

BMJ Open Difluprednate versus Prednisolone Acetate after Cataract Surgery: a Systematic Review and Meta-Analysis

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ABSTRACT

Objective Topical steroids are the cornerstone in controlling the inflammation after cataract surgery. Prednisolone acetate and difluprednate are the two main products for this purpose. However, it is unclear which one should be used in terms of effectiveness and safety.

Design Systematic review and meta-analysis.

Data sources Medline via PubMed, Cochrane Central Register of Controlled Trials, Web of science and clinicaltrials.gov were searched through 10 January 2018, and updated on 20 July 2019, in addition to researching the references' lists of the relevant articles.

Eligibility criteria Randomised-controlled trials (RCTs) comparing difluprednate and prednisolone acetate regardless of the dosing regimen used.

Data extraction and synthesis Two independent authors assessed the included RCTs regarding the risk of bias using the Cochrane tool. Relevant data were extracted, and meta-analysis was conducted using a random-effects model. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to appraise the evidence quality.

Results We included six RCTs with 883 patients: 441 received difluprednate and 442 received prednisolone acetate. The evidence quality was graded as moderate for corneal oedema and intraocular pressure and low for anterior chamber (AC) clearance. After small incision cataract surgery, difluprednate was superior in clearing AC cells at 1 week (OR=2.5, $p>0.00001$) and at 2 weeks (OR=2.5, $p=0.04$), as well as clearing the AC flare at 2 weeks (OR=6.7, $p=0.04$). After phacoemulsification, difluprednate was superior in terms of corneal clarity at 1 day (OR=2.6, $p=0.02$) and 1 week after surgery (OR=1.96, $p=0.0007$). No statistically significant difference was detected between both agents at 1 month in effectiveness. Also, both agents were safe, evaluated by the ocular hypertension (OR=1.23, $p=0.8$).

Conclusion With low-to-moderate certainty, difluprednate and prednisolone acetate are safe agents for controlling the inflammation after cataract surgery. Difluprednate showed significant superiority in terms of AC cells and AC flare at 2 weeks postoperatively.

INTRODUCTION

Cataract is the leading cause of blindness worldwide, mainly affecting the elderly population. Presently, surgery is the only therapeutic option for cataracts. That is why

Strengths and limitations of this study

- This is the first systematic review to summarize the evidence for topical steroids after cataract surgery in terms of effectiveness and safety.
- The comprehensive search of the databases (yielding three trials) and the hand searching (yielding three additional trials) provide a holistic approach for this question.
- The Grading of Recommendations Assessment, Development, and Evaluation approach is applied aiming to evaluate the certainty of the synthesised evidence to help clinicians make better decisions.
- The main limitation is the inherent bias and heterogeneity in the included studies.
- The subgroup analysis for the age and technique can alleviate that limitation.

about eight million cataract surgeries are performed annually. Moreover, increased life expectancy justifies the expectation that even more surgeries will be performed in the next years.¹ Fortunately, cataract surgery is among the most successful procedures, in particular the phacoemulsification or the small incision cataract surgery (SICS) techniques. Technological advances in this field have led to higher patient expectations regarding visual outcomes and comfort of the procedure.²

Postoperative inflammation is a commonly encountered event after cataract surgery. In most cases it is low grade and self-limiting, with slight patient's discomfort, which may persist for days after the surgery.³ Nevertheless, suboptimal vision is a rare, yet significant consequence of severe inflammation. Corneal oedema, secondary glaucoma, anterior or posterior synechia and macular oedema are reported events related to severe inflammation. Thus, adequate management of postcataract inflammation is essential.⁴ Although different anti-inflammatory agents are available, those with corticosteroids are the most common.⁵

Corticosteroids are potent inhibitors of phospholipase A2 enzyme, which control

synthesis of arachidonic acid, the precursor of many inflammatory mediators. That is how corticosteroids can suppress the inflammatory response and guard against complications. However, side effects are a major source of concern when using treatments containing these agents. Impaired healing and ocular hypertension are not rare events associated with corticosteroid use.⁶ Different agents are available, and prednisolone acetate is the most widely prescribed. Prednisolone acetate has broad and potent anti-inflammatory effects, which have been reported for decades. Being lipophilic, it is available in a suspension form that requires shaking before administration. With low patient compliance, dose uniformity is a great concern.⁷ To overcome this, some physicians practice more frequent dosing of prednisolone, which in turn increases the risk of the previously reported complications.

In 2008, the Food and Drug Administration (FDA) approved the use of difluprednate to control pain and inflammation after ocular surgery.⁸ Difluprednate is a butyrate ester derivative of prednisolone, with two fluorine atoms at C6 and C9. As an emulsion, difluprednate drops provide consistent and uniform doses without requiring shaking.⁷ In addition, the difluorination of the molecule increases its affinity to glucocorticoid receptors,

and thereby its potency, compared with all other steroid molecules. Moreover, difluprednate has enhanced penetration to the uvea, due to the acetate ester group at C21. Since 2008, many studies have investigated the safety and effectiveness of the new drug, which has shown encouraging results, with growing use in clinical practice, alongside prednisolone.⁹

Many randomised-controlled trials (RCTs) were conducted to compare both agents in real-life settings after cataract surgery. However, no quantitative evidence exists. In this review, we aim to compare the two major anti-inflammatory agents: prednisolone acetate and difluprednate after cataract surgery using either the phacoemulsification method or the SICS method. Such comparison will help elucidate the safety and effectiveness of both agents after routine cataract surgery.

METHODS

Eligibility criteria for considering studies for this review

Types of studies

We considered RCTs in which difluprednate was compared with prednisolone acetate regardless of the dosing regimen used. Given that it is a recent clinical question

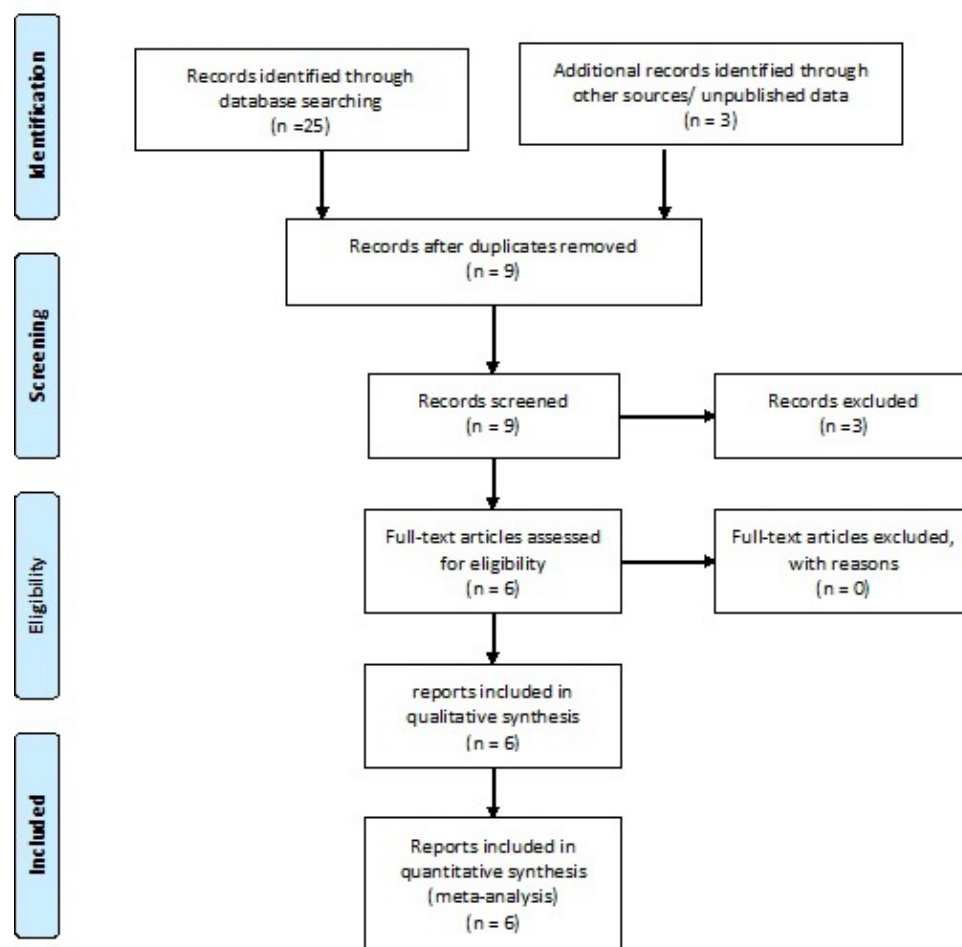


Figure 1 Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

with few RCTs conducted to date, quasi-randomised trials as well as conference abstracts were considered.

