



REVIEW ARTICLE

Efficacy and safety of sustained-release intraocular drug therapy for glaucoma: a systematic review of randomized controlled trials

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Date of first submission, March 15, 2026

Date of final revised submission, October 4, 2026

Date of acceptance, October 19, 2026

Cite this article as: Oktabiriya R, Ermawati S, Prasetyo RA. Efficacy and safety of sustained-release intraocular drug therapy for glaucoma: a systematic review of randomized controlled trials. Univ Med 2026;45:XXX

ABSTRACT

BACKGROUND

Glaucoma is a leading cause of irreversible blindness worldwide. Although intraocular pressure (IOP) reduction remains the cornerstone of treatment, limitations of long-term topical therapy, including poor adherence and ocular surface complications, have increased interest in sustained-release intraocular drug delivery systems. This systematic review evaluated the efficacy and safety of sustained-release intraocular implants in patients with glaucoma or ocular hypertension.

METHODS

A systematic search of PubMed, ScienceDirect, Scopus, and the Cochrane Library was conducted for randomized controlled trials (RCT) published between January 2021 and September 2025. Double-blind RCT were selected according to PRISMA guidelines and appraised using the JBI Critical Appraisal Checklist. Data were synthesized narratively. Four RCTs met the eligibility criteria and were included. The studies evaluated travoprost and bimatoprost intracameral implants with follow-up durations of 12-36 months.

RESULTS

All studies demonstrated significant IOP reduction and non-inferiority to timolol. Least-squares mean diurnal IOP reduction ranged from -5.4 to -8.5 mmHg with travoprost implants and -6.2 to -7.8 mmHg with bimatoprost implant. The proportion of patients remaining free from adjunctive topical therapy ranged from 63% to 81%. Adverse events were generally mild and transient. However, travoprost implants showed no clinically significant corneal endothelial cell loss (CECL), whereas bimatoprost implant resulted in CECL $\geq$ 20% in 8.1% (10 μ g) and 24.4% (15 μ g) of patients, leading to restriction of single administration per eye.

CONCLUSION

Sustained-release intraocular implants provide effective and durable IOP reduction while potentially improving treatment adherence. However, implant selection should consider ocular anatomy and corneal endothelial safety.

Keywords: Glaucoma; sustained-release; intraocular implant; intraocular pressure

INTRODUCTION

Glaucoma is a disease characterized by elevated intraocular pressure (IOP), which leads to irreversible optic nerve damage and may result in blindness if not adequately managed.^(1–3) Elevated IOP is a modifiable risk factor for delaying glaucoma onset and slowing disease progression. One emerging therapeutic approach is sustained-release medications using implant-based delivery systems.^(4,5) Sustained-release therapies may reduce treatment burden, improve quality of life, and minimize ocular surface disease associated with long term topical therapy, particularly from benzalkonium chloride (BAK). Exposure to this substance can cause discomfort during instillation, foreign body sensation, ocular irritation, and dry eye symptoms, with the risk increasing according to the number and frequency of eye drops used.^(6–10) Sustained-release intraocular therapies may also improve outcomes in patients with poor medication adherence by reducing glaucoma related complications.^(11–15) Bimatoprost sustained-release is a biodegradable intracameral implant that gradually releases the drug into the anterior chamber, providing sustained IOP reduction for several months.^(16,17) Phase 3 trials demonstrated efficacy comparable to timolol, although repeated administration was associated with corneal endothelial cell loss, limiting its use to a single implantation per eye.⁽¹⁸⁾ Travoprost is another intracameral implant comprising a titanium reservoir and anchor with nanoporous ethylene-vinyl acetate (EVA) membrane that enables continuous drug release into the anterior chamber, maintaining stable drug concentrations, reducing topical therapy requirements, and sustaining long-term IOP reduction.^(19,20) This review aims to systematically evaluate evidence from randomized controlled trials on the efficacy and safety of sustained-release intraocular therapies for glaucoma. By assessing IOP reduction and safety outcomes, this review provides evidence on their potential to reduce the topical therapeutic burden, improve adherence, and limit disease progression.

