Clinical Ophthalmology

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REVIEW

# Efficacy of Oxymetazoline 0.1% in Acquired Blepharoptosis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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**Purpose:** Abnormal eyelid drooping is a defining feature of blepharoptosis, a disorder that can affect the superior vision field. The standard of care is surgical intervention but may be associated with complications. There is emerging evidence that the direct-acting α-adrenergic agonist ophthalmic solution, oxymetazoline, is effective for blepharoptosis. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of oxymetazoline in the management of blepharoptosis.

**Patients and Methods:** A total of five databases were searched. The inclusion was limited only to randomized controlled trials (RCTs) that evaluated the efficacy of oxymetazoline versus placebo. The efficacy endpoint was the mean change in the marginal reflex distance 1 (MRD 1) from baseline. The safety endpoints were mortality and adverse events (AEs). The weighted mean difference (WMD) was implemented for continuous outcomes. For risk of bias assessment, the Revised Cochrane risk of bias tool for randomized trials was used.

**Results:** 4 RCTs (n = 448) met the eligibility criteria. The meta-analysis yielded a statistically significant higher difference in the WMD in the oxymetazoline group [0.65 mm (95% CI: 0.44 mm to 0.86 mm)] compared to the placebo group [0.26 mm (95% CI: 0.30 mm to 0.48 mm) [p=0.012]. There were no statistically significant differences between the oxymetazoline group [1.2% (95% CI: 0.4–3.6%)] and the placebo group [1.6% (95% CI: 0.5–5.3%), p = 0.73] in terms of serious adverse events.

**Conclusion:** Oxymetazoline is an effective and safe medication in the management of acquired blepharoptosis.

**Keywords:** oculoplastic, ptosis, oxymetazoline 0.1%, alpha-adrenergic, eyelid drooping

## Introduction

Blepharoptosis, commonly referred to as "ptosis", is characterized by the abnormal descent of the upper eyelids in the primary gaze position.[1] This condition is classified as either acquired or congenital, depending on the underlying structural or neurological abnormalities contributing to its etiology.[2] The pathophysiology of blepharoptosis is multi-factorial, warranting a comprehensive analysis of both anatomical and neurological components to fully elucidate its origins and implications.[2]

Blepharoptosis is among the most frequently encountered eyelid disorders, with a reported prevalence ranging from 4.7% to 13.5%.[3,4] Clinically, it is often perceived as a cosmetic concern due to the characteristic "sleepy" appearance it imparts, which may affect one or both eyes.[5,6] Beyond aesthetics, blepharoptosis can impair quality of life by reducing functional independence and increasing the risk of psychological distress, including anxiety and depression.[7,8] Functionally, even mild cases may obstruct the superior visual field, contributing to declines in health-related quality of life.[9–11]

Received: 14 April 2025
Accepted: 21 July 2025
Published: 23 August 2025

Surgical correction remains the primary treatment for blepharoptosis.[1] A variety of surgical procedures and techniques are available, with the selection of an appropriate approach determined by a comprehensive clinical evaluation.[12,13] Evidence suggests that surgery can substantially improve functional and quality-of-life outcomes.[14–16] However, surgery may not be suitable for all patients—particularly those with mild ptosis or contraindications to surgery.[1,5] In such cases, the potential benefits of surgery must be weighed against the risk of adverse events, which range from minor complications, such as infection and bleeding, to more serious outcomes like eyelid asymmetry, over- or undercorrection, atypical lid creases, and scarring.[1,5]

Thus, a compelling demand for pharmacological intervention has emerged in response to evolving clinical challenges. Müller's muscle, a sympathetically innervated smooth muscle within the upper eyelid responsible for approximately 1 to 2 millimeters of eyelid elevation, represents a viable therapeutic target.[2,17] Activation of the alpha-adrenergic receptors on Müller's muscle induces contraction, leading to elevation of the upper eyelid and consequently improvement in the superior visual field.[2,3] Accordingly, alpha-adrenergic agonists provide a non-invasive treatment modality for patients with blepharoptosis, especially for those opting against surgical intervention. Numerous clinical trials have investigated the efficacy of a topical adrenergic agonist, specifically oxymetazoline topical solution, in patients afflicted with blepharoptosis.[17–20] Oxymetazoline has consistently demonstrated significant improvements in both functional (visual field) and anatomical (marginal reflex distance) outcomes among affected individuals.[17–19]

