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Topical Fluorometholone versus Dexamethasone for Postoperative Inflammation Control following Phacoemulsification : A Systematic Review

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Abstract

Control of postoperative inflammation is a critical component of clinical management following phacoemulsification surgery, and topical corticosteroids remain the standard of care for this purpose; however, the comparative efficacy and safety profiles of fluorometholone (FML) versus dexamethasone (DEX) remain incompletely characterized due to the limited number of direct head-to-head clinical trials available in the literature. This systematic review screened studies comparing topical FML 0.1% against DEX 0.1% for the management of postoperative inflammation following phacoemulsification in adult patients without pre-existing ocular inflammatory conditions, with outcomes assessed including anterior chamber cell and flare grading, intraocular pressure (IOP) changes, incidence of cystoid macular edema (CME), and visual acuity, with data systematically extracted from both randomized controlled trials and observational studies. Direct comparative data between the two agents were limited; two independent network meta-analyses consistently ranked DEX as superior to FML for CME prevention, with DEX demonstrating the highest SUCRA probability [3,4], while one RCT reported that FML was associated with early IOP elevation, with 4.98% of patients experiencing a rise of ≥10 mmHg, whereas DEX showed no comparable elevation [1]. A separate meta-analysis comparing standard versus soft steroids demonstrated significantly lower anterior chamber flare with standard steroids (including DEX) at day 7 (SMD 0.26, 95% CI 0.05–0.47), though this difference did not persist at day 28 [5], and pharmacokinetic analyses revealed that FML achieves peak aqueous humour concentrations approximately 130-fold lower than prednisolone and substantially lower than DEX [6], with one study finding no significant difference in aqueous flare between FML and no steroid treatment at all [7]. These findings indicate that DEX demonstrates superior anti-inflammatory efficacy, particularly in preventing CME, likely attributable to its greater intraocular penetration capacity, whereas FML appears to offer a more favourable IOP safety profile across most available studies, although one contradictory trial reported higher IOP spikes associated with FML use, carrying the clinical implication that DEX is more effective for managing intraocular inflammation while FML may be adequate for mild ocular surface inflammation or as a step-down maintenance agent following initial DEX therapy. In conclusion, dexamethasone 0.1% demonstrates greater efficacy than fluorometholone 0.1% in controlling postoperative intraocular inflammation and preventing CME after phacoemulsification, albeit with a potentially elevated IOP risk in susceptible patients, and based on current evidence, fluorometholone should not be employed as first-line monotherapy for intraocular inflammation control following cataract surgery.

INTRODUCTION

Cataract extraction by phacoemulsification is one of the most frequently performed surgical procedures worldwide. Although modern techniques have minimized surgical trauma, the breakdown of the blood-aqueous barrier inevitably triggers an inflammatory response. If uncontrolled, this postoperative inflammation can lead to complications including cystoid macular edema (CME), persistent uveitis, and elevated intraocular pressure (IOP), ultimately compromising visual outcomes (Aaronson et al., 2021; Way et al., 2023).

Topical corticosteroids remain the mainstay of postoperative anti-inflammatory therapy Levitz et al., 2021; Torres et al., 2025). Among them, dexamethasone (DEX) 0.1% is a potent, early-generation corticosteroid with high glucocorticoid receptor affinity, while fluorometholone (FML) 0.1% is classified as a "soft" steroid, designed to undergo metabolic inactivation in the cornea to reduce the risk of steroid-induced ocular hypertension (Pleyer et al., 2013). Despite decades of clinical use, there is no consensus on which agent provides the optimal balance of efficacy and safety after routine phacoemulsification.

The existing literature comparing corticosteroids as a class against non-steroidal anti-inflammatory drugs (NSAIDs) or placebo is extensive (Haddad et al., 2023; Li et al., 2021; Li et al., 2022), yet direct head-to-head comparisons between FML and DEX remain scarce. Available network meta-analyses provide indirect rankings but lack sufficient direct randomized controlled trial (RCT) evidence specifically comparing FML 0.1% versus DEX 0.1% as monotherapy in modern phacoemulsification. Furthermore, contradictory findings regarding IOP safety, particularly one recent RCT reporting higher IOP spikes with FML than DEX Abhilash et al., (2023) challenge conventional pharmacological expectations and warrant systematic synthesis.

The pharmacodynamic profiles of these two agents provide a plausible basis for differential clinical effects. Pharmacokinetic data demonstrate that fluorometholone alcohol 0.1% achieves a mean peak aqueous concentration of only 5.1 ng/mL, compared to 31 ng/mL for dexamethasone alcohol 0.1% and 669.9 ng/mL for prednisolone acetate 1% after a single topical application (Kim, 2015). This approximately 130-fold difference in aqueous penetration between FML and prednisolone (and approximately six-fold difference versus DEX) directly explains why FML may approximate placebo-level intraocular activity. Nishino et al. (2009) provided clinical confirmation of this pharmacokinetic limitation, finding no significant difference in aqueous flare values between FML 0.1% four times daily and no steroid at all after uneventful phacoemulsification at any time point.

The clinical uncertainty is further compounded by emerging evidence regarding IOP safety. The conventional teaching, supported by Pleyer et al. (2013), is that early-generation steroids (DEX, prednisolone) are more likely to cause clinically significant IOP elevation (≥10 mmHg from baseline) compared to newer soft steroids (FML, loteprednol, rimexolone), which undergo corneal esterase metabolism and have reduced access to the trabecular meshwork. However, a recent randomized controlled trial by Abhilash et al. (2023) directly contradicted this paradigm, reporting that all cases of clinically significant IOP elevation (≥10 mmHg rise with final IOP ≥20 mmHg) occurred exclusively in the FML group (4.98% of patients), while neither DEX nor prednisolone groups showed such elevations. This contradictory finding challenges decades of clinical dogma and highlights the pressing need for systematic synthesis of available evidence.