Types of participants

We included trials in which participants underwent uncomplicated cataract surgery with or without intraocular lens (IOL) implantation. To be included, participants must be free from any ocular or systemic disease that could flare or suppress the inflammatory response, including but not limited to diabetes mellitus, uveitis and systemic immunological diseases. Either phacoemulsification or SICS procedures were eligible. No age restrictions were applied.

Patient and public involvement

No patients were involved in the analysis of the RCT data sets.

Types of interventions

Difluprednate and prednisolone acetate eye drops

Types of outcome measures

RCTs were considered if at least one of the following outcomes was reported:

Primary outcome measures

1. The effectiveness of the drug, indicated by the proportion of participants with no cell or flare at day 15 (± 2 days).
2. The safety of the drug, indicated by the proportion of participants who experienced intraocular pressure (IOP) elevations.

Secondary outcome measures

1. Other effectiveness measures: absence of anterior chamber (AC) cells or flare at days 1, 7 (± 1 day) and 28 (± 2 days), and absence of corneal oedema at days 1, 7 (± 1 day), 15 (± 2 days) and 28 (± 2 days).
2. Proportion of patients who achieved a best-corrected visual acuity (BCVA) of 6/6 (or its equivalents, 1.00 on decimal chart or 0 on Logarithm of the Minimum Angle of Resolution (LogMAR) chart) at day 14 (± 2 days).

Table 1 Main characteristics of included studies

Study	Country	N	Inclusion criteria	Exclusion criteria
Donnenfeld, 2011	USA	104	Patients 21 years of age and older, who require bilateral cataract surgery, scheduled to undergo standard cataract surgery with topical anaesthesia in both eyes within 6–25 days between surgeries; BCVA better than 20/100 in both eyes with a visual potential of 20/25 or better	Use of any eye medications other than study drugs; regional or general anaesthesia during surgery; pupillary dilatation less than 5 mm before surgery; any surgical complication; history of uveitis, glaucoma; macular pathological features; lack of an intact corneal epithelium; diabetes mellitus; and any condition requiring use of a systemic steroidal or non-steroidal anti-inflammatory drug during the study period. A history of steroid-related IOP rise and previous intraocular surgery also resulted in exclusion
Gundakalle, 2013 ¹⁴	India	100	Patients between the ages of 50 years and 80 years, scheduled for SICS with IOL	Allergy to any of the study medications, preoperative inflammation in either eye, history of ocular trauma, CL wear, previous intraocular surgery, glaucoma, uveitis, pseudoexfoliation syndrome "PEX", any intraoperative complications
Devi, 2014 ¹³	India	100	Patients who underwent SICS and IOL implantation	N/A
Garg, 2016 ¹¹	India	100	Patients above 18 years with visually significant cataract requiring cataract surgery	Patients with diabetes, hypertension or any other systemic disease, use of ophthalmic analgesics, any other ocular disease including uveitis and glaucoma, and any operative complications
Manna, 2016 ¹²	India	400	Patients more than 40 years with senile cataract, scheduled for cataract (manual small incision cataract) and posterior chamber "PC" IOL (Polymethyl methacrylate "PMMA" IOL), by the same experienced surgeon	Allergy to any study drug, uveitis, iritis, intraocular inflammation due to any previous ocular surgery in either eye, single-eyed patients
Wilson, 2016	USA	79	Paediatric patients (0–3 years), with uncomplicated cataract surgery in one eye \pm IOL implantation	Active uveitis, or any active or suspected infection in the study eye; systemic use of steroids or non-steroidal anti-inflammatory drugs; a history of steroid-induced increases in IOP; medications for ocular hypertension or glaucoma in the study eye; traumatic cataract; suspected permanent low vision or blindness in the non-study eye; or diabetes

BCVA, best-corrected visual acuity; IOL, intraocular lens; IOP, intraocular pressure; SICS, small incision cataract surgery.

Table 2 Interventions and outcomes of included studies

Study	Arms	Outcomes
Donnenfeld, 2011	<ul style="list-style-type: none"> ▶ Experimental (n=52): difluprednate 0.05%, <u>On the day of surgery (day 0):</u> 1 drop every 15 min during the hour before arrival to the surgery centre. <u>On arrival,</u> staff-administered 1 drop every 15 min (three drops total). <u>After surgery,</u> a single drop was instilled immediately on entry to surgical recovery, another drop was administered while in surgical recovery, and a final drop was given on leaving surgical recovery. <u>After discharge,</u> 1 drop of medication every 2 hours for the remainder of day 0. <u>Starting on the day after surgery (day 1),</u> four times a day for 1 week and two times per day for the subsequent week. ▶ Control(n=52): prednisolone acetate 1%, following the same schedule described above. 	<ul style="list-style-type: none"> ▶ Primary: change from baseline in corneal thickness at day 1. ▶ Secondary: corneal thickness at day 15±2 days and at day 30±3 days; UCVA at all time points; BCVA at all time points; corneal oedema (epithelial and stromal) at all time points; endothelial cell counts at day 30±3 days; OCT-CRT at day 15±2 days and at day 30±3 days; and IOP at all time points.
Gundakalle, 2013 ¹⁴	<ul style="list-style-type: none"> ▶ Experimental (n=50): difluprednate 0.05% six times a day. Duration wasn't reported. ▶ Control (n=50): prednisolone acetate 1% six times a day. Duration wasn't reported. 	<ul style="list-style-type: none"> ▶ Primary: the proportion of patients with an mRS Score of 3–6 at 1 year. ▶ Secondary: results based on actual treatment as opposed to the primary intent-to-treat analysis and separate evaluation of patients' crossing over from their assigned group to the alternative treatment group.
Devi 2014 ¹³	<ul style="list-style-type: none"> ▶ Experimental (n=50): difluprednate 0.05% for 3 weeks. Dosing frequency wasn't provided. ▶ Control (n=50): prednisolone acetate 1% for 3 weeks. Dosing frequency wasn't provided. 	<ul style="list-style-type: none"> ▶ Primary: effectiveness (clearing of inflammation) at day 14: AC cells, AC flare, chemosis, ocular pain and visual acuity. ▶ Secondary: Effectiveness and safety at days 0, 1, 7, 28 and 35. Safety measures were IOP and any AEs.
Garg 2016 ¹¹	<ul style="list-style-type: none"> ▶ Experimental (n=50): 0.05% difluprednate ophthalmic emulsion drops, six times a day for 4 weeks. ▶ Control (n=50): prednisolone acetate 1% ophthalmic suspension drops, six times a day for 4 weeks. 	<ul style="list-style-type: none"> ▶ Primary: Effectiveness of the drug on day 1, first week, second week, fourth week with following parameters: ocular pain, anterior chamber reaction in the form of aqueous cells and flare and final visual acuity. ▶ Secondary: Safety and adverse events (including IOP changes).
Manna 2016 ¹²	<ul style="list-style-type: none"> ▶ Experimental (n=200): Difluprednate 0.05% ophthalmic emulsion, starting 24 hours after surgery: 1 drop four times a day for 2 weeks, then 1 drop two times per day for 1 week, then one drop once a day for 1 week. ▶ Control (n=200): Prednisolone acetate 1% ophthalmic suspension, starting 24 hours after surgery: 1 drop eight times a day for 1 week, then 1 drop six times a day for 1 week, then 1 drop four times a day for 1 week, then 1 drop two times per day for 1 week. 	<ul style="list-style-type: none"> ▶ Primary: Effectiveness measured at day 1, first week, second week and fourth week after surgery. Measure of effectiveness were AC cells and flare. ▶ Secondary: Safety assessed at 6 weeks after the surgery via BCVA and IOP.
Wilson 2016	<ul style="list-style-type: none"> ▶ Experimental (n=39): difluprednate 0.05% (durezol ophthalmic emulsion, Alcon Laboratories, Fort Worth, Texas, USA). Dosing regimen was: day 0 one drop, then four times a day for 14 days, then tapering for 14 days according to investigator's assessment. ▶ Control (n=40): prednisolone acetate 1% (PredForte ophthalmic suspension, Allergan, Irvine, California, USA). The same dosing regimen as the experimental arm was applied. 	<ul style="list-style-type: none"> ▶ Primary: Safety assessed via IOP changes and any other AEs at days 0, 1, 8 (±1 day) and 15 (±2 days), and at the end of study (day 29±2 days). ▶ Secondary: Effectiveness evaluated at days 0, 1, 8 (±1 day) and 15 (±2 days), and at the end of study (day 29±2 days). Measures of effectiveness were number and percentage of patients with an anterior cell grade of 0 (no cells) at the end of the 14day treatment period (day 15±2 days) as a primary end point, and at other time points as secondary measures.