METHODS

Protocol registration and reporting

A systematic literature search was conducted in PubMed, ScienceDirect, Scopus, and the Cochrane Library on 12 September 2025. The

search was limited to English language full-text articles published between 1 January 2021 and 12 September 2025. Database-specific search strategies used Boolean operators to combine controlled vocabulary, where available, with free-text terms related to glaucoma, ocular hypertension, sustained release intraocular drug delivery systems, and randomized controlled trials. This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261329209

(<https://www.crd.york.ac.uk/PROSPERO/view/CRD420261329209>).

Study selection

The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and included three stages: identification, screening, and eligibility assessment. During the identification stage, the database search yielded 467 records: PubMed (n = 41), ScienceDirect (n = 189), Scopus (n = 231), and the Cochrane Library (n = 6). After removing 42 duplicate records, 425 unique articles remained for screening. Titles and abstracts were screened by one reviewer and independently verified by two additional reviewers. A total of 408 articles were excluded because they did not evaluate sustained release intraocular drug delivery systems for glaucoma or did not meet the predefined study design criteria. The remaining 17 articles underwent abstract screening. Seven full-text articles were subsequently assessed for eligibility against the predefined inclusion and exclusion criteria. Three studies were excluded because one was a study protocol, one used an open label design that did not meet the double-masked eligibility criterion, and one was a secondary analysis rather than a primary RCT. The study selection process is summarized in Figure 1. Ultimately, four studies met all eligibility criteria and were included in the final synthesis.

Eligibility criteria

Studies eligible for inclusion were double-blind RCTs reporting pre- and post-intervention data, involving patients with open-angle glaucoma or ocular hypertension, available as full-text articles in English, and employing valid and standardized diagnostic criteria and intraocular pressure measurement methods. Exclusion criteria

comprised non-RCT studies and study protocols; studies involving populations predominantly affected by other ocular diseases without a clear diagnosis of glaucoma; studies evaluating non-pharmacological interventions, such as drainage devices without intraocular drug delivery; animal, preclinical, or in vitro studies; studies focusing solely on pharmacokinetic outcomes without reporting clinical endpoints; and articles reporting outcomes not relevant to the efficacy or safety of long-term intraocular pharmacological therapy.

Risk of bias assessment

The methodological quality and risk of bias of the included studies were assessed using the JBI

critical appraisal checklist for randomized controlled trials. The results of the methodological appraisal are presented in Table 1 and were considered during interpretation of the review findings.

Data synthesis

Owing to the heterogeneity in implant design, drug formulation, follow-up duration, and reported outcome measures, a quantitative meta-analysis was not performed. Therefore, the findings were synthesized narratively by comparing the efficacy and safety outcomes across the included studies.