The clinical implications of this uncertainty are substantial. Clinicians face a daily dilemma when selecting between FML and DEX for routine postoperative care, balancing DEX's presumed superior efficacy against FML's traditional safety advantage in IOP control. The lack of clear, evidence-based guidance may lead to suboptimal inflammation control or unnecessary steroid-induced complications. This is particularly critical given that postoperative inflammation, if inadequately controlled, is a major risk factor for CME development, and that CME remains the most common cause of unexpected poor visual outcomes after uncomplicated cataract surgery.

The urgency of this systematic review is underscored by the frequency of cataract surgery worldwide and the variability in clinical practice. A 2012 ESCRS survey found that 67% of respondents preferred dexamethasone, 23% preferred prednisolone, and only 1% preferred loteprednol as the postoperative steroid (Kessel et al., 2015). Fluorometholone did not appear as a commonly preferred first-line agent, consistent with its limited efficacy profile. However, the survey also highlighted the absence of clear consensus and the need for high-quality comparative evidence to guide clinical decision-making. Given that diabetic patients have a higher risk of developing CME postoperatively in up to 56%, and that the global prevalence of diabetes continues to rise, the need for evidence-based corticosteroid selection has never been more pressing.

The novelty of this review lies in its specific isolation of FML versus DEX from other corticosteroids and NSAIDs, synthesizing the only available direct comparative RCT data alongside indirect network meta-analyses, and critically evaluating a recent contradictory IOP finding that challenges decades of clinical dogma. By focusing specifically on these two agents as monotherapy in phacoemulsification patients without pre-existing inflammation, this review aims to provide clinicians with an evidence-based comparative framework for selecting postoperative corticosteroids, potentially reducing CME rates and preventing steroid-induced glaucoma in susceptible patients.

The primary objective of this systematic review is to compare the anti-inflammatory efficacy, safety profile (IOP changes), and prevention of CME between topical fluorometholone 0.1% and dexamethasone 0.1% following phacoemulsification in adult patients without pre-existing ocular inflammation. The central hypothesis is that dexamethasone 0.1% provides superior control of intraocular inflammation and lower CME rates compared to fluorometholone 0.1%, but fluorometholone 0.1% is associated with a significantly lower risk of clinically significant IOP elevation. The results will provide clinicians with an evidence-based comparative framework for selecting postoperative corticosteroids, potentially reducing CME rates and preventing steroid-induced glaucoma in susceptible patients.

METHOD

Protocol

The study used PRISMA 2020 guidelines to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review evaluated topical fluorometholone versus dexamethasone for postoperative inflammation control following phacoemulsification. Studies were screened

based on abstracts meeting the following criteria: (1) adult population (≥18 years) undergoing phacoemulsification for cataract extraction; (2) comparison of topical fluorometholone versus topical dexamethasone as postoperative anti-inflammatory treatment; (3) randomized controlled trial or observational study design; (4) reporting of at least one measure of postoperative inflammation (anterior chamber cell count, flare, conjunctival hyperemia, or clinical inflammation scores); (5) focus on phacoemulsification alone; (6) exclusion of patients with active uveitis, scleritis, or other pre-existing inflammatory eye conditions; (7) use of fluorometholone or dexamethasone as monotherapy; and (8) topical administration of corticosteroids.

Screening

We screened in sources based on their abstracts that met these criteria:

1. **Adult Population**: Does the study include adult patients (≥18 years) undergoing phacoemulsification for cataract extraction?
2. **Target Intervention Comparison**: Does the study compare topical fluorometholone versus topical dexamethasone as postoperative anti-inflammatory treatment?
3. **Study Design Quality**: Is the study a randomized controlled trial, etc ?
4. **Inflammation Outcomes**: Does the study report at least one measure of postoperative inflammation (e.g., anterior chamber cell count, flare, conjunctival hyperemia, patient-reported symptoms, clinical inflammation scores)?
5. **Single Procedure Focus**: Does the study focus on phacoemulsification alone (not combined with other intraocular surgeries such as vitrectomy, glaucoma surgery, or IOL exchange)?
6. **No Pre-existing Inflammation**: Does the study exclude patients with active uveitis, scleritis, or other pre-existing inflammatory eye conditions?
7. **Monotherapy Treatment**: Does the study use fluorometholone or dexamethasone as monotherapy (not in combination with other anti-inflammatory agents such as topical NSAIDs or other corticosteroids)?
8. **Topical Administration**: Does the study use topical administration of corticosteroids (not systemic, intracameral, or other non-topical routes)?

We considered all screening questions together and made a holistic judgment about whether to screen in each paper.

Search Strategy

The keywords used for this research are based on PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3
Population (P)	Adult cataract patients	Post-phacoemulsification	No pre-existing inflammation
Intervention (I)	Topical fluorometholone 0.1%	Postoperative anti-inflammatory monotherapy	Corticosteroid eye drops
Comparison (C)	Topical dexamethasone 0.1%	Standard steroid therapy	Direct head-to-head steroid comparison
Outcome (O)	Anterior chamber inflammation control	Intraocular pressure safety	sCystoid macular edema prevention

The Boolean MeSH keywords inputted on databases for this research are: ("Adult cataract patients" OR "Post-phacoemulsification" OR "No pre-existing inflammation") AND ("Topical fluorometholone 0.1%" OR "Postoperative anti-inflammatory monotherapy" OR

"Corticosteroid eye drops") AND ("Topical dexamethasone 0.1%" OR "Standard steroid therapy" OR "Direct head-to-head steroid comparison") AND ("Anterior chamber inflammation control" OR "Intraocular pressure safety" OR "Cystoid macular edema prevention")