Additionally, certain studies have indicated that the cosmetic enhancements afforded by Oxymetazoline may boost self-confidence and psychological well-being, thereby positively impacting the overall quality of life for patients.[21] Notably, these effects may be comparable to those achieved through surgical intervention, yet with a reduced incidence of adverse effects.[19] Despite these promising findings, the definitive conclusion regarding the efficacy of Oxymetazoline remains elusive. Therefore, this meta-analysis seeks to assess the efficacy and safety of Oxymetazoline 0.1% ophthalmic solution in patients with blepharoptosis.

## Materials and Methods

This systematic review and meta-analysis were conducted according to a pre-registered protocol on PROSPERO (CRD42024555846) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### Search Strategy

A comprehensive search was conducted from database inception to June 5th, 2024, using Medline, Web of Science, Google Scholar, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). Additionally, to identify ongoing or recently completed trials, we searched through ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry, the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, and the International Standard Randomized Controlled Trial Number (ISRCTN) registry. Reference lists of included studies were also manually searched to find any possibly pertinent RCTs that may have been missed. The search strategy incorporated terms such as "blepharoptosis", "ptosis", and "oxymetazoline hydrochloride". Full search details are provided in the supplementary material.[19,22–24]

### Eligibility Criteria

We included only randomized controlled trials (RCTs) comparing oxymetazoline 0.1% ophthalmic solution to placebo in the treatment of acquired ptosis, and that assessed efficacy using the marginal reflex distance 1 (MRD1). Studies not reporting MRD1 as an outcome were excluded. Additional exclusion criteria were: nonhuman studies, non-RCTs, reviews, case reports, cohort studies, duplicates, inaccessible articles, studies on congenital ptosis, and studies involving ocular or systemic confounding conditions. Articles lacking sufficient clinical data (eg, demographic or outcome measures) or not published in English were also excluded.

The primary efficacy outcome was the mean change in MRD1 from baseline to 14 days post-intervention. Secondary outcomes included the mean change in the Leicester Peripheral Field Test (LPFT) and the incidence of adverse events

(AEs) and serious adverse events (SAEs). Reported adverse events included eye pruritus, conjunctival hyperemia, punctate keratitis, dry eye, and headache.

## Study Selection and Data Extraction

Two reviewers (RB and OB) independently screened titles and abstracts, followed by full-text assessments based on eligibility criteria. Disagreements were resolved through consensus.

Data were extracted independently by two authors (OB and RH) using a standardized data extraction form. Extracted data included study characteristics, patient demographics (eg, age, gender), efficacy outcomes, and adverse events. Any discrepancies were resolved by mutual agreement.

## Risk of Bias Assessment

Two reviewers (OB and RH) independently assessed the risk of bias using the Revised Cochrane Risk of Bias Tool (RoB 2).[25] Each domain was evaluated and assigned a score of high, low, or some concerns. Discrepancies were resolved through discussion and consensus.

## Meta-Analysis

Statistical analyses were performed using Stata (StataCorp, 2024).[26] For categorical variables, logit-transformed proportions and 95% confidence intervals (CIs) were calculated. Continuous variables were reported as weighted means with 95% CIs. A random-effects model was used for all meta-analyses.[27,28] The differences between intervention groups were evaluated using subgroup analyses of weighted mean differences (WMDs) and logit-transformed proportions, each with 95% CIs.[29,30] Heterogeneity was assessed using Higgins' $I^2$ and the chi-square ($\chi^2$) test. A two-sided p-value $<0.05$ was considered statistically significant.[31] Publication bias was evaluated using Egger's test and funnel plots, with no significant bias detected (all $p > 0.05$; Figure 1a and b).[32]

## Certainty of Evidence

The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.[33] This structured approach considered study design, consistency, directness, precision, publication bias, and other relevant factors. Evidence quality was categorized as very low, low, moderate, or high.

