

We compared the effect of mannitol on vitrectomized versus non-vitrectomized eyes. At 30 min, the ROM in IOP reduction was 1.006 (95% CI: 0.950; 1.065). At 60 min, the ROM was 1.014 (95% CI: 0.951; 1.082, still not sta-

TABLE 1. Characteristics of Included Studies.

| Study | Country | Study Design | Type of Participants | Type of Intervention | Participants in the Vitrectomized Group | Participants in non-Vitrectomized Group | Mean Age in Years | Key Results |
|----------------------------------|----------|----------------------------------|--|---|---|---|--|---|
| Ramachandra (2019) ¹⁵ | India | Prospective comparative study | Patients with post-vitrectomy elevated IOP (≥ 40 mm Hg) and open-angle glaucoma | 20% mannitol IV at a dosage of 1 g/kg body weight over 30 min | 30 | 30 | Vitrectomized = 48.5, non-Vitrectomized = 54 | Mannitol reduces IOP significantly in both vitrectomized and nonvitrectomized eyes. |
| Takkar (2017) ¹⁶ | India | Prospective comparative study | Post-vitreoretinal surgery patients treated for raised IOP with timolol maleate (0.5%) and brimonidine tartrate (0.15%) for ≥ 1 month | 20% mannitol IV at a dosage of 1 g/kg body weight over 30 min | 31 | NA | Vitrectomized = 40.16 | Mannitol is useful for short-term IOP reduction in vitrectomized eyes. Compared to normal eyes, the reduction in IOP is sustained, higher, and independent of baseline IOP. |
| Sahu (2023) ⁹ | India | Prospective comparative study | Phakic eyes of patients with IOP measuring ≥ 40 mmHg and open angles on gonioscopy | 20% mannitol IV at a dosage of 1 g/kg body weight over 30 min | 25 | 25 | Vitrectomized = 47, non-Vitrectomized = 54 | IOP was significantly reduced with mannitol in both the groups. |
| Feng (2019) ²⁹ | China | Retrospective case-control study | Patients who underwent pars plana vitrectomy (PPV) for ocular hypertension | 20% mannitol | 23 | NA | Vitrectomized = 45.6 | In eyes with different intraocular tamponades, 20% mannitol was useful for short-term IOP reduction after vitrectomy. |
| Ahmad (2022) ³⁰ | Pakistan | Prospective comparative study | Patients with open angles on gonioscopy and an IOP lower than 38 mm Hg | 20% mannitol IV at a dosage of 1 g/kg body weight over 30 min | 36 | 36 | non-Vitrectomized = 46.4, non-Vitrectomized = 46.9 | Mannitol has been shown to dramatically lower IOP in both vitrectomized eyes with silicon fillings and non-vitrectomized eyes. |

Abbreviations: IOP: Intraocular Pressure, IV: Intravenous, mm Hg: Millimeters of Mercury, NA: Not Available or Applicable, PPV: Pars Plana Vitrectomy.