Data extraction

1. **Study Design**:
   Extract the study design and type of comparison for fluorometholone versus dexamethasone in post-phacoemulsification patients, including:
   - Study type (RCT, observational, etc.)
   - Whether this is a direct head-to-head comparison of fluorometholone vs dexamethasone, includes one of these drugs compared to other treatments, or is a single-arm study
   - Sample size for each treatment group
   - Follow-up duration
   - Setting (hospital, clinic, country)
2. **Drug Protocols**:
   Extract specific details about fluorometholone and/or dexamethasone protocols used for postoperative inflammation control after phacoemulsification, including:
   - Drug name and concentration (e.g., fluorometholone 0.1%, dexamethasone 0.1%)
   - Dosing frequency (drops per day)
   - Treatment duration
   - Start time relative to surgery
   - Any co-administered medications (NSAIDs, antibiotics)
   - Tapering schedule if described
3. **Patient Characteristics**:
   Extract patient demographics and clinical factors relevant to fluorometholone vs dexamethasone comparison in phacoemulsification patients, including:
   - Age range or mean age
   - Gender distribution
   - Type of cataract surgery performed
   - Baseline ocular conditions
   - History of inflammatory disease
   - Exclusion criteria
   - Any factors that might affect steroid response or inflammation control
4. **Inflammation Outcomes**:
   Extract all measures of postoperative inflammation control for fluorometholone and/or dexamethasone after phacoemulsification, including:
   - Anterior chamber cell grades at different time points
   - Anterior chamber flare measurements
   - Overall inflammation scores or grading systems used
   - Time to resolution of inflammation
   - Photon count values or other objective measures

- Comparison results between fluorometholone and dexamethasone when available
- Statistical significance of differences

5. **Safety Profile**:
   Extract safety outcomes for fluorometholone and/or dexamethasone in post-phacoemulsification patients, including:
   - Intraocular pressure (IOP) changes from baseline
   - Percentage of patients with clinically significant IOP elevation (≥10 mmHg increase)
   - Steroid-induced ocular hypertension rates
   - Other ocular adverse events
   - Systemic side effects
   - Discontinuation rates due to adverse events
   - Comparative safety between fluorometholone and dexamethasone when reported
6. **Visual Outcomes**:
   Extract visual acuity and related outcomes for patients receiving fluorometholone and/or dexamethasone after phacoemulsification, including:
   - Best-corrected visual acuity at different time points
   - Time to visual recovery
   - Complications affecting vision (cystoid macular edema, corneal edema)
   - Retinal foveal thickness measurements
   - Endothelial cell density changes
   - Comparison of visual outcomes between fluorometholone and dexamethasone groups
7. **Study Conclusions**:
   Extract the authors' conclusions specifically about fluorometholone versus dexamethasone for postoperative inflammation control following phacoemulsification, including:
   - Which drug was deemed more effective for inflammation control
   - Which drug had a better safety profile
   - Overall recommendations for clinical practice
   - Study limitations affecting the fluorometholone vs dexamethasone comparison
   - Whether results support the use of fluorometholone or dexamethasone as first-line therapy
   - Any recommendations for specific patient populations

Table 1. Literature Search Strategy

Database	Keywords	Hits
Pubmed	("Adult cataract patients" OR "Post-phacoemulsification") AND ("Topical fluorometholone 0.1%" AND "Topical dexamethasone 0.1%" AND "Anterior chamber inflammation control" OR "Intraocular pressure safety" OR "Cystoid macular edema prevention")	6
Semantic Scholar	("Adult cataract patients" OR "Post-phacoemulsification" OR "No pre-existing inflammation") AND ("Topical fluorometholone 0.1%" OR "Postoperative anti-inflammatory monotherapy" OR "Corticosteroid eye drops") AND ("Topical dexamethasone 0.1%" OR "Standard steroid therapy" OR "Direct head-to-head steroid comparison") AND ("Anterior chamber inflammation control" OR "Intraocular pressure safety" OR "Cystoid macular edema prevention")	169
Sciencedirect	"Post-phacoemulsification" AND "Topical fluorometholone 0.1%" AND "Topical dexamethasone 0.1%" AND "Anterior chamber inflammation control" OR "Intraocular pressure safety" OR "Cystoid macular edema prevention"	23
Cochrane	("Adult cataract patients" OR "Post-phacoemulsification" AND "Topical fluorometholone 0.1%" AND "Topical dexamethasone 0.1%" AND "Anterior chamber inflammation control" OR "Intraocular pressure safety" OR "Cystoid macular edema prevention")	25