# Results

## Study Selection

A total of 87 articles were yielded from the initial search of databases. After removing duplicates, only 57 articles remained. Fifty studies were eliminated after titles and abstracts were screened. Seven papers were then obtained and evaluated for inclusion through a full text review.

Finally, three articles failed to meet the inclusion criteria and were therefore excluded, resulting in four, level II evidence articles being incorporated into the analysis. (Figure 2).[19,22–24]

## Demographics and Clinical Characteristics

Our cohort comprised 448 patients who were diagnosed with blepharoptosis and received either oxymetazoline 0.1% (n = 275/448, 61.4%) or placebo (n = 173/448, 38.6%). The weighted mean age was 57.7 years (95% CI: 44.5 years – 70.9 years) in the oxymetazoline group and 52.2 years (95% CI: 35.5 years – 68.9 years) in the placebo group (p = 0.61). An overall female predominance was noticed in both groups [oxymetazoline group: 73.6% (95% CI: 67.3–79.0%) and placebo group: 69.3% (95% CI: 62.0–75.7%), p = 0.36]. See Table 1 and Supplementary Table 1.[19,22–24]

There were no statistically significant differences between the oxymetazoline group [1.2% (95% CI: 0.4–3.6%)] and the placebo group [1.6% (95% CI: 0.5–5.3%), p = 0.73] in terms of serious adverse events (Table 1). In both groups, punctate keratitis was the most common adverse event [oxymetazoline group: 5.8% (95% CI: 3.3–10.0%) and placebo group: 3.2% (95% CI: 1.1–8.8%), p =0.33]. In the oxymetazoline group, the second most common adverse event was