AC, anterior chamber; BCVA, best-corrected visual acuity; CRT, central retinal thickness; IOP, intraocular pressure; OCT, optical coherence tomography; UCVA, uncorrected visual acuity.

Search methods for identifying studies

Different electronic databases were searched for relevant RCTs through 10 January 2018 and updated on 20 July 2019. Included databases were MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials and Web of Science. Additionally, Clinicaltrials.gov was searched for completed and ongoing clinical trials. Search strategies were constructed and applied, in addition to researching the reference lists of the relevant studies (see the online

supplementary appendix). No language restrictions were applied.

Study selection

Search results were screened by two independent authors for de-duplication. After that, title and abstract screening was performed. Full texts of relevant studies were obtained and screened based on the eligibility criteria specified

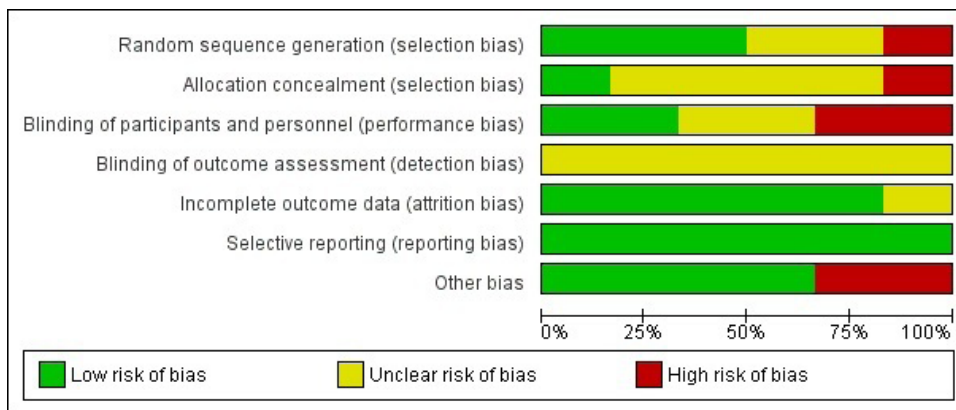


Figure 2 Risk of bias graph.

above. Any discrepancies were resolved by discussion or by consulting the third author.

Data collection and risk of bias assessment

Full texts of included studies were thoroughly appraised to extract relevant data by two independent authors. AC activity (cells and flare), corneal oedema, IOP and BCVA were extracted at different time points. Using the

Cochrane tool for assessing the risk of bias, each trial was assessed in six domains: sequence generation, allocation concealment, blinding, attrition bias, selective outcome reporting and other sources of bias. Each trial was labelled as high, low or unclear in each domain with the rationale for each decision.

Data synthesis and analysis

Dichotomous outcomes were reported with their OR and 95% CI by determining the number of participants who experienced a certain outcome and the total number of participants. We used a random-effects model, which was found to be superior to a fixed-effect one, to obtain a pooled estimate of ORs, and we created a forest plot for each treatment outcome when possible. In the case of substantial heterogeneity, subgroup analysis for the surgical technique (phacoemulsification vs SICS) was planned. Substantial heterogeneity was defined as $I^2 < 50\%$. We determined that subgroup analysis of dosing regimen would be unreliable due to the wide variation in dosing schedules.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Devi 2014	?	?	●	?	?	+	+
Donnenfeld 2011	+	+	+	?	+	+	●
Garg 2016	+	?	?	?	+	+	+
Gundakalle 2013	?	?	?	?	+	+	+
Manna 2016	●	●	●	?	+	+	+
Wilson 2016	+	?	+	?	+	+	●

Figure 3 Risk of bias summary.

RESULTS

Eligible studies

Searching different databases yielded 24 papers. After de-duplication, nine were screened for eligibility. This yielded three RCTs matching the prespecified criteria. Moreover, three trials were retrieved through researching the reference lists of included articles. In total, six RCTs were included in the analysis.¹⁰⁻¹⁵ Figure 1 illustrates the flow of article selection according to the Preferred reporting Items for Systematic Reviews and Meta-Analyses.

Descriptive analysis of the included studies

In all, six RCT studies were included in the analysis. They included 883 patients who underwent uncomplicated cataract surgery, with 441 having received difluprednate and 442 prednisolone acetate. Manna and Puzari's was the largest study with 400 patients, so it was the most influential in the outcomes reported here.¹²

Baseline characteristics of participants were variable among the studies, mainly age and surgical technique.

**Table 3** Risk of bias in included studies

Bias	Judgement	Justification
Donnenfeld, 2011		
Random sequence generation (selection bias)	Low risk	'patients were assigned randomly to receive either difluprednate or prednisolone for treatment of the first eye; the second eye was assigned the alternative medication'
Allocation concealment (selection bias)	Low risk	'Allocation of the medication was concealed from the investigators based on a random number list generated using randomizer.org'
Blinding of participants and personnel (performance bias)	Low risk	'Both investigators and patients were masked to the treatment condition. Study medication (obtained from commercial sources) was relabeled in a manner so as to obscure the bottle shape and contents'
Blinding of outcome assessment	Unclear risk	Not reported
Incomplete outcome data	Low risk	All relevant outcomes were reported in detail
Selective reporting (reporting bias)	Low risk	All study patients were included in the analysis
Other bias	High risk	'Publication of this article was supported with an unrestricted grant from Sirion Therapeutics, Tampa, Florida'. Donnenfeld, Holland and Solomon have received consulting fees, honoraria and research support from Alcon Laboratories, Allergan, Bausch and Lomb, and Sirion
Manna, 2016		
Random sequence generation (selection bias)	High risk	'odd number patients were included in group -A (Difluprednate) and the even number patients were included in group -B (Prednisolone)'
Allocation concealment (selection bias)	High risk	'odd number patients were included in group -A (Difluprednate) and the even number patients were included in group -B (Prednisolone)'
Blinding of participants and personnel (performance bias)	High risk	'It is a single-blinded study'
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All enrolled patients were included in the analysis
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	Not detected
Wilson, 2016		
Random sequence generation (selection bias)	Low risk	'Patients were randomly assigned to treatment groups in accordance to a planned ratio of 1:1. Randomisation numbers were generated using computer software (PROC PLAN, SAS Institute, Cary, North Carolina, USA)'
Allocation concealment (selection bias)	Unclear risk	No specified method reported
Blinding of participants and personnel (performance bias)	Low risk	'Patients, caregivers, and investigators were masked to the medication being instilled. Because prednisolone acetate 1% is a suspension that needs to be shaken before instillation, parents or legal guardians of patients were instructed to shake the assigned medication bottle before instillation to preserve masking'
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All enrolled patients were included
Selective reporting (reporting bias)	Low risk	All specified outcomes are reported
Other bias	High risk	'The study was sponsored and supported, in part, by a grant from Alcon Laboratories, Inc. (Fort Worth, TX, USA). Alcon Laboratories, Inc. participated in the design and conduct of the study, data collection, data management, data analysis, interpretation of the data, preparation, review, and approval of the manuscript'
Garg, 2016		
Random sequence generation (selection bias)	Low risk	'They were randomly divided into two groups'

Continued

Table 3 Continued

Bias	Judgement	Justification
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All enrolled patients were followed for the study duration
Selective reporting (reporting bias)	Low risk	Main outcomes were reported
Other bias	Low risk	No other bias could be detected
Gundakalle; 'A 1 year randomised controlled trial to compare the effectiveness and safety of difluprednate ophthalmic emulsion 0.05% with topical prednisolone acetate 0.1% ophthalmic suspension in the control of postoperative inflammation following cataract surgery'		
Random sequence generation (selection bias)	Unclear risk	Randomisation method wasn't specified
Allocation concealment (selection bias)	Unclear risk	Concealment method wasn't reported
Blinding of participants and personnel (performance bias)	Unclear risk	Authors didn't report if blinding was applied or not
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All study personnel were followed, and the master data sheet was included in the online supplementary appendix
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported and analysed
Other bias	Low risk	No other form of bias could be detected
Devi, 2014		
Random sequence generation (selection bias)	Unclear risk	Authors reported that '100 patients were randomised 1:1 into two groups', however, randomisation method wasn't specified
Allocation concealment (selection bias)	Unclear risk	Concealment method wasn't reported
Blinding of participants and personnel (performance bias)	High risk	'open-labelled study'
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	The authors didn't report the proportion of patients assessed at each follow-up visit
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	No other form of bias could be detected

Wilson evaluated difluprednate in paediatric patients (0–3 years) after uncomplicated phacoemulsification with or without IOL implantation,¹⁰ while all other studies included only adults after uncomplicated cataract surgery (either phacoemulsification or SICS) with IOL implantation. Donnenfeld *et al*, Wilson *et al* and Garg *et al*¹¹ compared both agents after uncomplicated phacoemulsification, with a total of 283 patients.^{10 11 15} On the other hand, Devi *et al*, Gundakalle *et al*^{13 14} and Manna and Puzari¹² performed SICS with a total of 600

patients.^{12–14} Tables 1 and 2 plot the main characteristics of the included studies.