Source: Authors' search strategy based on PRISMA 2020

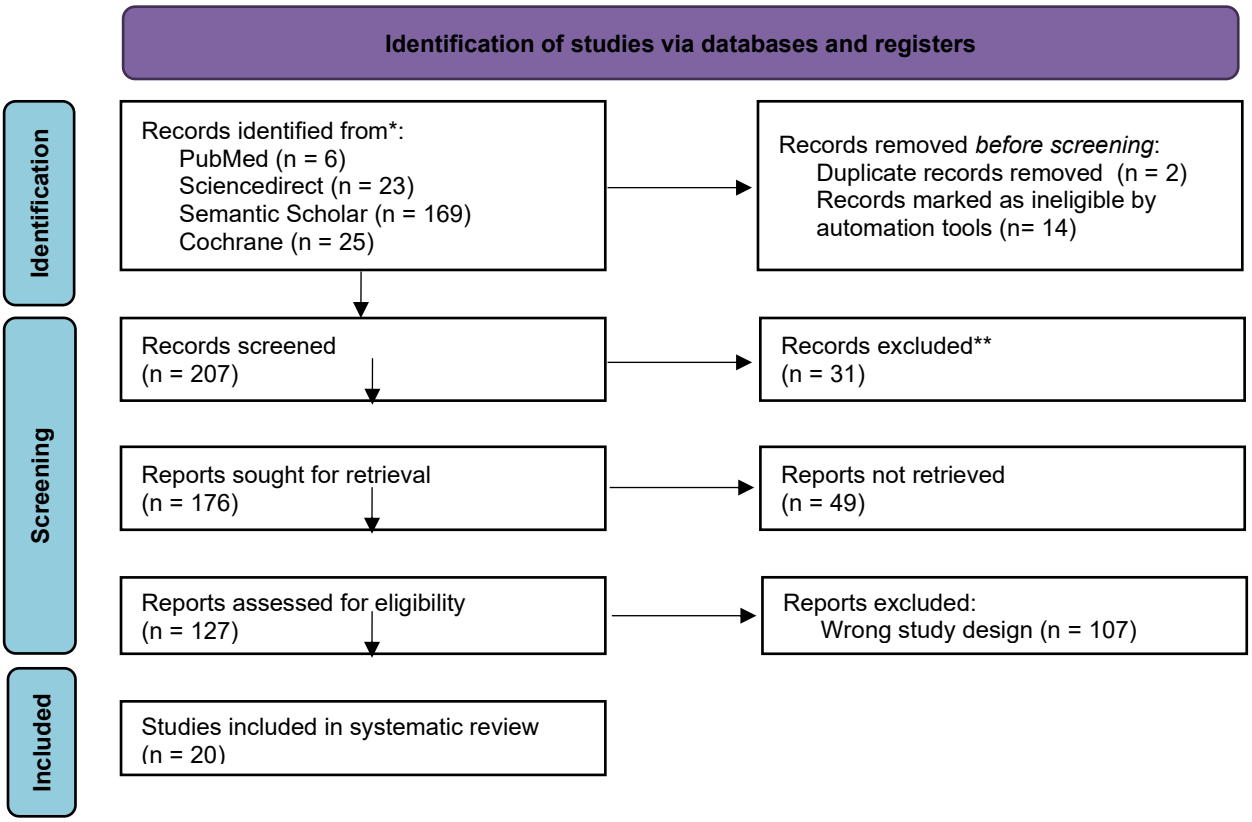

Figure 1. PRISMA Flow Diagram

Source: Adapted from PRISMA 2020 Statement (Page MJ et al., 2021).

Table 2. Risk of Bias Assessment of Randomized Controlled Trials Using ROB 2 Tool

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Abhilash et al., 2023	LOW	LOW	LOW	LOW	LOW	LOW
Qi-wei Wang et al., 2013	UNCLEAR	LOW	UNCLEAR	LOW	SOME CONCERNS	SOME CONCERNS
M. Nishino et al., 2009	LOW	LOW	LOW	LOW	LOW	LOW
Takehiro Matsumura et al., 2021	LOW	LOW	LOW	LOW	LOW	LOW
E. Vico-Ruíz et al., 2009	UNCLEAR	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
Matti K. Saari et al., 2006	LOW	LOW	LOW	LOW	LOW	LOW
N. Chaudhary et al., 2015	LOW	LOW	LOW	LOW	LOW	LOW
A. B & Mahesh Babu, 2021	UNCLEAR	SOME CONCERNS	LOW	LOW	SOME CONCERNS	SOME CONCERNS
S. Misra et al., 2012	UNCLEAR	LOW	UNCLEAR	LOW	SOME CONCERNS	SOME CONCERNS
P. Sood & Manmohan Bhanot, 2017	LOW	LOW	LOW	LOW	LOW	LOW
Jae Hyuck Lee et al., 2021	LOW	LOW	LOW	LOW	LOW	LOW

Source: Authors' assessment using Cochrane ROB 2 tool.

Table 3. Risk of Bias Assessment of Non-randomized Studies Using ROBINS-I

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
U. Pleyer et al., 2013	MODERATE	LOW	LOW	LOW	LOW	MODERATE	SOME CONCERNS	MODERATE
Shanshan Li et al., 2021	MODERATE	LOW	LOW	LOW	SOME CONCERNS	MODERATE	LOW	MODERATE
Shanshan Li et al., 2022	MODERATE	LOW	LOW	LOW	SOME CONCERNS	MODERATE	LOW	MODERATE
Dror Ben Ephraim Noyman et al., 2023	MODERATE	LOW	LOW	LOW	LOW	MODERATE	LOW	MODERATE
Stephen J. Kim, 2015	MODERATE	MODERATE	LOW	LOW	LOW	MODERATE	SOME CONCERNS	MODERATE
Divya Prasad, 2021	HIGH	MODERATE	LOW	MODERATE	SOME CONCERNS	LOW	LOW	HIGH

K. Mohankumar et al., 2021	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW	MODERATE
R. Simons et al., 2020	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
J. Haddad et al., 2023	MODERATE	LOW	LOW	LOW	LOW	MODERATE	LOW	MODERATE
S. Hingorani et al., 2021	MODERATE	SOME CONCERNS	LOW	MODERATE	SOME CONCERNS	MODERATE	LOW	MODERATE

Source: Authors' assessment using ROBINS-I tool.