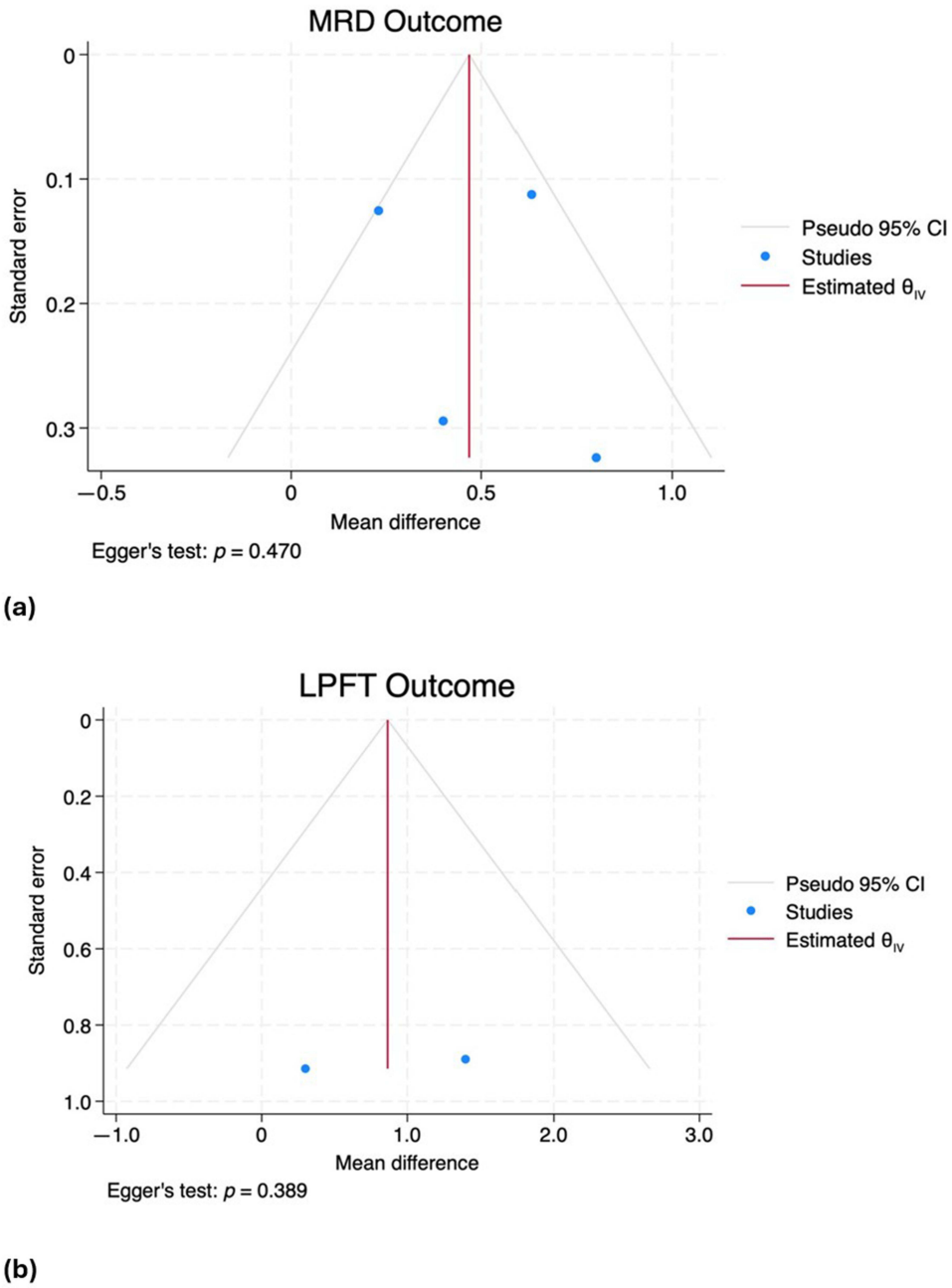


**Figure 1** Funnel plots of (a) MRD1 and (b) LPFT outcomes.
**Abbreviations**: MRD, marginal reflex distance 1 in mm; LPFT, Leicester peripheral field test; CI, confidence interval.

conjunctival hyperemia [4.6% (95% CI: 2.4–8.6%), p =0.20]. In contrast, the second most common adverse event in the placebo group was eye pruritus [3.1% (95% CI: 1.1–8.4%), p = 0.50; Table 1].

## Risk of Bias Assessment

All four included RCTs demonstrated a low risk of bias in terms of bias of measurement of outcome, missing data, and deviation from intended intervention.[19,22–24] Where two of the included studies demonstrated unclear risk in terms of random sequence generation and selection bias.[22,24] See Figure 3 [19,22–24] and Figure 4.[19,22–24]