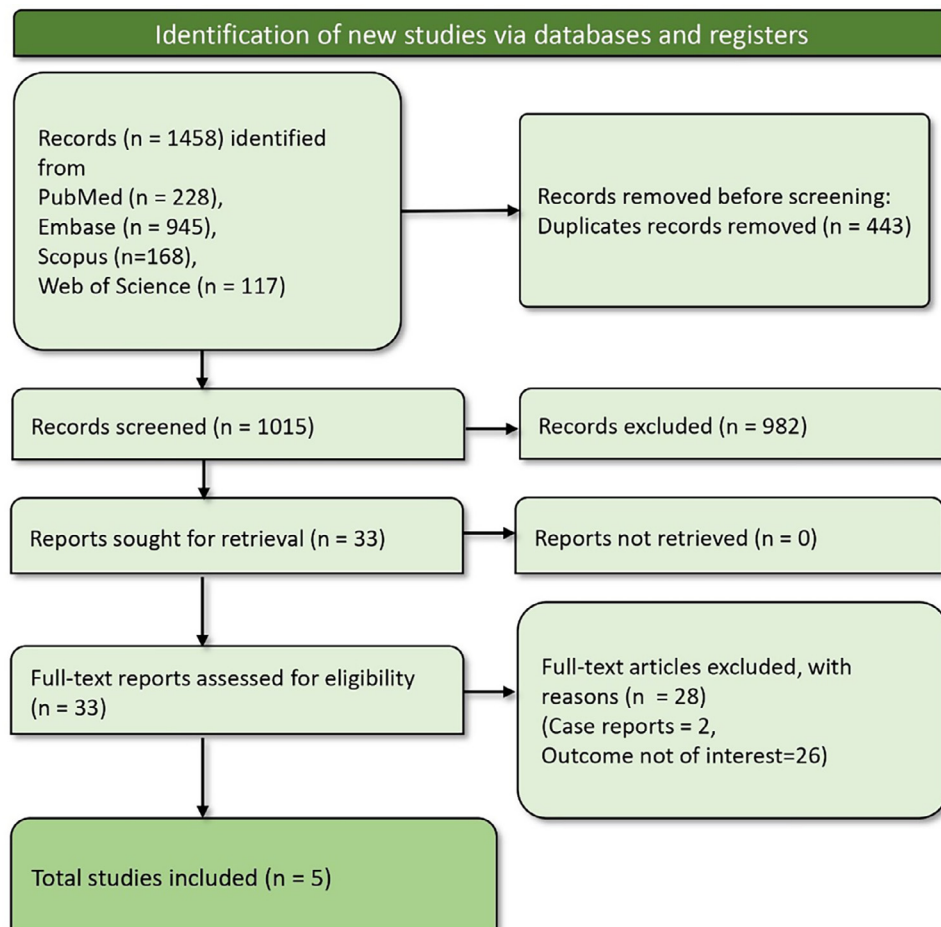


FIGURE 1. PRISMA flow diagram showing article screening and study selection process.

tistically significant. At 90 min, the effect of mannitol appeared to stabilize, with a ROM of 1.006 (95% CI: 0.937; 1.081). By the 2-hour mark, the ROM was 0.988 (95% CI: 0.909; 1.075), suggesting no significant reduction in IOP in vitrectomized eyes compared to non-vitrectomized eyes. At 3 h, the ROM was 0.996 (95% CI: 0.905; 1.095), continuing the trend of significant IOP reduction. At 4 h, the ROM was 1.001 (95% CI: 0.869; 1.153), indicating that the effects of mannitol had leveled off, with the confidence interval including 1 again (Figure 3).

- **PUBLICATION BIAS:** Publication bias evaluation was not possible in our meta-analysis due to the small sample size of included studies. This type of bias happens when the outcome of research affects its publication probability, often leading to the preferential publication of studies with positive findings. Adequate evaluation of publication bias usually necessitates a substantial number of studies for a valid statistical test, such as funnel plot asymmetry or Egger's regression. Given the constrained number of studies in our analysis, the assessment of publication bias is limited, which may affect the interpretation of our results.

DISCUSSION

The current study is the first meta-analysis to assess the effect of intravenous mannitol on IOP changes in both vitrectomized and non-vitrectomized eyes. Our findings suggest that mannitol is an effective agent for reducing IOP in both groups, with significant reductions observed at various time points post-treatment. The evidence presented indicates a consistent and clinically relevant decrease in IOP, supporting mannitol's utility in the acute management of elevated IOP during and after ophthalmic surgeries. The sustained IOP reduction observed at multiple time points post-mannitol administration highlights its potential for short-term ocular hypertension management. However, the variability in effect size at different time intervals suggests that the timing of mannitol administration relative to surgery or the onset of elevated IOP might influence its efficacy.

Vitrectomy alters the eye's internal dynamics by removing the vitreous body, potentially affecting the distribution and efficacy of osmotic agents like mannitol. Our meta-analysis indicates that despite these changes, mannitol