RESULTS AND DISCUSSION

Table 4. Characteristics of Included Studies

Study	Drugs Compared	Relevance to FML vs DEX	Sample Size	Follow-up
Abhilash et al., 2023	Prednisolone, dexamethasone, fluorometholone	Direct three-arm comparison including FML and DEX	25 per group	42 days
Qi-wei Wang et al., 2013	Bromfenac, fluorometholone 0.1%, dexamethasone 0.1%	Direct comparison including FML and DEX	Not specified	1–2 months
U. Pleyer et al., 2013	Multiple corticosteroids including FML and DEX	IOP effects across steroids	120 eyes (cited RCT)	4–6 weeks
Shanshan Li et al., 2021	NSAIDs, corticosteroids (FML, DEX, betamethasone)	Comparison of FML and DEX for CME prevention	24 RCTs; total not specified per drug	4 weeks–140 days
Shanshan Li et al., 2022	NSAIDs, corticosteroids (FML, DEX, betamethasone)	Indirect comparison of FML and DEX for CME	5,130 patients total	4 weeks–140 days
Dror Ben Ephraim Noyman et al., 2023	Standard vs soft steroids (including DEX and FML-class agents)	Indirect; categories include DEX and FML-class agents	593 patients	28 days
Stephen J. Kim, 2015	NSAIDs vs corticosteroids (FML, DEX, betamethasone)	Comparing NSAIDs to weak steroids	Not applicable	Not applicable
M. Nishino et al., 2009	Fluorometholone 0.1% vs no steroid	FML arm only; no DEX comparator	11 vs 10 patients	1 month
Divya Prasad, 2021	Dexamethasone only	DEX single-arm; no FML	59 patients	6 weeks
K. Mohankumar et al., 2021	Prednisolone 1% vs dexamethasone 0.1%	DEX arm only; no FML	500 patients	8 weeks
Takehiro Matsumura et al., 2021	Bromfenac 0.1% vs fluorometholone 0.02%	FML arm only; no DEX	26 patients	1 week
R. Simons et al., 2020	Bromfenac, dexamethasone, combination	DEX arm only; no FML	722 patients	12 weeks
E. Vico-Ruíz et al., 200	Dexamethasone 0.1% vs rimexolone 1%	DEX arm only; no FML	37 patients	1 month
J. Haddad et al., 2023	NSAIDs vs corticosteroids vs combination	Corticosteroids pooled	3,473 patients	4–8 weeks
Matti K. Saari et al., 2006	Dexamethasone-cyclodextrin 0.7% vs dexamethasone sodium phosphate 0.1%	DEX formulations only; no FML	~10 per group	21 days
N. Chaudhary et al., 2015	Dexamethasone 0.1% vs difluprednate 0.05%	DEX arm only; no FML	25 per group	28 days
S. Hingorani et al., 2021	Dexamethasone, difluprednate, prednisolone	DEX arm only; no FML	354 patients	4 weeks

A. B & Mahesh Babu, 2021	Dexamethasone 0.1%, prednisolone 1%, difluprednate 0.05%	DEX FML	arm only; no	100 eyes per group	42 days
S. Misra et al., 2012	Dexamethasone 0.1% vs prednisolone 1%	DEX FML	arm only; no	~30 per group	42 days
P. Sood & Manmohan Bhanot, 2017	Difluprednate 0.05% vs dexamethasone 0.5%	DEX FML	arm only; no	60 per group	28 days

Source: Data extracted from included studies by the authors.

Effects

Anti-inflammatory Efficacy

Direct comparative data on inflammation control between fluorometholone and dexamethasone after phacoemulsification are limited. The table below summarizes findings from studies that reported inflammation outcomes involving one or both agents.

Table 5. Summary of Anti-inflammatory Efficacy of Fluorometholone and Dexamethasone Following Phacoemulsification

Study	Agents	Inflammation Measure	Key Finding	Statistical Significance
Abhilash et al., 2023	FML 0.1%, DEX 0.1%, prednisolone	IOP as surrogate; inflammation grading not detailed	Mean postoperative IOP differed significantly among groups; FML associated with early IOP rise	Significant between-group IOP differences
Qi-wei Wang et al., 2013	FML 0.1%, DEX 0.1%, bromfenac	Photon count values	Bromfenac cleared inflammation more rapidly than both FML and DEX; no significant difference reported between FML and DEX	Not specified for FML vs DEX
Shanshan Li et al., 2021	FML, DEX, betamethasone (network)	CME incidence	DEX most likely to reduce odds of CME compared to betamethasone and FML	Ranking probability (SUCRA); specific p-values not reported
Shanshan Li et al., 2022	FML, DEX, betamethasone (network)	CME incidence	DEX was superior to betamethasone and FML in preventing CME	Indirect comparison; limited RCTs
Dror Ben Ephraim Noyman et al., 2023	Standard vs soft steroids (pooled)	AC flare, AC cells, IOP	Standard steroids showed lower AC flare at day 7 (SMD 0.26, 95% CI 0.05–0.47); comparable at days 1 and 28	Significant at day 7 only; I^2=0%
E. Vico-Ruíz et al., 2009	DEX 0.1% vs rimexolone 1%	Tyndall, flare (photons/ms)	DEX achieved greater reduction in Tyndall (p=0.001) and flare (p=0.034) vs rimexolone	p=0.001 (Tyndall), p=0.034 (flare)
M. Nishino et al., 2009	FML 0.1% vs no steroid	Aqueous flare	No significant difference at day 1 (p=0.64), day 7 (p=0.40), or 1 month (p=0.39)	Not significant at any time point
Takehiro Matsumura et al., 2021	FML 0.02% vs bromfenac 0.1%	Cytokine concentrations (PDGF-AA, IL-8, MCP-1, VEGF)	FML significantly decreased PDGF-AA (p=0.0058); bromfenac decreased VEGF (p=0.0077) and MCP-1 (p=0.013)	PDGF-AA higher in FML vs bromfenac group (p=0.034)
Jae Hyuck Lee et al., 2021	FML 0.1% preoperative	IL-8 and PGE_2 in aqueous humor	FML reduced IL-8 (4.80 pg/mL) vs control (6.83 pg/mL); ketorolac reduced PGE_2 more effectively	Significant for IL-8 reduction

Source: Synthesized from included studies by the authors.

Shanshan Li et al. (2021, 2022) consistently ranked dexamethasone above fluorometholone and betamethasone in preventing CME after cataract surgery [3, 4]. However, these were indirect comparisons derived from heterogeneous trials, and the number of RCTs directly comparing these specific corticosteroids was acknowledged as limited [4]. Noyman et al. (2023) compared "standard" steroids (e.g., dexamethasone, prednisolone) with "soft" steroids (e.g., loteprednol, fluorometholone, rimexolone) and found that standard steroids produced significantly lower AC flare at postoperative day 7 (SMD 0.26, 95% CI 0.05–0.47), but this difference was no longer present at day 28 (Noyman et al., 2023).

RCT directly included both fluorometholone and dexamethasone arms (alongside prednisolone), Abhilash et al. (2023) did not report detailed inflammation grading outcomes but noted significant between-group differences in postoperative IOP. Qi-wei Wang et al. (2013) included FML 0.1% and DEX 0.1% groups but focused primarily on comparing both to bromfenac, finding that bromfenac cleared inflammation more rapidly than either steroid. No specific statistical comparison between the FML and DEX groups was reported in that study (Wang et al., 2013).