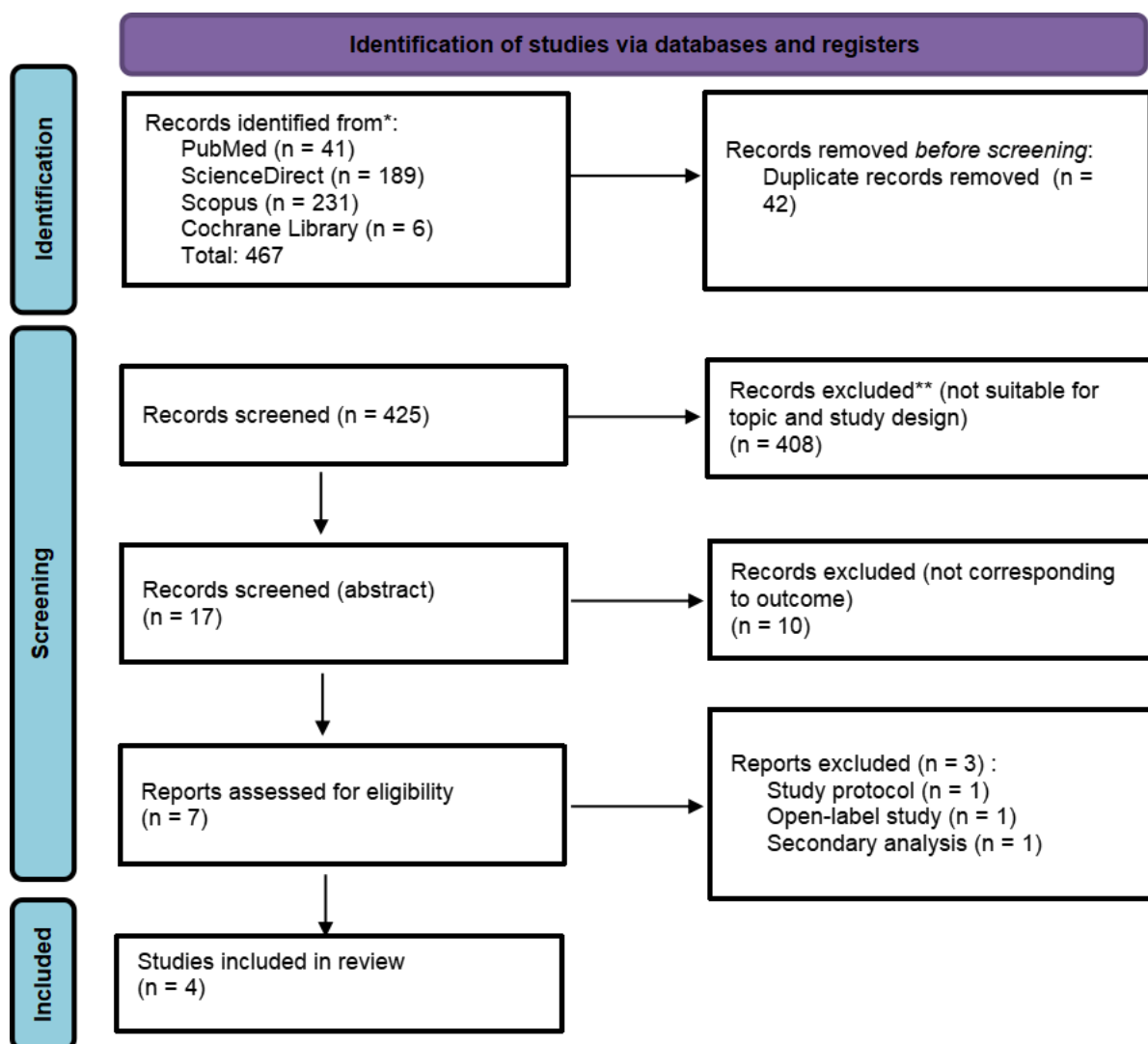


Figure 1. PRISMA flow diagram of study selection

Table 1. Summary of methodological quality assessment using the JBI critical appraisal checklist

JBI appraisal item	Bacharach et al. ⁽¹⁸⁾	Singh et al. ⁽²¹⁾	Berdahl et al. ⁽²²⁾	Sarkisian et al. ⁽¹⁹⁾
True randomization	Yes	Yes	Yes	Yes
Allocation concealment	Yes	Unclear	Unclear	Yes
Baseline similarity	Yes	Yes	Yes	Yes
Participant blinding	Yes	Yes	Yes	Yes
Outcome assessor blinding	Yes	Yes	Yes	Yes
Follow-up complete	Yes	Yes	Yes	Yes
ITT analysis	Yes	Yes	Yes	Yes
Appropriate statistics	Yes	Yes	Yes	Yes
Overall appraisal	Include	Include	Include	Include

Note: JBI: Joanna Briggs Institute, RCT: randomized controlled trial, ITT: intention to treat

RESULTS

Four RCTs were included in the qualitative synthesis. Overall, the included studies demonstrated good methodological quality, with most JBI appraisal items rated “Yes”. Allocation concealment was judged as unclear in two travoprost trials, whereas all other domains were adequately addressed.

All included studies were RCTs, double-blind controlled trials comparing sustained release intraocular implants with topical timolol and/or sham procedures in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Three studies evaluated travoprost implants, whereas one study evaluated a bimatoprost implant. Baseline mean age ranged from 62 to 65 years, and follow-up periods varied from 12 to 36 months. The main characteristics of the included studies are summarized in Table 2.