Risk of bias

Using the Cochrane tool for risk of bias assessment, all included studies were assessed in different domains. In the selection bias domain, three studies (Donnenfeld *et al*,¹¹ Garg *et al* and Wilson *et al*) were adequately randomised,^{10 11 15} one study¹² was quasi-randomised¹² and two studies did not report a randomisation method.^{13 14}

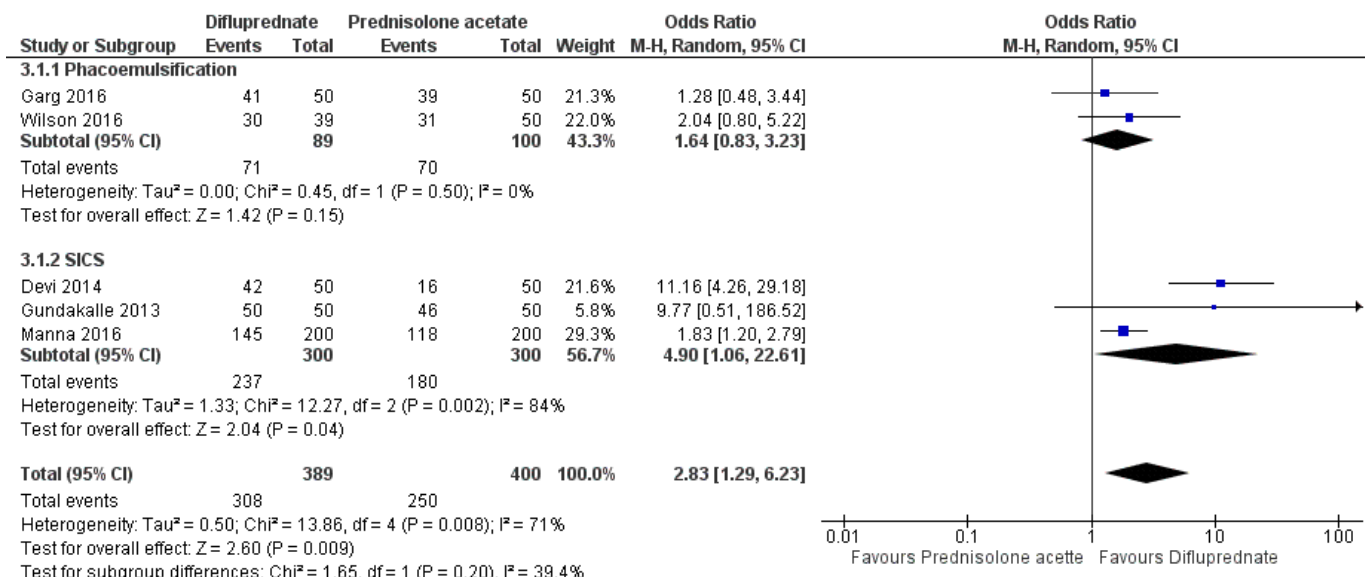


Figure 4 Forest plot for anterior chamber AC cells at 15 days. SICS, small incision cataract surgery. M-H: Mantel-Haenszel test, I²: a test for heterogeneity.

Only Donnenfeld *et al* was judged to be low risk regarding allocation concealment.¹⁵ Out of the six trials, only two were double-masked (Donnenfeld *et al* and Wilson *et al*), while Devi *et al*¹³ was an open label study and Manna and Puzari¹² was a single-blinded study.^{10 12 13 15} None of the included studies reported whether the outcomes' assessors were blinded or not. Figures 2 and 3 show the risk of bias in different domains for all the included studies, and table 3 explains the judgement for all domains. Contrary to initial plans, publication bias was not assessed due to the relatively low number of included studies (less than 10). Also, the included studies had similar sample sizes ranging from 79 to 104, except for Manna and Puzari¹² which included 400 eyes.

Primary outcomes

In this review, the primary goal was to assess the effectiveness of both agents to control postoperative inflammation. AC reaction, assessed as the proportion of patients free from AC cells and/or flare at 15±2 days, was used as a measure of effectiveness. At 15±2 days, all studies, except Donnenfeld *et al*¹⁵ reported the proportion of patients that were free from AC cells, totalling 779 patients: 389 and 390 in the difluprednate and prednisolone arms, respectively. Absent AC cells (or grade 0) were observed in 308 and 250 patients in the difluprednate and prednisolone arms, respectively, with a significantly improved outcome in the difluprednate group (OR=2.83, 95% CI 1.29 to 6.23, p=0.009).

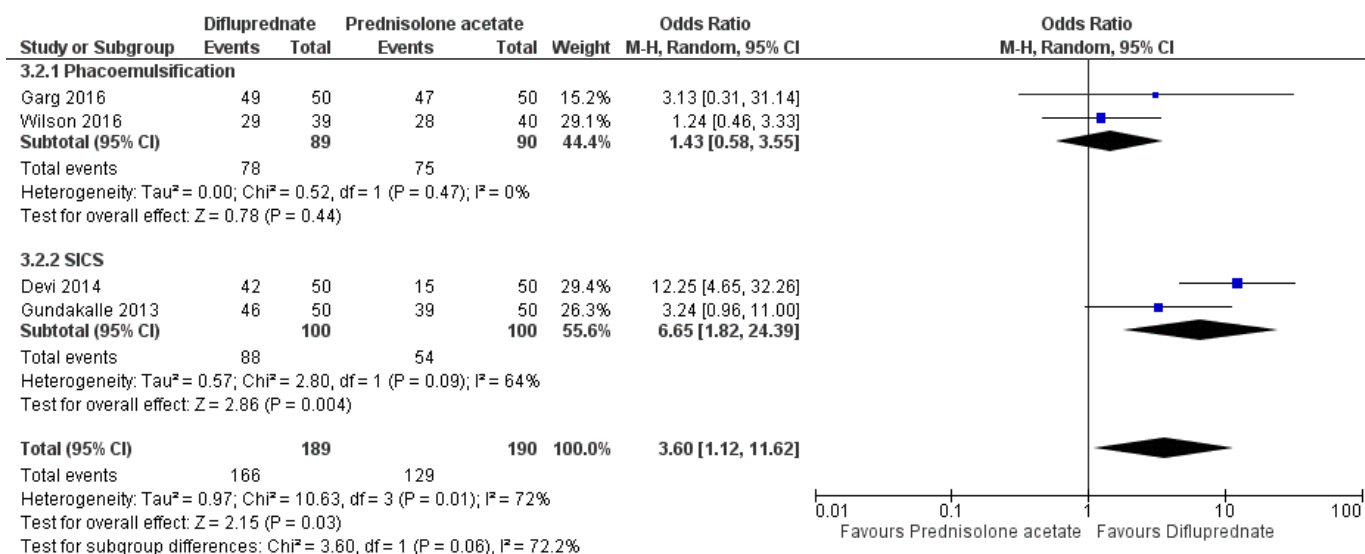


Figure 5 Forest plot for anterior chamber (AC) flare at 15 days. SICS, small incision cataract surgery.

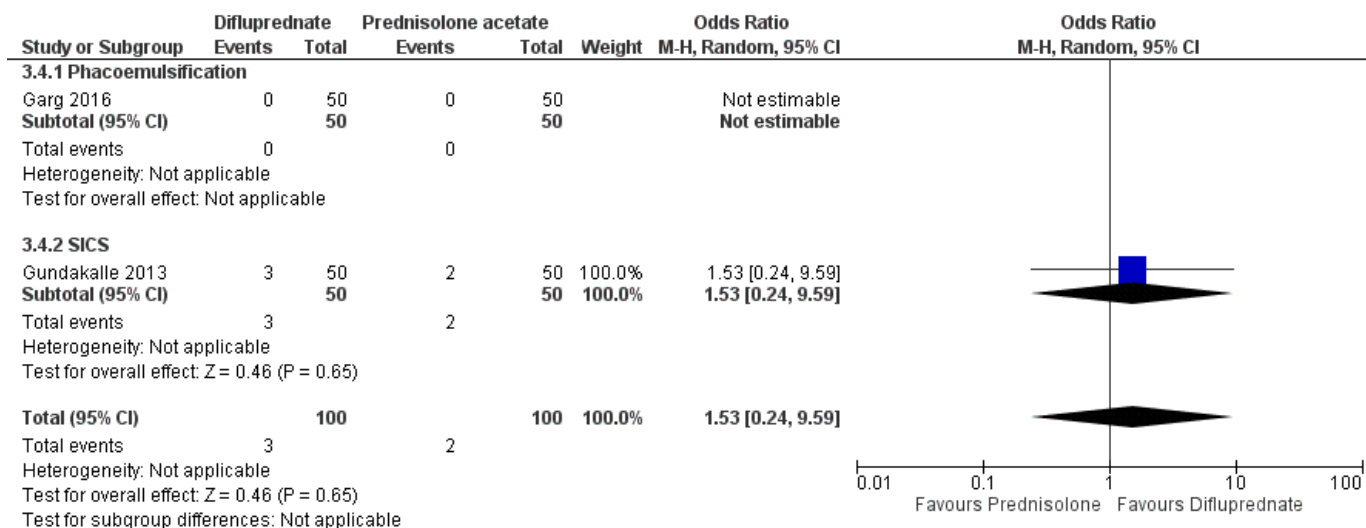


Figure 6 Forest plot for anterior chamber (AC) cells at day 1. SICS, small incision cataract surgery.