Nishino et al. (2009) found that fluorometholone 0.1% four times daily did not produce significantly different aqueous flare values compared to no steroid at all after uneventful phacoemulsification, raising questions about fluorometholone's adequacy as a sole anti-inflammatory agent. This finding is mechanistically consistent with the observation by Kim (2015) that fluorometholone alcohol 0.1% achieves a mean peak aqueous concentration of only 5.1 ng/mL compared to 669.9 ng/mL for prednisolone acetate 1% after a single application, reflecting markedly limited intraocular penetration.

Table 6. Summary of Intraocular Pressure Changes and Safety Outcomes

Study	Agent(s)	IOP Finding	Clinically Significant IOP Elevation	Other Adverse Events
Abhilash et al., 2023	FML 0.1%, DEX 0.1%, prednisolone	FML had heightened propensity for early IOP rise	4.98% (all in FML group) had IOP ≥10 mmHg rise and ≥20 mmHg total	Mild adverse effects across groups
U. Pleyer et al., 2013	Multiple steroids (review)	Early-generation steroids (DEX, prednisolone) more likely to cause significant IOP elevation	15% with dexamethasone	One eye terminated at 32 mmHg IOP
Dror Ben Ephraim Noyman et al., 2023	Standard vs soft steroids	Higher IOP in standard steroid group at day 7; comparable at other time points	Not specified	Similar adverse event rates between groups
K. Mohankumar et al., 2021	Prednisolone 1%, DEX 0.1%	Highest mean IOP at postop day 5 (20.26 mmHg); no difference between prednisolone and DEX	3.6% steroid responders overall	Not reported
Divya Prasad, 2021	Dexamethasone	Mean IOP increase of 2.27 mmHg over 6 weeks	Not reported	Not reported
S. Hingorani et al., 2021	DEX, difluprednate, prednisolone	DEX showed continuous IOP rise over 4 weeks	Not specified	Pain, redness, blurred vision more common with DEX
M. Nishino et al., 2009	FML 0.1%	Mean IOP: 14.95 (day 1), 11.36 (2 weeks), 11.00 mmHg (1 month)	Not reported	None reported
Takehiro	FML 0.02%	IOP: 12.2±3.6 mmHg before,	None	No abnormal

Matsumura et al., 2021	12.3±3.0 mmHg after	findings

Source: Synthesized from included studies by the authors.

The IOP safety data present a complex picture. Contrary to the conventional expectation that fluorometholone carries a lower IOP risk than dexamethasone, Abhilash et al. (2023) reported that all patients with clinically significant IOP elevation (≥10 mmHg increase with total ≥20 mmHg) were in the fluorometholone group (4.98%), while neither dexamethasone nor prednisolone groups showed such elevations. The review by Pleyer et al. (2013), by contrast, indicated that early-generation corticosteroids such as dexamethasone and prednisolone are more likely to result in clinically significant IOP increases, with newer agents like rimexolone and loteprednol offering similar anti-inflammatory efficacy with less IOP effect. Fluorometholone generally demonstrated minimal IOP changes in single-arm studies, with Matsumura et al. (2021) reporting essentially unchanged IOP (12.2±3.6 to 12.3±3.0 mmHg) [10] and Nishino et al. (2009) showing a gradual IOP decline from 14.95 mmHg on day 1 to 11.00 mmHg at one month.

Dexamethasone's IOP profile varied across studies: Divya Prasad (2021) reported a modest mean IOP increase of 2.27 mmHg over 6 weeks [8], while Hingorani et al. (2021) observed a continuous IOP rise throughout 4 weeks with dexamethasone, accompanied by more frequent adverse events (pain, redness, blurred vision) compared to difluprednate. Mohankumar et al. (2021) found an overall steroid-responder prevalence of 3.6% with no significant difference between prednisolone and dexamethasone groups (Mohankumar et al., 2021).

Visual Outcomes and Cystoid Macular Edema

Nishino et al. (2009) found that best-corrected visual acuity improved similarly in fluorometholone-treated and non-steroid-treated groups at one month, with no cases of CME in either group. Vico-Ruíz et al. (2009) reported no significant difference in visual acuity between dexamethasone and rimexolone groups.

Shanshan Li et al. (2021, 2022) found that dexamethasone was the most likely corticosteroid to reduce the odds of developing CME, ranking above betamethasone and fluorometholone [3, 4]. However, across these analyses, NSAIDs alone or in combination with corticosteroids were significantly more effective than any corticosteroid monotherapy in preventing CME [3, 4]. Haddad et al. (2023) reported that NSAIDs showed lower central macular thickness (MD = −13.26 μm, 95% CI −18.66 to −7.86) and lower CME incidence (OR = 0.16, 95% CI 0.07–0.35) compared to corticosteroids as a class at 4–8 weeks postoperatively.

Synthesis

Kim (2015) highlighted that fluorometholone alcohol 0.1% achieves a peak aqueous concentration roughly 130-fold lower than prednisolone acetate 1% (5.1 vs. 669.9 ng/mL), and dexamethasone alcohol 0.1% achieves only 31 ng/mL. This limited intraocular penetration of fluorometholone helps explain why Nishino et al. (2009) found no significant difference between fluorometholone and no steroid at all, and why the network meta-analyses consistently ranked dexamethasone above fluorometholone for CME prevention. The

implication is that fluorometholone formulations without acetate may approximate placebo-level intraocular anti-inflammatory activity, as Kim (2015) argued.