Sarkisian et al.⁽¹⁹⁾ demonstrated that both slow-eluting (SE) and fast-eluting (FE) travoprost implants were non-inferior to timolol, with sustained IOP reduction for up to 12 months in the SE group and 9 months in the FE group. Approximately 77-81% of patients remained free from adjunctive topical therapy.

Similarly, Singh et al.⁽²¹⁾ showed sustained IOP reduction through 12 months for both travoprost implant formulations, with 77.6% of FE and 81.4% of SE implant recipients remaining free from additional topical medication.

Berdahl et al.⁽²²⁾ reported the longest follow-up, demonstrating sustained IOP reduction for up to 36 months after a single travoprost implant administration. Approximately 63-72% of patients maintained the same or fewer topical medications throughout follow-up.

The Phase 3 ARTEMIS-2 trial by Bacharach et al.⁽¹⁸⁾ demonstrated that both 10 µg and 15 µg bimatoprost implants were non-inferior to timolol, with approximately 70% to 79% of patients remaining free from adjunctive topical therapy following repeated implant administrations.

Overall, both travoprost and bimatoprost implants produced clinically meaningful and sustained reductions in IOP while achieving non-inferiority to topical timolol. Travoprost implants demonstrated durable IOP control for up to 36 months after a single implantation⁽²¹⁻²³⁾, whereas the bimatoprost implant showed sustained efficacy during repeated implantation.⁽¹⁸⁾ However, these findings should be interpreted cautiously because the included studies differed in implant design, drug release characteristics, follow-up duration, dosing strategy, and evaluated outcomes.

Most adverse events reported across all studies were mild, transient, and procedure-related. In travoprost studies, the most frequent ocular adverse events were iritis, ocular inflammation, and conjunctival hyperemia, with stable best corrected visual acuity (BCVA), central corneal thickness, visual field (VF) parameters, and no clinically meaningful endothelial cell loss (ECL) during follow-up.⁽²¹⁻²³⁾ In contrast, the bimatoprost implant was associated with a higher incidence of corneal endothelial cell loss (CECL), particularly the 15 µg dose, although most other adverse events were transient.⁽¹⁸⁾ Overall, both implant systems demonstrated acceptable safety profiles.