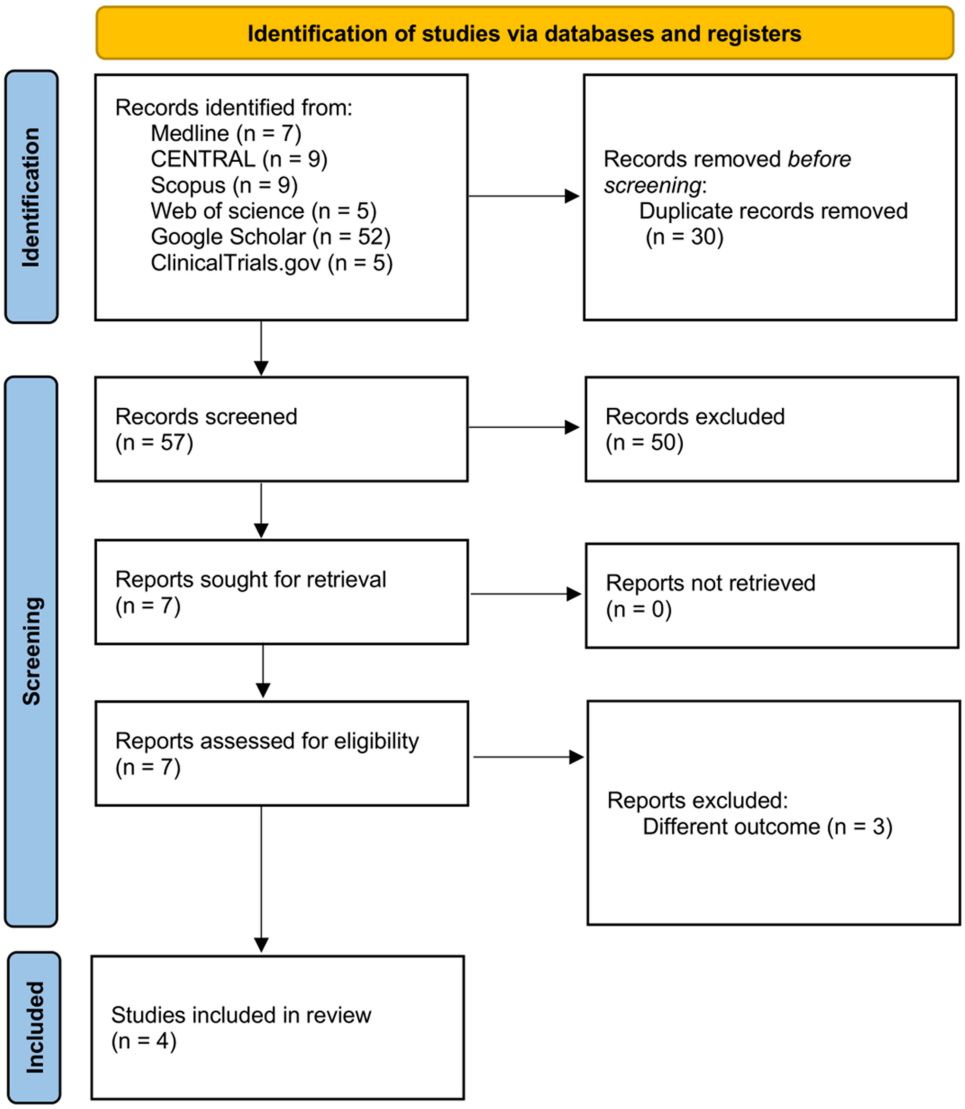


**Figure 2** PRISMA flowchart for articles screening process.

## Intervention vs Placebo Outcomes

In the subgroup meta-analysis of studies including data from baseline to day 14 of the trial, there was a statistically significant weighted mean difference (WMD) in both outcome measures: MRD1 and Leicester peripheral field test (LPFT). The overall pooled WMD for the MRD1 outcome [0.37 (95% CI: 0.13–0.6), z = 3.04] showed that oxymetazoline significantly increases MRD1 compared to placebo ($p<0.01$; Figure 5). Using the GRADE criteria, the quality of

**Table 1** Demographic Characteristics and Clinical Outcomes

| Variable | Oxymetazoline (n = 275) | Placebo (n = 173) | *p*-value |
|---|---|---|---|
| Age | 57.7 (44.5–70.9) | 52.2 (35.5–68.9) | 0.61 |
| Female | 73.6% (67.3–79.0%) | 69.3% (62.0–75.7%) | 0.36 |
| Male | 26.4% (21.0–32.7%) | 30.7% (24.3–38.0%) | 0.36 |

(*Continued*)


https://doi.org/10.2147/OPTH.S529633

**Table 1** (Continued).

| Variable | Oxymetazoline (n = 275) | Placebo (n = 173) | *p*-value |
|---|---|---|---|
| **Other (not serious) adverse events** | | | |
| Eye pruritus | 1.5% (0.2–9.2%) | 3.1% (1.1–8.4%) | 0.50 |
| Conjunctival hyperemia | 4.6% (2.4–8.6%) | 1.5% (0.3–7.2%) | 0.20 |
| Punctate keratitis | 5.8% (3.3–10.0%) | 3.2% (1.1–8.8%) | 0.33 |
| Dry eye | 4.3% (1.7–10.3%) | 3.0% (1.1–8.2%) | 0.62 |
| Headache | 3.3% (1.4–7.6%) | 1.8% (0.4–6.9%) | 0.47 |
| Serious adverse events | 1.2% (0.4–3.6%) | 1.6% (0.5–5.3%) | 0.73 |
| **Outcome measures** | | | |
| MRD | 0.37 (0.13–0. 6) | 0.26 (0.30–0.48) | **0.001*** |
| LPFT | 4.72 (3.37–6.08) | 0.3 (−1.5–2.1) | **0.001*** |
| Mortality | 0.9% (0.2–3.5%) | 1.3% (0.3% - 4.9%) | 0.73 |