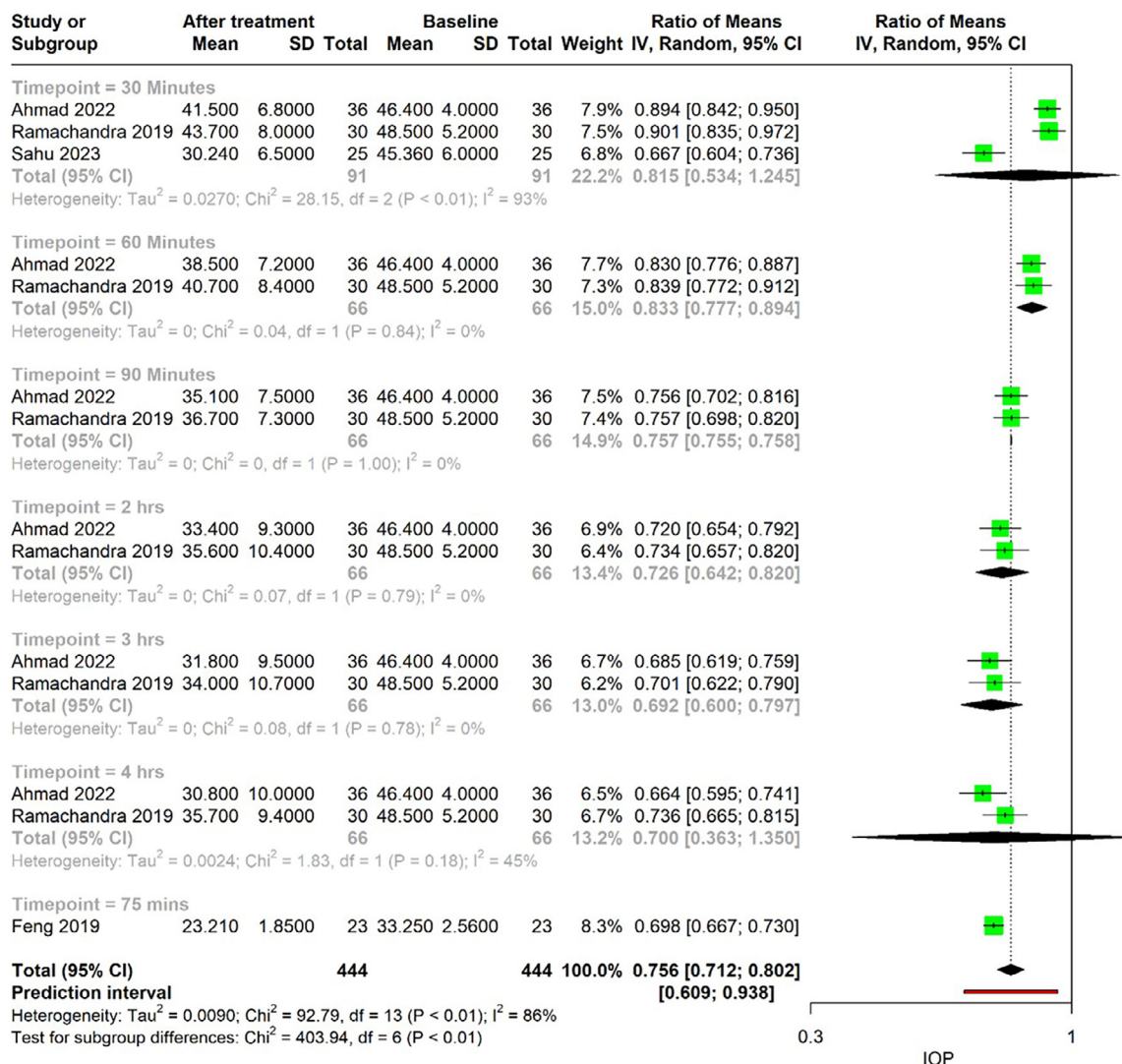


FIGURE 2. Effect of mannitol on IOP of vitrectomized eyes.

remains effective in reducing IOP in vitrectomized eyes. This suggests that the osmotic gradient established by mannitol across the blood-ocular barrier is sufficient to prompt fluid egress from the eye, regardless of the presence of the vitreous body. However, the exact impact of vitrectomy on mannitol's pharmacodynamics warrants further investigation to optimize dosing and administration protocols in this subgroup.

The mechanisms by which mannitol exerts its effect are multifaceted, primarily involving an increase in plasma osmolality that facilitates water transfer from the vitreous body into the bloodstream, resulting in vitreous dehydration and consequent IOP reduction. This process is augmented by mannitol's effect on osmoreceptors in the hypothalamus, leading to a decrease in aqueous humor production.^{9,15} These findings are in line with the physiological actions of mannitol and underscore its role in managing

ocular hypertension, especially in surgical settings where optimal IOP levels are crucial for preventing complications such as retinal detachment, hemorrhage, and optic nerve damage.³¹⁻³³

While studies have shown a decrease in IOP after mannitol administration in vitrectomized eyes, several factors might influence the impact. One potential area of exploration is the role of the remaining structures. Since mannitol's mechanism of action partly involves drawing fluid from the vitreous, the completeness of the vitrectomy and the presence of any residual vitreous gel could affect its effectiveness. Additionally, factors like inflammation and silicone oil tamponade might influence fluid dynamics within the eye, potentially impacting mannitol's ability to reduce IOP. Further investigation into these areas could help refine the use of mannitol in this specific patient population.