Table 2. Characteristics of included studies

Authors	Research methods	Population	Baseline	Intervention	Follow-up	Endpoint	Efficacy	Safety
Sarkisian et al. ⁽¹⁹⁾	Phase 3, multicenter, randomized, double-masked, active & sham controlled study	OAG/OHT; ITT population: SE n=197, FE n=200, timolol n=193	Mean age 64 years; baseline mean diurnal IOP 24 mmHg;	SE or FE travoprost implant + placebo eye drops BID versus timolol 0.5% BID + sham surgery	Primary evaluation at 3 months, with follow-up up to 36 months	Primary endpoint: Change in IOP from baseline (Δ IOP) assessed at six time points, with a non-inferiority margin of < 1.5 mmHg at all six time points and < 1.0 mmHg at ≥ 3 of the six time points. Statistical analysis: Analysis of covariance (ANCOVA) with baseline values as covariates.	- SE and FE were non-inferior to timolol at all six time points. - Least-squares mean ΔIOP: SE -6.6 to -8.5; FE -6.6 to -8.4; timolol -6.5 to -7.7 mmHg. - Adjunctive medication at Month 3: SE 4.2%, FE 5.1%, timolol 7.0%.	- TEAEs (study eye): SE 27.2%, FE 21.5%, timolol 10.8%; mostly mild–moderate (irritation, hyperemia). - Severe TEAEs: ~2% in SE and FE. - SAEs: one SE patient (endophthalmitis). - ECD and BCVA: stable.
Singh et al. ⁽²¹⁾	Pooled analysis of two phase III RCT, double masked; active & sham controlled trials.	OAG/OHT; N=1150 (FE 385; SE 380; timolol/sham 385);	Mean diurnal IOP was 24.2 mmHg; at baseline, the mean was 0.9 medications per eye, with approximately 22% already using 2–3 medications.	Travoprost implant FE/SE + placebo BID vs sham procedure + timolol 0.5% BID	12 months; 96% completed the study.	Δ IOP up to 12 months; NI margin 1.5 mmHg; ANCOVA and t-test, χ^2 /Fisher's exact test; multiple imputation; $p < 0.05$.	- NI was achieved at all visits. Diurnal ΔIOP: FE -5.4 to -8.2 mmHg; SE -5.4 to -8.4 mmHg; timolol -6.1 to -7.2 mmHg. - ΔIOP at 8 a.m.: FE -6.9 to -8.5 mmHg; SE -6.8 to -8.5 mmHg; timolol -7.3 to -7.5 mmHg. - At month 12: free from additional medications—FE 77.6%, SE 81.4%; same/fewer drops—FE 89.9%, SE 93.0%; timolol 66.9%.	- TEAEs: FE 35.8%, SE 35.7%, timolol 18.9% (mostly mild–moderate, transient). - Serious TEAEs: FE 0.3%, SE 0.8% (IOP increase, retinal detachment, endophthalmitis; resolved). - Treatment-related TEAEs: FE 19.2%, SE 18.5%, timolol 2.3% (IOP increase, iritis, hyperemia). - ECD, BCVA, VF, and CCT: stable.
Berdahl et al. ⁽²²⁾	Phase 2, randomized, double masked, sham controlled, parallel group, multicenter	OAG/OHT N=154 (FE 51; SE 54; timolol 49)	Mean age was 62.7 years; baseline mean diurnal IOP (mmHg): FE 25.4 $\pm$ 3.6; SE 24.8 $\pm$ 3.9; timolol 24.8 $\pm$ 3.0.	Single administration travoprost implant (FE & SE) + placebo tears vs timolol 0.5% BID (sham surgery)	Up to 36 months.	Δ IOP at 8 a.m. up to 36 months; same/fewer drops versus screening; ITT; t-test; chi-square.	- ΔIOP at 8 a.m.: FE -7.6 to -8.8 mmHg; SE -7.3 to -8.0 mmHg; timolol -7.3 to -7.9 mmHg. - Same/fewer drops: at 12 months—FE 86%, SE 92%, timolol 58%; at 24 months—FE	- AE: FE 54.9%, SE 40.7%, timolol 28.6% (mostly mild–moderate; ocular inflammation, pain, iritis; resolved). - Treatment-related cataract: FE 3.9%, SE 1.9%. - Iris discoloration: one case in the SE group.

							72%, SE 72%, timolol 50%; at 36 months—FE 63%, SE 69%, timolol 45%.	- SAE: one case of myasthenia gravis (timolol). - VF, MD, ECD, and CCT: stable up to 36 months.
Bacharach et al. ⁽¹⁸⁾	Phase 3, multicenter, randomized, parallel-group, double-masked, active-controlled study	OAG/OHT: ITT population n = 528 (10 µg n = 176; 15 µg n = 176; timolol n = 176);	Mean age was 62.6 years; baseline diurnal IOP ranged from 23.7 to 23.9 mmHg, and baseline ECD ranged from 2434 to 2488 cells/mm ² .	Bimatoprost implant 10 µg or 15 µg versus timolol maleate 0.5% BID; IOP stratification ≤25/>25 mmHg; washout ≤42 days.	Primary endpoint at week 12; active follow-up through week 52; extended safety follow-up up to month 20	Primary endpoint: IOP at hours 0 and 2 at weeks 2, 6, and 12. MMRM analysis with a non-inferiority margin ≤1.5 mmHg; superiority testing if non-inferiority was achieved.	- Both doses were non-inferior to timolol; ΔIOP -6.2 to -7.8 mmHg (implant) versus -6.1 to -6.7 mmHg (timolol). - Superiority: achieved at 1/7 time points (10 µg) and 4/6 time points (15 µg); effects were consistent after the second and third administrations. At week 52, IOP was approximately 17–18 mmHg in all groups. - VF MD: more stable with 10 µg (-0.08 vs -0.96 dB with timolol at week 52).	- TEAEs: 74.9% (10 µg), 88.1% (15 µg), 70.5% (timolol); treatment-related TEAEs 48.0%, 61.9%, and 20.8% (mostly mild–moderate, transient). - Serious TEAEs: 3.4% (10 µg), 7.4% (15 µg), 0% (timolol), mainly CECL. ECD at week 20: -5% (10 µg), -1% (timolol); ≥20% loss: 8.1% (10 µg), 24.4% (15 µg), 0.6% (timolol). - Implant removal due to TEAEs: 2.9% (10 µg), 10.8% (15 µg).