In the *phacoemulsification* subgroup, absent AC cells (or grade 0) were achieved in 71 (out of 89) and 70 (out of 100) patients in the difluprednate and prednisolone arms, respectively (OR=1.64, 95% CI 0.83 to 3.23, $p=0.15$). While for SICS, absent AC cells (or grade 0) were achieved in 237 (out of 300) and 180 (out of 300) patients in the difluprednate and prednisolone arms, respectively, which shows a statistically significant better AC clearance in the difluprednate group (OR=4.9, 95% CI 1.06 to 22.6, $p=0.04$).

Regarding AC flare, only four trials reported the proportion of patients that were free from AC flare at 15 ± 2 days. A total of 379 patients were free from AC flare, with 166 out of 189 in the difluprednate arm and 129 out of 190 in prednisolone arm. Again, difluprednate was significantly superior in clearing AC flare (OR=3.06, 95% CI 1.13 to 11.62, $p=0.03$). In the *phacoemulsification* subgroup, absent AC flare was reported for 78 (out of 89) and 75 (out of 90) patients in the difluprednate and prednisolone arms, respectively (OR=1.43, 95% CI 0.58 to 3.55, $p=0.44$). While for SICS, absent AC flare was achieved in 166 (out of 189)

and 129 (out of 190) patients in the difluprednate and prednisolone arms, respectively, which shows a statistically significant effect for the difluprednate arm (OR=6.65, 95% CI 1.82 to 24.39, $p=0.04$).

For both outcomes (AC cells and flare), the phacoemulsification subgroup showed negligible heterogeneity ($I^2=0\%$ for both outcomes). On the other hand, a substantial heterogeneity was detected in the SICS subgroup, with I^2 84% and 64% for AC cells and flare, respectively. Figures 4 and 5 illustrate the forest plots for the AC cells and flare at 15 ± 2 days.

Secondary outcomes

Effectiveness at different time points

The absence of AC cells and flare was compared between difluprednate and prednisolone groups at different time points postoperatively: 1 day, 7 ± 1 days and 30 ± 2 days. At day 1, two studies (Garg *et al*¹¹ in the phacoemulsification subgroup and Gundakalle and Rekha¹⁴ in the SICS subgroup) reported the AC cells and flare outcomes. No significant difference could be detected between

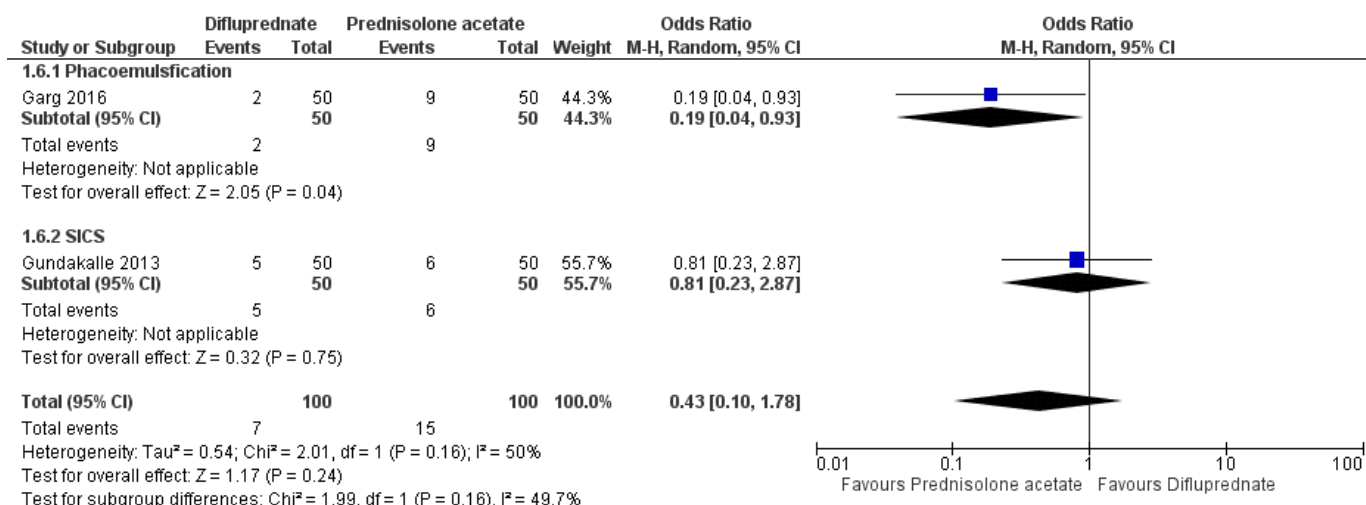


Figure 7 Forest plot for anterior chamber (AC) flare at day 1. SICS, small incision cataract surgery.

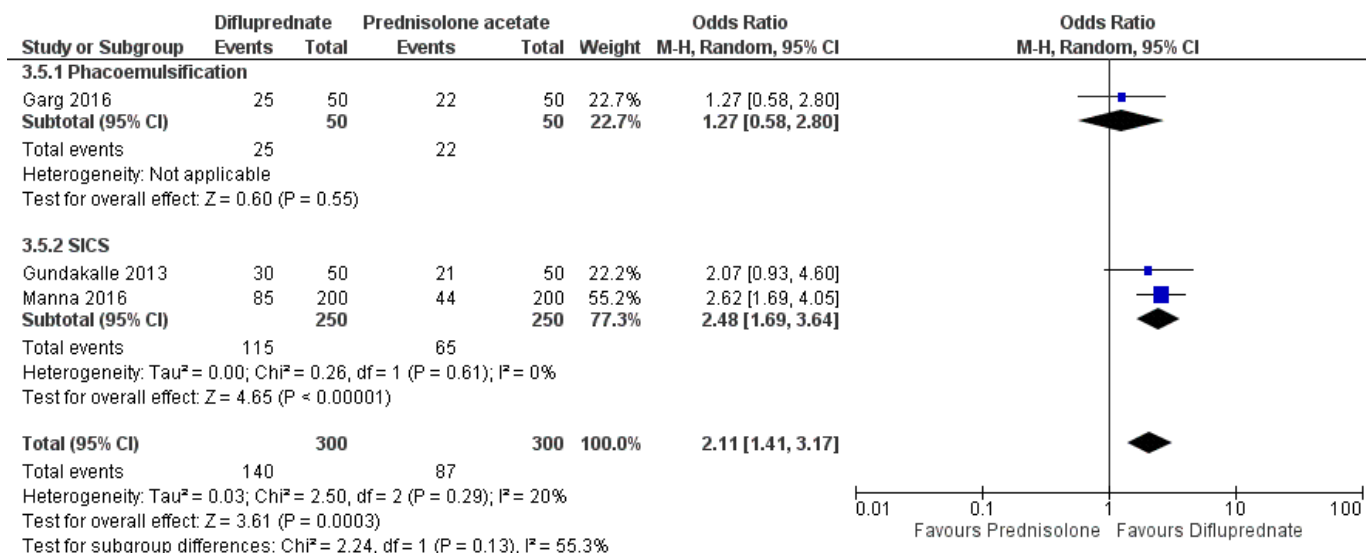


Figure 8 Forest plot for anterior chamber (AC) cells at 1 week. SICS, small incision cataract surgery.

difluprednate and prednisolone for either AC cells (OR=1.53, 95% CI 0.24 to 9.6, p=0.65) or flare (OR=0.43, 95% CI 0.1 to 1.78, p=0.24) as shown in figures 6 and 7, respectively. In the phacoemulsification subgroup, no patients were free from the AC cells at day 1 in either arm, while 2 out of 50 and 9 out of 50 were free from AC flare in the difluprednate and prednisolone groups, respectively (OR=0.19, 95% CI 0.04 to 0.93, p=0.04), which shows significantly higher effectiveness for prednisolone. In the SICS subgroup, no significant difference could be detected between difluprednate and prednisolone for either AC cells (OR=1.53, 95% CI 0.24 to 9.6, p=0.65) or flare (OR=0.81, 95% CI 0.23 to 2.78, p=0.8).