**Notes**: All data are reported as weighted mean differences (95% confidence intervals) or logit-proportions % (95% confidence intervals), derived from meta-analyses. *Bold indicates statistical significance.
**Abbreviations**: MRD 1, marginal reflex distance 1 in mm; LPFT, Leicester peripheral field test.

evidence for this outcome yielded moderate certainty of evidence (Table 2). In terms of LPFT outcome, the overall pooled WMD [4.72 (95% CI: 3.37–6.08), z = 6.84] revealed that oxymetazoline significantly improves LPFT outcome compared to placebo (p<0.01; Figure 6). Using the GRADE criteria, the quality of evidence was assessed and yielded moderate certainty (Table 2). The weighted mortality rates between the groups were statistically non-significant (p = 0.73). While the mortality rate of the Oxymetazoline group was 0.9% (95% CI: 0.2–3.5%), the mortality rate of the placebo group was 1.3% (0.3–4.9%; Table 1).

## Discussion

Blepharoptosis is a common diagnosis encountered in oculoplastic clinics and is typically managed through surgical intervention. Although surgical correction of eyelid position is considered the standard of care, it carries risks such as infection, delayed wound healing, and eyelid scarring.[34] These potential complications may be avoided with the use of

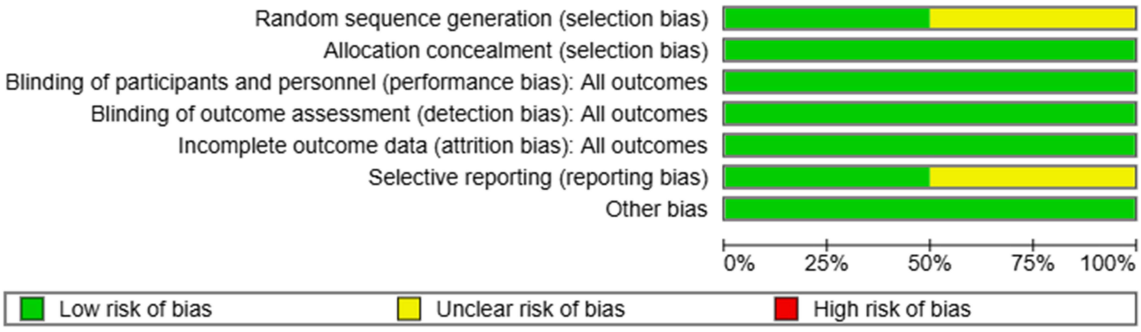


**Figure 3** Risk of bias graph. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

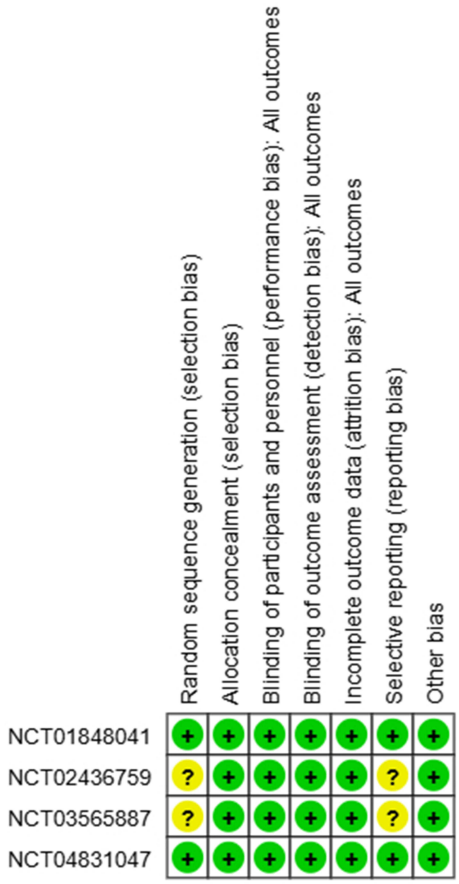


**Figure 4** Risk of bias summary.

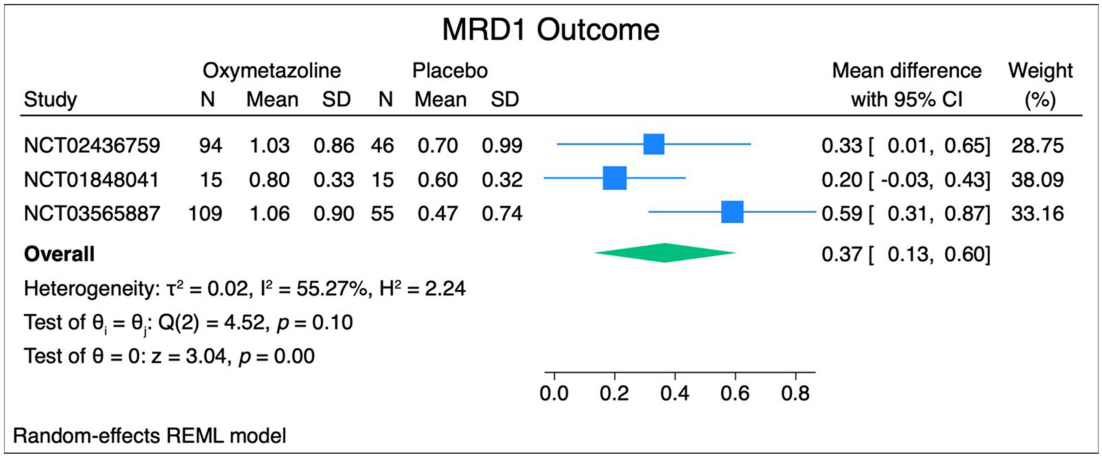


**Figure 5** Forest plots of mean change in MRD1 measurements.
**Abbreviations**: MRD1, marginal reflex distance 1 in mm; SD, standard deviation; NCT, national clinical trial; CI, confidence interval.

oxymetazoline eye drops, which act on Müller's muscle to elevate the upper eyelid and thereby improve ptosis.[35,36] Additionally, through its alpha-adrenergic agonist properties, oxymetazoline may also reduce ocular redness.[37]