RCT : randomized controlled trial; ITT: intention to treat; NI: non-inferiority; MMRM: mixed model repeated measures; ANCOVA: analysis of covariance; LS mean: least squares mean; X²: Chi square test; OAG: open angle glaucoma; OHT: ocular hypertension; FE: fast eluting; SE: slow eluting; IOP: intraocular pressure; VF: visual field; MD: mean deviation; CCT: central corneal thickness; BCVA: best corrected visual acuity; ECD: endothelial cell density; AE: adverse event; TEAE: treatment emergent adverse event; SAE: serious adverse event; RD: retinal detachment; BID: bis in die; WK: week; µg: microgram.

DISCUSSION

Glaucoma is a group of progressive optic neuropathies characterized by optic nerve damage and irreversible visual field loss, with primary open-angle glaucoma (OAG) being the most common form. Lowering IOP, the only modifiable risk factor, remains the cornerstone of glaucoma treatment.^(1,24–26)

However, the effectiveness of topical prostaglandin analogs (PGAs) is limited by low ocular bioavailability (<5%) due to corneal and tear film barriers, fluctuations in intraocular drug concentrations, and poor patient adherence. In addition, topical bimatoprost exhibits a pharmacodynamic plateau effect, while conjunctival and episcleral vasodilatation may increase episcleral venous pressure (EVP), limiting further IOP reduction.^(27–31)

In contrast, intracameral PGA implants provide sustained drug delivery directly to the anterior chamber, bypassing corneal absorption and maintaining more consistent intraocular drug concentrations over several months.^(27,32,33) The biodegradable bimatoprost implant provides sustained intracameral drug release for approximately 3–4 months before gradually degrading.^(19,34–36)

Bimatoprost implants are associated with ECL, which has been attributed to their free-floating biodegradable design and prolonged contact with the corneal endothelium, particularly in eyes with narrow angles (Shaffer grade 3). This safety concern led the Food and Drug Administration (FDA) to restrict the implant to a single administration per eye.^(22,37–40) Because corneal endothelial cells have limited regenerative capacity, excessive cell loss may result in corneal edema and visual impairment.^(22,41,42) In the ARTEMIS-2 study, CECL $\geq 20\%$ occurred in 8.1% (10 μg) and 24.4% (15 μg) of patients.⁽¹⁸⁾

In contrast, the travoprost implant provided sustained IOP reduction for up to 36 months without clinically significant endothelial cell loss.⁽²³⁾ The implant consists of a titanium reservoir with a nanoporous ethylene-vinyl acetate (EVA) membrane that is anchored within the trabecular meshwork and provides sustained travoprost release into the anterior chamber.^(19,43,44) The EVA membrane enables sustained travoprost release, maintaining stable intraocular drug concentrations.^(19,45,46)

The EVA membrane enables sustained travoprost release, maintaining stable intraocular drug concentrations.^(19,45,46)

Overall, both bimatoprost and travoprost implants achieved clinically meaningful IOP reductions and were non inferior to topical timolol during their respective primary evaluation periods. The reported IOP reductions were broadly comparable, however direct numerical comparison is inappropriate because the trials differed in implant design, dosing regimen, follow-up duration, IOP measurement schedule, statistical analysis, and outcome assessment.^(19,21,22)