At 1 week, difluprednate was significantly more effective in clearing AC cells but not flare. At 7±1 days, 140 out of 300 and 87 out of 300 in the difluprednate and the prednisolone groups, respectively, were free from the AC cells (OR=2.11, 95% CI 1.41 to 3.17, p=0.0003). This significant difference was revealed to be in the SICS

group (OR=2.48, 95% CI 1.69 to 3.64, p>0.00001) not the phacoemulsification one (OR=1.27, 95% CI 0.58 to 2.8, p=0.5). For the AC flare, 60 out of 100 and 51 out of 100 were free from AC flare in the difluprednate and the prednisolone groups, respectively (OR=1.45, 95% CI 0.71 to 2.96, p=0.3).

At 30±2 days, difluprednate and prednisolone were similarly effective in clearing the AC cells (OR=0.9, 95% CI 0.39 to 2.07, p=0.8). In the phacoemulsification subgroup, Garg *et al*¹¹ reported AC clearance of cells in 50 (out of 50) and 49 (out of 50) patients in the difluprednate and the prednisolone arms, respectively (p=0.5). Similarly, in the SICS subgroup 188 (out of 200) and 190 (out of 200) patients were free from the AC cells at 1 month follow-up (p=0.7). For flare, only Garg *et al*¹¹ reported the 30 days' flare results when all patients were free. Figures 8–10 show the forest plots of the absence of AC cells and flare at days 1, 7±1 days and 30±2 days, respectively.

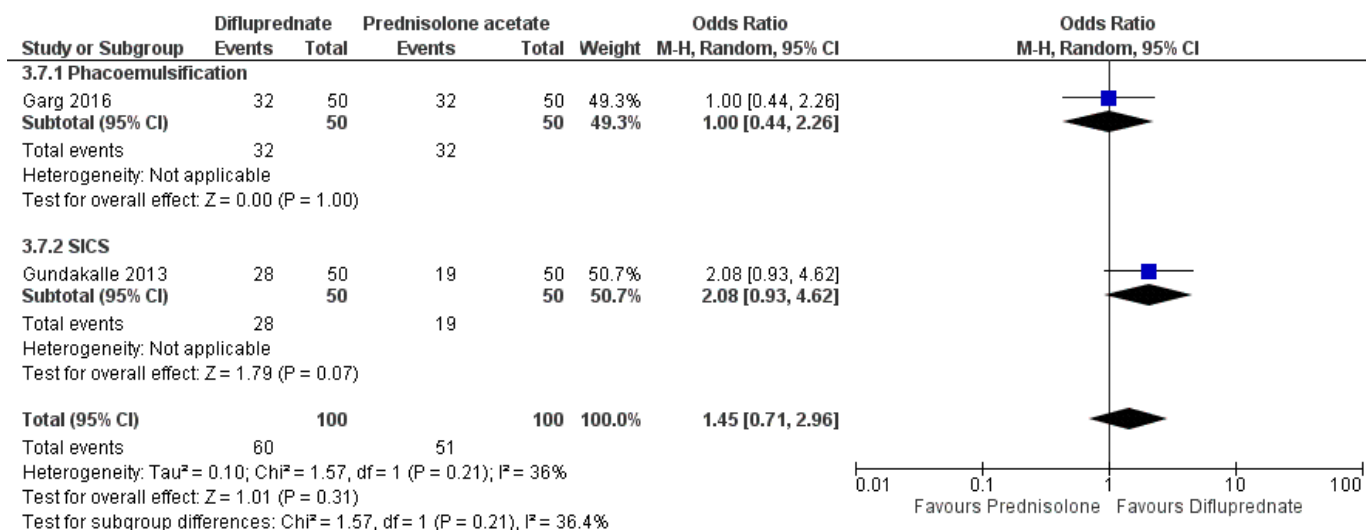


Figure 9 Forest plot for anterior chamber (AC) flare at 1 week. SICS, small incision cataract surgery.

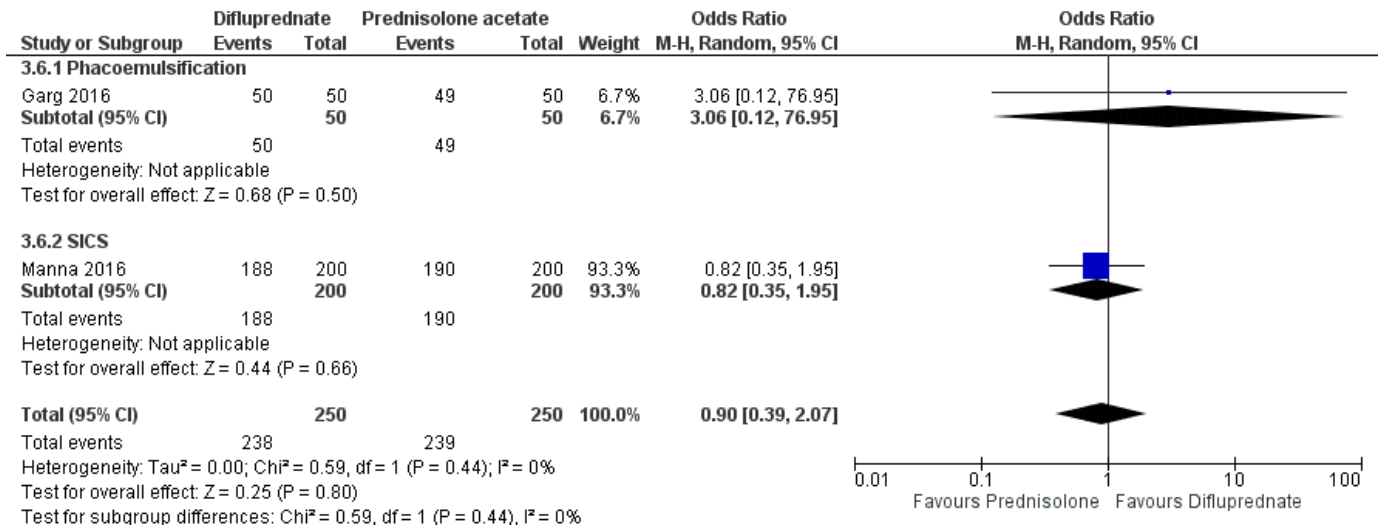


Figure 10 Forest plot for anterior chamber (AC) cells at 1 month. SICS, small incision cataract surgery.

Corneal oedema is another important outcome to assess the effectiveness. At *day 1*, the difluprednate group showed significantly better clearance of corneal oedema in the phacoemulsification subgroup (OR=2.56, 95% CI 1.2 to 5.7, p=0.02) but not the SICS one (OR=1.3, 95% CI 0.76 to 2.1, p=0.4). At *7±1 days*, Manna and Puzari¹² and Gundakalle and Rekha¹⁴ (both in the SICS subgroup), reported significantly higher effectiveness for the difluprednate group (179/250 and 143/250 had clear cornea in the difluprednate and the prednisolone arms, respectively (OR=1.96, 95% CI 1.33 to 2.88, p=0.0007)).

At *15±2 days*, no significant difference was detected between both arms, either in the phacoemulsification group (all patients had clear cornea) or in the SICS one (OR=1.46, 95% CI 0.6 to 3.34, p=0.4). Similarly, at 1 month, both arms had comparable outcomes with no significant difference (OR=1.35, 95% CI 0.67 to 2.73, p=0.4). **Figures 11–14** show the forest plots for the absence

of corneal oedema at days 1, 7±1 days, 15±2 days and 30±2 days, respectively.