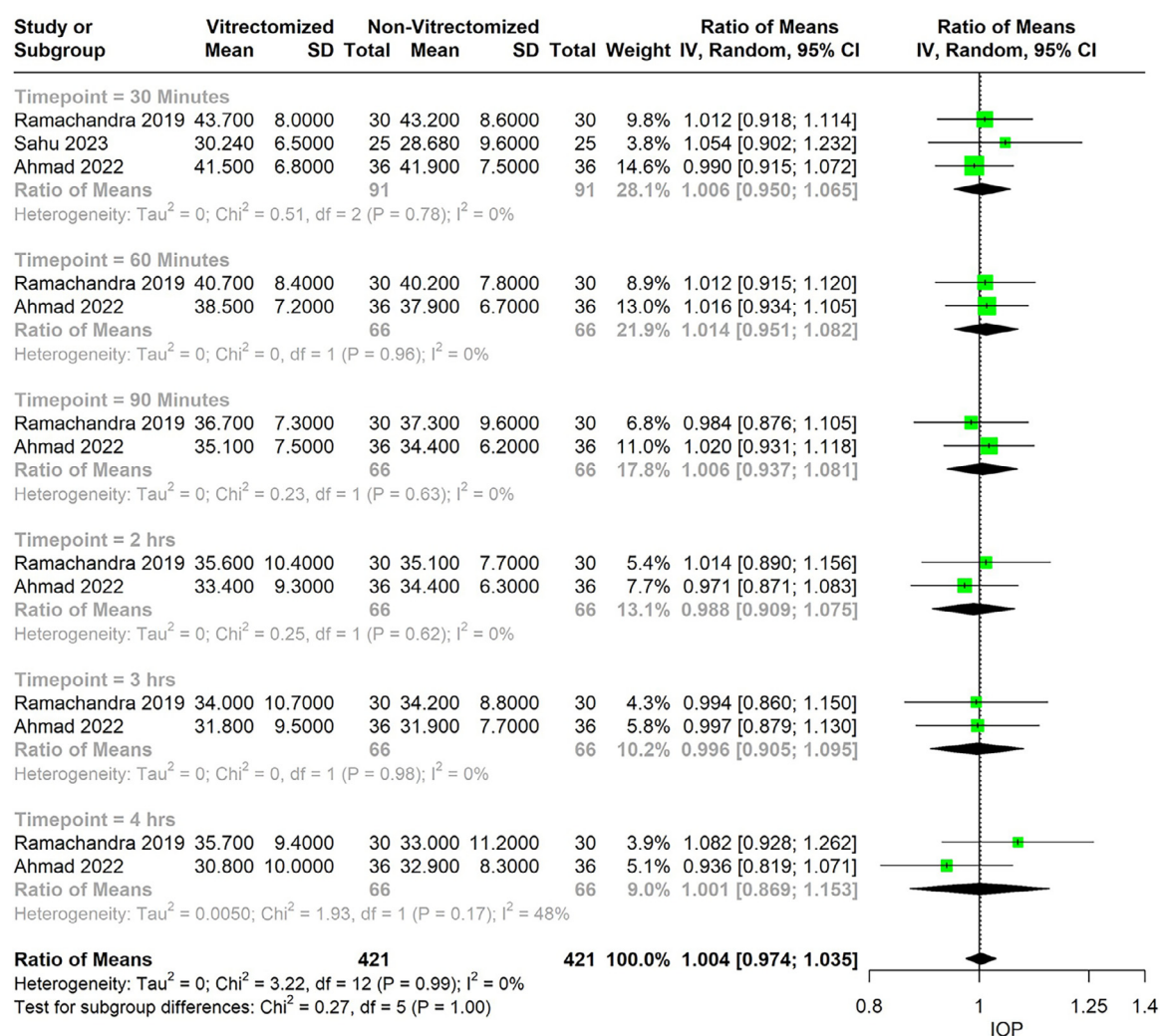


FIGURE 3. Effect of mannitol on IOP of vitrectomized versus non-vitrectomized eyes.