Our findings demonstrated the superiority of oxymetazoline over placebo in improving ptosis. Daily administration of oxymetazoline significantly enhanced both marginal reflex distance 1 and Leicester Peripheral Field Test scores. Across

**Table 2** Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Evidence Profile

| Certainty Assessment | | | | | | | Certainty |
|---|---|---|---|---|---|---|---|
| **Outcome** | **Study Design** | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other Consideration** | |
| MRD1 | Randomized trials | Not serious | Not serious | Not serious | Serious[a] | None | ⊕⊕⊕◯ Moderate[a] |
| LPFT | Randomized trials | Not serious | Not serious | Not serious | Serious[a] | None | ⊕⊕⊕◯ Moderate[a] |

**Note**: [a]small sample size.

the included studies, MRD1 improvement from baseline ranged from 0.80 mm to 1.06 mm.[22–24] Notably, a previous study by Uragdar et al reported a potential increase in MRD1 of up to 1.9 mm.[38] This is clinically relevant, as ptosis that improves by at least 1 mm in MRD1 may be functionally and cosmetically significant. Furthermore, LPFT scores were significantly higher in the oxymetazoline group, further supporting the efficacy of the medication.

Both treatment and placebo groups reported a small number of non-serious adverse events, including pruritus, conjunctival hyperemia, punctate keratitis, dry eye, and headache. Serious adverse events and mortality rates were comparable between the two groups, with no statistically significant differences observed. These findings suggest that oxymetazoline may be considered safe for short-term use over a 14-day period.