Safety profile

Another important concern to address is the safety profile of both agents. High IOP is a major concern with steroid use, hence it is importance to report. High IOP was defined as IOP ≥21 mm Hg or a change from baseline of ≥10 mm Hg at any time point. All included trials reported this adverse event, showing that difluprednate and prednisolone were safe to use after cataract surgery. Only 5 out of 441 in the difluprednate arm and 4 out of 442 in the prednisolone arm experienced high IOP (OR=1.23, 95% CI 0.29 to 5.81, p=0.78). In the phacoemulsification subgroup, 4 out of 141 and 2 out of 142 experienced high IOP in the difluprednate and prednisolone groups, respectively (OR=2.02, 95% CI 0.34 to 11.9, p=0.4). In the SICS subgroup, only two high IOP events were

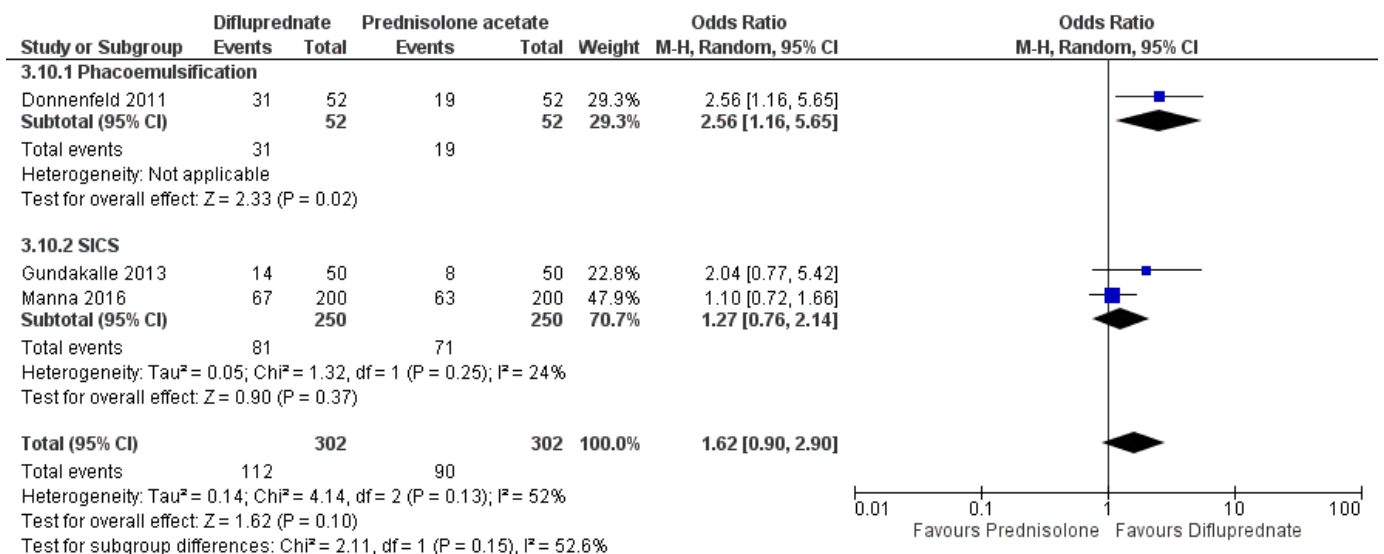


Figure 11 Forest plot for corneal oedema at day 1. SICS, small incision cataract surgery.

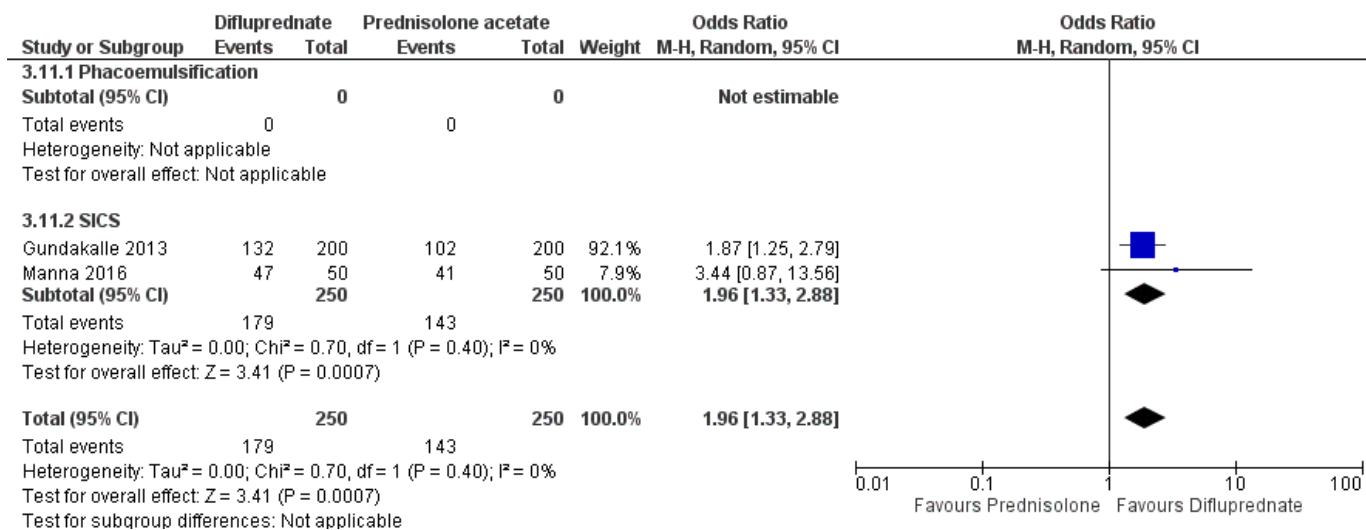


Figure 12 Forest plot for corneal oedema at 1 week. SICS, small incision cataract surgery.

encountered compared with one in the phacoemulsification subgroup, with no significant difference detected between both groups (OR=1.23, 95% CI 0.29 to 5.18, $p=0.8$). **Figure 15** shows the forest plot of high IOP events in both groups.

For visual acuity, two studies (Wilson *et al* and Devi *et al*³) did not report any visual acuity (VA) data. Garg *et al*¹¹ reported that 42 out of 50 in the difluprednate group could achieve BCVA of 6/6 at 2 weeks compared with 43 out of 50 in the prednisolone group, with no significant difference between both groups. Donnenfeld *et al*¹⁵ reported VA as a mean and SD not as a proportion of patients. On LogMAR, BCVA was 0.045 ± 0.107 in the difluprednate group compared with 0.038 ± 0.077 in the prednisolone group, with no significant difference between both groups. Manna and Puzari¹² reported VA at 1 week and at the end of study (179 out of 200 in the difluprednate group and 182 out of 200 in prednisolone group achieved BCVA between 6/9 and 6/6 at 6 weeks).

Meanwhile, Gundakalle and Rekha¹⁴ reported VA only at 6 weeks postoperatively (13 out of 50 in the difluprednate group and 9 out of 50 in the prednisolone group achieved BCVA of 6/6 at 6 weeks). Given the formerly reported data, meta-analysis was not applicable for VA data.

DISCUSSION

Cataract surgery is the most commonly performed eye surgery worldwide, with high patient demand for a safe and effective procedure and rapid rehabilitation.² Thanks to the advancing technology, the success rate as well as safety have been largely improved.¹⁶ Nonetheless, postoperative inflammation is an annoying concern the effects of which range from mild anxiety to visually threatening situations. Many anti-inflammatory agents have been in use with different levels of effectiveness and safety. Corticosteroids have a potent, broad range of action, thus, they were the cornerstone agents after cataract surgery.⁵

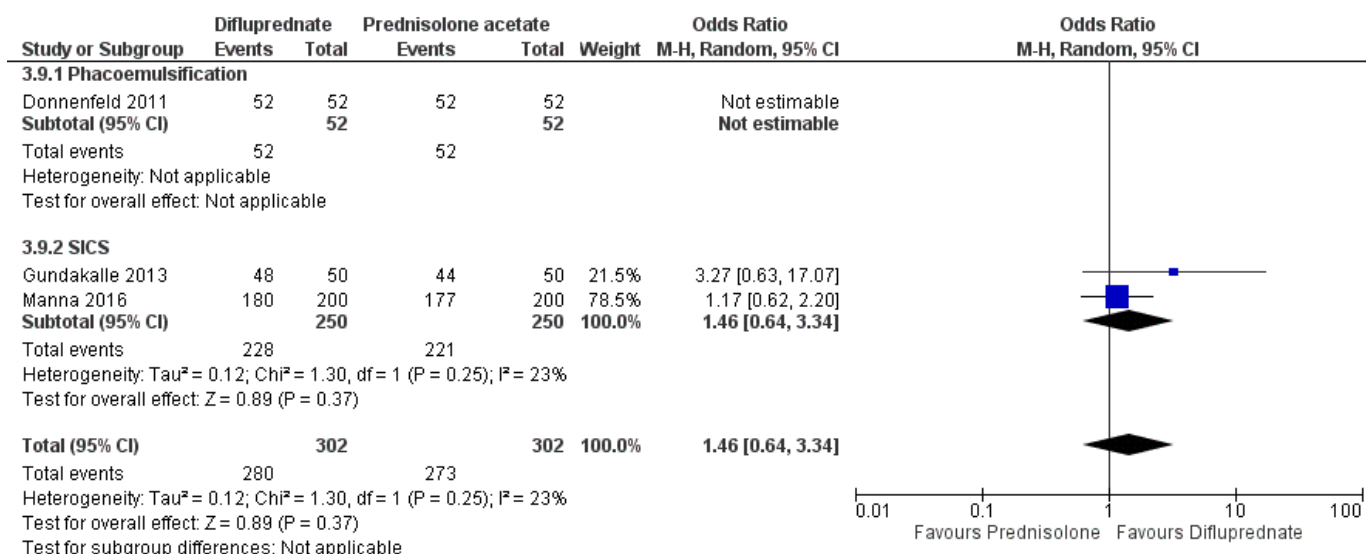


Figure 13 Forest plot for corneal oedema at 2 weeks. SICS, small incision cataract surgery.