Treatment durability differed between the two implant systems. A single travoprost implantation provided sustained IOP control for up to 36 months, with 63–72% of patients remaining on the same or fewer topical medications at month 36.⁽²²⁾ In the pooled phase 3 analysis, 77.6% of patients receiving the FE formulation and 81.4% receiving the SE formulation remained free from adjunctive topical therapy at month 12.⁽²¹⁾ In contrast, patients in ARTEMIS-2 received up to three bimatoprost implant administrations at approximately 16 week intervals.⁽¹⁸⁾ Therefore, the durability of travoprost following a single implantation cannot be directly compared with the efficacy achieved through repeated bimatoprost administration.^(18,21,22)

Safety findings were clinically important and differed between the implant systems. In ARTEMIS-2, CECL $\geq 20\%$ occurred in 8.1% of patients receiving the 10 μg bimatoprost implant and 24.4% receiving the 15 μg implant, compared with 0.6% in the timolol group. Implant removal was required in 2.9% and 10.8% of patients in the 10 μg and 15 μg groups, respectively, indicating a dose-related safety concern.⁽¹⁸⁾ These findings are particularly relevant because progressive ECL may lead to corneal edema and visual impairment.^(47,48) The risk has been associated with repeated implant administration and the persistence of biodegradable implant remnants within the iridocorneal angle, which may increase the likelihood of contact with the corneal endothelium.^(18,36)

In contrast, clinically significant CECL was not reported in the included travoprost trials during follow-up of up to 36 months.^(19,21,22) This difference may be related to the anchored position of the travoprost implant within the trabecular meshwork, which is designed to remain fixed and stable away from the corneal endothelium, thereby

potentially reducing direct contact with endothelial cells.⁽⁴⁹⁾ Nevertheless, evidence beyond 36 months remains unavailable, and the long term tissue response to this permanently implanted device warrants further investigation.

Ocular inflammation, including iritis and conjunctival hyperemia, occurred more frequently in the implant groups than in the timolol groups. Most inflammatory events were mild to moderate and resolved during follow-up.^(18,19,21,22) These events may be particularly relevant when considering implantation in patients with a history of ocular inflammation. Rare serious adverse events, including endophthalmitis, were also reported in the travoprost trials.^(19,21) Although uncommon, these procedure-related events should be clearly communicated during patient counseling because endophthalmitis is a vision-threatening complication that may result in irreversible visual loss and represents a risk that is not associated with topical therapy.^(19,21,50)

These findings suggest that patient selection is an important determinant of the benefit-risk profile of sustained-release therapy, particularly when repeated bimatoprost implantation is considered. Eyes with wide open (Shaffer grade 4) angles, baseline corneal endothelial cell density (CECD) ≥ 1800 cells/mm², no persistent or progressive (>15%) reduction in CECD, no persistent intraocular inflammation, and no residual implant that could interfere with subsequent administration may be appropriate candidates for retreatment. Careful patient selection and pre-retreatment assessment may therefore improve the benefit-risk balance of sustained-release therapy.^(18,38)

Overall, both implant systems reduced IOP and decreased dependence on topical medication, but their durability and safety profiles were not directly comparable.^(18,19,21,22) The available evidence supports careful patient selection and continued endothelial monitoring rather than a general conclusion that one implant is superior to the other. Head-to-head trials using standardized efficacy and safety outcomes, longer endothelial surveillance, and patient-reported outcomes are needed to guide implant selection in clinical practice.

CONCLUSION

Sustained-release intraocular implants offer multiple advantages in achieving stable IOP reduction, reducing drug level fluctuations,

increasing therapeutic concentrations, and minimizing ocular surface adverse effects commonly associated with topical therapy. However, selection of implant type should consider ocular anatomical factors and safety risks, particularly those related to corneal endothelial health.

Acknowledgement

The authors would like to thank all individuals who provided support and valuable input during the preparation of this manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this work.

Authors' Contributions

RO conducted the literature search, collected and analyzed the data,

and drafted the manuscript. SE conceived and supervised the study, and critically reviewed the manuscript. RAP contributed to data interpretation and manuscript revision. All authors approved the final version of the manuscript.

Funding

This research received no external funding.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of AI Usage in Scientific Writing

Nothing to declare.

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