The present study holds significant clinical implications, providing ophthalmologists and surgical teams with valuable insights for managing IOP during and after ophthalmic surgeries. The demonstrated efficacy of intravenous mannitol in reducing IOP across both vitrectomized and non-vitrectomized eyes underscores its versatility as a tool for acute IOP management. This evidence supports the strategic use of mannitol to mitigate surgery-related complications like retinal detachment, hemorrhage, and optic nerve damage by maintaining optimal IOP ranges. Furthermore, our findings highlight the potential importance of timing mannitol administration to maximize its effectiveness, suggesting the possibility of personalized treatment strategies for enhanced patient outcomes. As the first meta-analysis to evaluate mannitol's impact on IOP changes in these distinct patient groups, our study lays the groundwork for informed clinical decision-making. This paves the way for the integration of mannitol into perioperative care protocols, potentially improving surgical success and patient recovery.

Future research should delve into the optimal timing and dosage of mannitol administration specifically for vitrectomized patients. Additionally, a crucial step will be to carefully weigh the potential benefits of IOP reduction against any possible side effects associated with mannitol use. Establishing clear guidelines tailored to the specific needs of vitrectomized patients will be vital for safe and effective integration into their perioperative care.

Limitations in the existing literature, as revealed by our systematic review, include a relatively small number of studies meeting the inclusion criteria and the absence of randomized controlled trials comparing mannitol with other osmotic agents or treatments for IOP management. Additionally, the lack of long-term follow-up data limits our understanding of mannitol's efficacy beyond the acute post-operative period. These gaps highlight areas for future research, particularly randomized trials with larger sample sizes and studies exploring the comparative effectiveness of mannitol and other IOP-lowering interventions.

Our study is subject to some limitations that underscore the need for further research. The reliance on observational studies and the absence of randomized controlled trials (RCTs) limit the robustness of our findings. The small number of studies included raises concerns about the comprehensiveness of our analysis and introduces the potential for publication bias, as the limited dataset may not adequately represent the spectrum of existing research. The geographical concentration of these studies restricts the generalizability of our results across different patient demographics. Observational study designs inherently carry the risk of confounding factors, and the lack of long-term follow-up data constrains our understanding of mannitol's prolonged effects and safety profile. The focus on specific surgical contexts may not accurately capture mannitol's efficacy across the diverse landscape of ophthalmic procedures. Together, these limitations highlight the necessity for RCTs, broader demographic studies, standardized methodologies, and detailed evaluations of long-term outcomes and safety profiles to deepen our understanding of mannitol's role in ocular surgery and its wider implications for patient care. This call for more comprehensive and methodologically sound research is crucial to inform clinical practices with robust, generalizable evidence.

CONCLUSION

Our analysis supports the use of intravenous mannitol for reducing IOP in both vitrectomized and non-vitrectomized eyes. The evidence suggests that mannitol is a valuable tool in the ophthalmologist's arsenal for managing elevated IOP, particularly in the context of surgery. It is important to interpret these findings with caution due to the small size of

the studies contributing to the meta-analyses. Future studies should focus on optimizing mannitol's use in different patient populations and surgical contexts, exploring its long-term efficacy and safety, and comparing its performance with other IOP-lowering strategies.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

HASHEM ABU SERHAN: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Funding acquisition, Conceptualization. **PARUL CHAWLA GUPTA:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **MAHALAQUA NAZLI KHATIB:** Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **BIJAYA K. PADHI:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources. **SHILPA GAIDHANE:** Software, Resources, Project administration, Methodology, Formal analysis, Data curation. **QUAZI SYED ZAHIRUDDIN:** Writing – review & editing, Writing – original draft, Visualization, Validation. **ABHAY M. GAIDHANE:** Supervision, Software, Resources, Project administration, Data curation, Conceptualization. **NEELIMA KUKRETI:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **SARVESH RUSTAGI:** Writing – review & editing, Writing – original draft, Visualization, Project administration. **PRAKASINI SATAPATHY:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision.

Funding/Support: Qatar National Library funded the publication of this article. Financial Disclosures: No financial disclosures. Acknowledgments: The authors acknowledge Nested-Knowledge, MN, USA for providing the access to the software. Qatar National Library funded the publication of this article. Ethical Approval: Not required. Data Availability: The data is with the authors and available on request.

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