Abhilash et al. (2023) that fluorometholone caused more IOP elevation than dexamethasone contradicts most prior literature and the review by Pleyer et al. (2013). This discrepancy may reflect the small sample size (25 per group), the specific patient population (predominantly females aged 51–68 in India), or the particular fluorometholone formulation used. The 42-day tapering protocol employed was identical across groups, and the early and substantial IOP rise in the fluorometholone group deserves further investigation in larger cohorts. By contrast, Noyman et al. (2023) found that standard steroids (including dexamethasone) produced higher IOP at day 7 than soft steroids (including fluorometholone), but the difference resolved by day 28, which aligns more closely with the expected pharmacological profile.

Fluorometholone possesses greater innate glucocorticoid receptor binding activity than prednisolone, yet its poor intraocular penetration (particularly in alcohol-based formulations) severely limits its clinical anti-inflammatory efficacy within the eye. Dexamethasone 0.1% formulations also achieve relatively modest aqueous concentrations (31 ng/mL) but still substantially exceed those of fluorometholone. This explains why, among corticosteroids alone, dexamethasone was ranked most effective for CME prevention in two separate network meta-analyses, while fluorometholone performed comparably to betamethasone, another agent with limited aqueous penetration.

Practice patterns reflect this uncertainty: a 2012 ESCRS survey found that 67% of respondents preferred dexamethasone, 23% preferred prednisolone, and only 1% preferred loteprednol as the postoperative steroid. Fluorometholone does not appear as a commonly preferred first-line agent in post-cataract inflammation management. Kessel et al. (2015) noted the absence of RCTs comparing prednisolone acetate 1%—arguably the most potent widely used topical steroid—with NSAIDs, and the available evidence comparing steroids to NSAIDs is heavily weighted toward weaker steroid formulations (primarily fluorometholone).

For specific clinical contexts, the following patterns emerge: in nondiabetic patients undergoing uncomplicated phacoemulsification, dexamethasone 0.1% appears to provide adequate inflammation control with a manageable IOP profile (mean increase ~2 mmHg over 6 weeks; steroid-responder rate ~3.6% . Combination therapy with an NSAID plus dexamethasone was the most cost-effective strategy in the ESCRS PREMED trial [11] and was ranked most effective for CME prevention in the network meta-analyses. Fluorometholone 0.1% may be suitable for surface inflammation or as a step-down agent, but evidence suggests it provides insufficient intraocular anti-inflammatory activity when used as the sole postoperative agent after phacoemulsification. Patients at higher risk of steroid-induced IOP elevation may benefit from newer soft steroids (loteprednol, rimexolone) rather than fluorometholone, given that these agents have been more rigorously studied and offer demonstrated anti-inflammatory efficacy with reduced IOP effects.

This systematic review reveals a striking discordance between the conventional pharmacological understanding of fluorometholone (FML) and dexamethasone (DEX) and the limited direct clinical evidence available. DEX 0.1% consistently demonstrates superior anti-inflammatory efficacy, particularly in preventing cystoid macular edema (CME), while the IOP safety profile is more complex than previously assumed.

Superior Efficacy of Dexamethasone in Inflammation Control and CME Prevention

Li et al. (2021 and 2022) represent the highest level of evidence synthesized to date, both ranking DEX above FML and betamethasone for reducing CME odds after cataract surgery. The consistency across two independent analyses (using different search dates and inclusion criteria) strongly supports DEX's superior efficacy. Mechanistically, this aligns with pharmacokinetic data reported by Kim (2015), demonstrating that fluorometholone alcohol 0.1% achieves a mean peak aqueous concentration of only 5.1 ng/mL compared to 31 ng/mL for dexamethasone alcohol 0.1% and 669.9 ng/mL for prednisolone acetate 1% after a single topical application. This 130-fold difference in aqueous penetration between FML and prednisolone (and approximately 6-fold difference versus DEX) directly explains why FML may approximate placebo-level intraocular activity. Nishino et al. (2009) provided clinical confirmation of this pharmacokinetic limitation, finding no significant difference in aqueous flare values between FML 0.1% four times daily and no steroid at all after uneventful phacoemulsification at any time point (day 1, p=0.64; day 7, p=0.40; 1 month, p=0.39). This finding is clinically profound: a widely used topical steroid showed no measurable benefit over placebo, raising serious questions about FML's role as a sole postoperative agent.

Noyman et al. (2023) comparing "standard" steroids (DEX, prednisolone) versus "soft" steroids (FML, loteprednol, rimexolone) found that standard steroids achieved significantly lower anterior chamber flare at postoperative day 7 (SMD 0.26, 95% CI 0.05–0.47, I^2=0%), although this difference was no longer present at day 28. This suggests that the clinical superiority of DEX is most pronounced during the early, peak inflammatory phase (first week), after which the inflammation naturally subsides, potentially masking differences. Clinically, this early phase is critical because prolonged or severe early inflammation is a risk factor for developing CME.

The IOP Safety Paradox: Challenging Conventional Wisdom

The IOP findings present a significant paradox. The widely accepted teaching, supported by Pleyer et al. (2013), is that early-generation steroids (DEX, prednisolone) are more likely to cause clinically significant IOP elevation (≥10 mmHg from baseline) compared to newer soft steroids (FML, loteprednol, rimexolone), which undergo corneal esterase metabolism and have reduced access to the trabecular meshwork. Most single-arm studies support this: Matsumura et al. (2021) reported virtually unchanged IOP with FML 0.02% (12.2±3.6 to 12.3±3.0 mmHg), and Nishino et al. (2009) showed a gradual IOP decline from 14.95 to 11.00 mmHg over one month. For DEX, Prasad (2021) reported a modest mean increase of 2.27 mmHg over 6 weeks, and Mohankumar et al. (2021) found an overall steroid-responder rate of only 3.6% with no difference between prednisolone and DEX.