Patients with ptosis may experience psychosocial impacts, including anxiety and depression due to concerns about appearance and social judgment.[8] Prior studies have shown that surgical correction of ptosis can positively influence self-perception and psychological well-being.[21,39,40] Similarly, quality of life has been reported to improve following ptosis correction.[14,39,41] One of the RCTs included in our analysis also reported that oxymetazoline improved patient-perceived eye appearance.[19] Moreover, a study by Wirta et al found that oxymetazoline had tolerability and safety profiles comparable to placebo, with most adverse events deemed unrelated to treatment.[42]

Given its favorable safety and efficacy profiles, oxymetazoline may serve as a valuable non-surgical option for patients with mild to moderate ptosis or those ineligible for surgery. However, our findings have certain limitations, including the short follow-up duration of existing studies, which evaluated outcomes over only 14 days. This is may partly be due to oxymetazoline's recent approval by the US Food and Drug Administration (FDA) in 2020. Additionally, the limited number of available RCTs and our inclusion of only English-language studies may have introduced selection bias and restricted the generalizability of our findings.

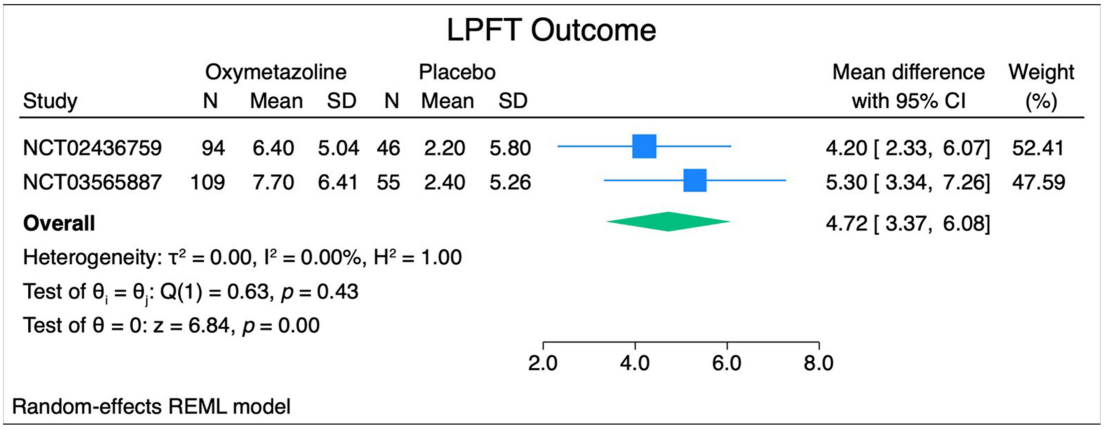


**Figure 6** Forest plots of mean change in LPFT measurements.
**Abbreviations**: LPFT, Leicester peripheral field test; SD, standard deviation; NCT, national clinical trial; CI, confidence interval.

## Conclusion

In conclusion, this meta-analysis suggests that oxymetazoline 0.1% ophthalmic solution may be an effective and well-tolerated short-term treatment for acquired blepharoptosis. The included randomized controlled trials generally demonstrated improvements in marginal reflex distance and peripheral visual field outcomes. Additionally, oxymetazoline was associated with a low incidence of adverse events, and no serious safety concerns were reported.

While these findings are promising, further research is warranted to evaluate the long-term efficacy and safety of oxymetazoline. Larger, high-quality randomized controlled trials and comparative studies against surgical interventions are needed to clarify their role in clinical practice. In the interim, oxymetazoline may offer a promising, non-invasive treatment alternative for patients who choose to forgo surgery, with the potential to improve functional vision and quality of life.

## Acknowledgments

We extend our sincere gratitude to all individuals who contributed to the success of this research project.

## Author Contributions

All authors contributed substantially to the work, including aspects such as the conception, study design, execution, data acquisition, analysis, and interpretation. They participated in drafting, revising, or critically reviewing the manuscript, approved the final version for publication, agreed on the selected journal, and accepted responsibility for all elements of the work.

## Funding

This research did not receive any specific grant from commercial, public funding agencies or non-profit sectors.

## Disclosure

The authors declare no conflicts of interest in this work.

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