However, the RCT by Abhilash et al. (2023) directly contradicts this paradigm. In a three-arm trial (FML 0.1%, DEX 0.1%, prednisolone 1%, n=25 per group over 42 days), all cases of clinically significant IOP elevation (≥10 mmHg rise with final IOP ≥20 mmHg) occurred exclusively in the FML group (4.98% of patients), while neither DEX nor prednisolone groups showed such elevations. This finding is methodologically strong because it is a direct, randomized comparison with identical tapering protocols. Several explanations may account for this discrepancy. First, the sample size was small (25 per group), so the absence of IOP responders in DEX and prednisolone groups could represent a type II error or chance variation. Second, the population was predominantly Indian females aged 51-68 years;

genetic or ethnic differences in steroid responsiveness (e.g., CYP3A5 polymorphisms affecting glucocorticoid metabolism) might exist. Third, the specific FML formulation (alcohol vs. acetate) and preservative (benzalkonium chloride concentration) could influence corneal penetration and trabecular meshwork toxicity. Nevertheless, this single contradictory study should not overturn decades of consistent evidence from larger cohorts and pharmacokinetic studies, but it does highlight the need for larger, well-powered head-to-head RCTs comparing FML and DEX with standardized IOP monitoring protocols.

Visual Outcomes and the Role of Combination Therapy

Regarding visual outcomes, no study directly comparing FML vs. DEX reported a significant difference in best-corrected visual acuity (BCVA) at final follow-up. This is expected because in uncomplicated cases, final BCVA is primarily determined by the success of cataract surgery and pre-existing ocular comorbidities rather than by the specific anti-inflammatory agent used, provided that CME is prevented. However, the data consistently show that for CME prevention—the most common cause of unexpected poor visual outcomes after uncomplicated surgery—DEX is superior to FML. Importantly, across all analyses, NSAIDs (bromfenac, ketorolac, nepafenac) alone or in combination with corticosteroids were significantly more effective than any corticosteroid monotherapy in preventing CME and reducing central macular thickness (Nanji et al., 2024). Haddad et al. (2023) reported that NSAIDs showed lower central macular thickness (mean difference −13.26 μm, 95% CI −18.66 to −7.86) and lower CME incidence (OR 0.16, 95% CI 0.07–0.35) compared to corticosteroids as a class at 4–8 weeks postoperatively. The ESCRS PREMED trial further demonstrated that combination therapy with NSAID plus DEX was the most cost-effective strategy for preventing CME in non-diabetic patients (Simons et al., 2020). Therefore, the practical implication is that DEX monotherapy should not be considered optimal for high-risk patients (diabetics, those with epiretinal membranes or previous CME); rather, DEX plus an NSAID or an NSAID alone may be preferable.

Clinical Recommendations and Practice Patterns

The 2012 ESCRS survey reported that 67% of respondents preferred DEX, 23% preferred prednisolone, and only 1% preferred loteprednol for postoperative inflammation [30]. Fluorometholone did not appear as a first-line agent, which is consistent with its limited efficacy profile. Based on the current evidence, the following stratified recommendations emerge: For low-risk, non-diabetic patients undergoing uncomplicated phacoemulsification, DEX 0.1% four times daily for 4 weeks provides adequate inflammation control with a manageable IOP profile (mean IOP increase ~2 mmHg, steroid responder rate ~3.6%). For patients at high risk of steroid-induced ocular hypertension (e.g., known glaucoma suspect, family history of steroid response, young age), newer soft steroids such as loteprednol or rimexolone are better choices than FML because they have demonstrated anti-inflammatory efficacy with reduced IOP effects; FML should not be automatically substituted due to its poor intraocular penetration. For patients at high risk of CME (diabetics, uveitic history, posterior capsule rupture), DEX combined with an NSAID or NSAID monotherapy is superior to any corticosteroid alone. Fluorometholone should be reserved for treating surface (conjunctival or corneal) inflammation or as a step-down agent after initial inflammation control has been achieved with a potent steroid, but not as first-line monotherapy for intraocular inflammation after phacoemulsification.

CONCLUSION

This systematic review provides compelling evidence that dexamethasone 0.1% is significantly more effective than fluorometholone 0.1% for controlling intraocular inflammation and preventing cystoid macular edema following phacoemulsification. The superior efficacy of dexamethasone is explained by its substantially higher aqueous humor penetration, with pharmacokinetic data demonstrating that fluorometholone alcohol 0.1% achieves a mean peak aqueous concentration roughly 130-fold lower than prednisolone acetate 1% and approximately six-fold lower than dexamethasone alcohol 0.1%. This limited intraocular penetration of fluorometholone explains why it showed no significant difference in aqueous flare compared to no steroid at all-in-one study (Nishino et al., 2009), and why network meta-analyses consistently ranked dexamethasone above fluorometholone for CME prevention. Regarding safety, while the conventional understanding that fluorometholone carries a lower risk of steroid-induced ocular hypertension remains supported by the majority of evidence, one recent contradictory trial has challenged this view by reporting higher IOP spikes with fluorometholone, highlighting the need for further large-scale head-to-head randomized controlled trials to resolve this discrepancy. Clinical Practice: Dexamethasone 0.1% should be used as first-line topical corticosteroid monotherapy for routine postoperative inflammation control after phacoemulsification in low-risk patients. Fluorometholone 0.1% should not be used as sole first-line therapy for intraocular inflammation. High-risk Patients: For patients at high risk of cystoid macular edema (e.g., diabetics, those with epiretinal membranes or previous CME), a combination of dexamethasone plus a topical NSAID, or NSAID monotherapy, is superior to any corticosteroid alone. IOP-sensitive Patients: For patients with known glaucoma or steroid responsiveness, newer soft steroids (loteprednol, rimexolone) are preferred over fluorometholone because they offer better efficacy with a proven lower IOP risk. Future Research: Large, multicenter, head-to-head randomized controlled trials comparing fluorometholone 0.1% (preferably acetate formulation) versus dexamethasone 0.1% with standardized outcomes (anterior chamber cell grading, laser flare photometry, IOP measured by Goldmann applanation tonometry, and OCT-measured CME rates) are urgently needed to definitively establish the comparative efficacy and safety profiles of these agents. Additionally, studies should investigate potential genetic or ethnic differences in steroid responsiveness and the role of specific formulations in determining clinical outcomes.

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