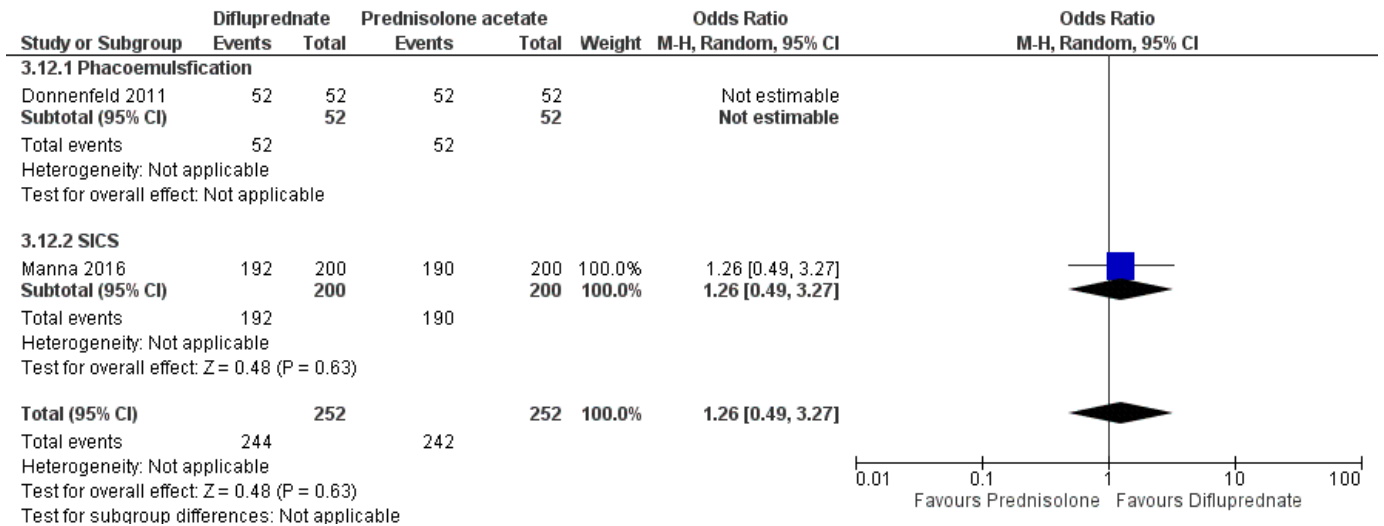


Figure 14 Forest plot for corneal oedema at 1 month. SICS, small incision cataract surgery.

Difluprednate is a butyrate ester derivative of prednisolone, with a higher potency and penetration, compared with other steroid molecules. As an emulsion, dose uniformity with higher bioavailability is an added advantage.^{9 17} In 2008, the FDA approved difluprednate emulsion after cataract surgery.⁸ Since then, many studies compared it to other anti-inflammatory agents regarding its safety and effectiveness. Prednisolone acetate was the main comparison arm. In clinical practice, the question about which one to apply is a matter of debate. Owing to the widespread application of prednisolone, trust in its safety is well established. Nonetheless, its effectiveness is questioned by the limited ocular penetration and the patients' non-compliance for proper shaking of the bottles. Meanwhile, difluprednate penetrates deeper in the ocular tissues which is a double-edged property: higher effectiveness but questionable safety in terms of IOP elevation.

Presently, no systematic review is available to summarise such a comparison. In our systematic review, different databases were searched for relevant studies with no language or period limitations. Six RCTs met our prespecified criteria to be considered for a meta-analysis.

Summary of the main outcomes

In this review, both difluprednate and prednisolone were effective in controlling postoperative inflammation. Similarly, both agents were safe in terms of IOP rise (OR=1.23, 95% CI 0.29 to 5.18, p=0.78). No significant difference could be detected between both arms at any time, except for AC cells clearance at 1 week (OR=2.11, 95% CI 1.41 to 3.17, p=0.0003) and absence of corneal oedema at 1 week (OR=1.96, 95% CI 1.33 to 2.88, p=0.0007). At 15±2 days, a significant heterogeneity was found for AC cells and flare analysis that wasn't resolved with a subgroup

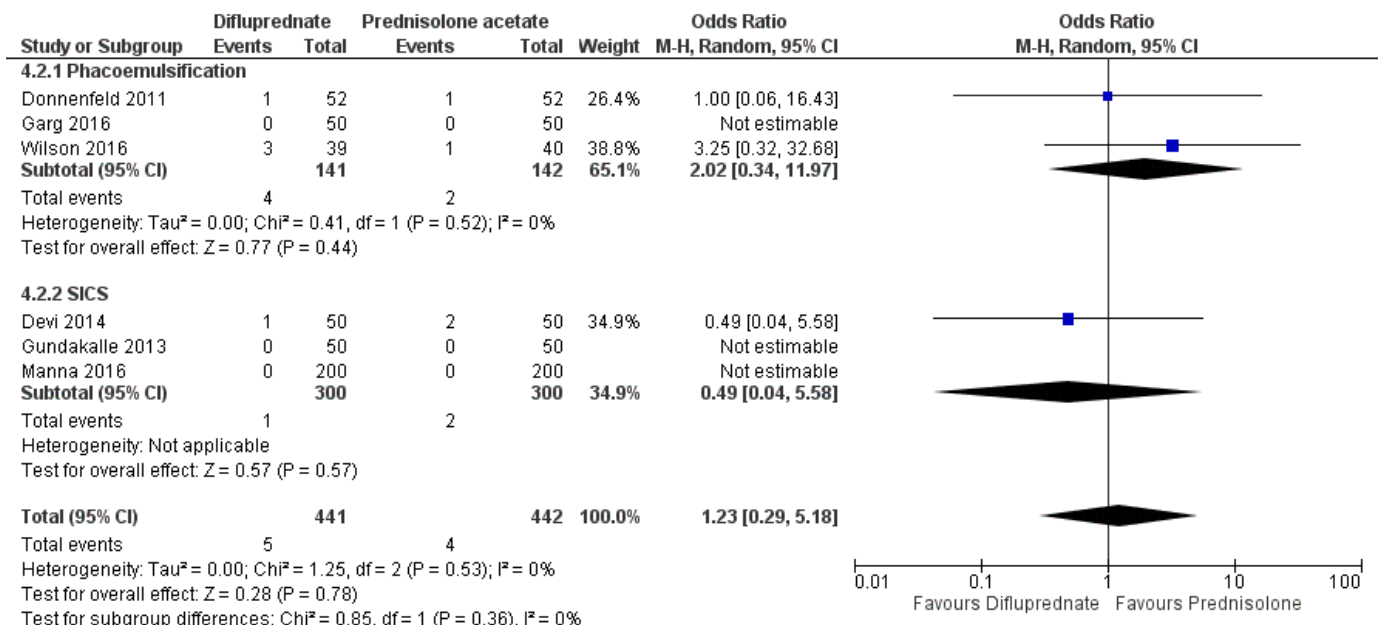


Figure 15 Forest plot for high intraocular pressure (IOP) events. SICS, small incision cataract surgery.

Table 4 Summary of findings table**Summary of findings****Effectiveness and safety of difluprednate compared with prednisolone acetate after cataract surgery****Patient or population:** patients who underwent cataract surgery**Intervention:** difluprednate**Comparison:** prednisolone acetate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with prednisolone acetate	Risk with effectiveness of difluprednate				
Absence of AC cells or grade 0 at 15±2 days	641 per 1000	816 per 1000 (648 to 914)	OR 2.48 (1.03 to 5.93)	779 (5 RCTs)	⊕⊕○○ LOW*†	
Absence of AC flare or grade 0 at 15±2 days	679 per 1000	884 per 1000 (703 to 961)	OR 3.60 (1.12 to 11.62)	379 (4 RCTs)	⊕⊕○○ LOW‡§	
Absence of corneal oedema at 15±2 days	732 per 1000	799 per 1000 (636 to 901)	OR 1.46 (0.64 to 3.34)	604 (3 RCTs)	⊕⊕⊕○ MODERATE¶	
Absence of corneal oedema at 30±2 days	754 per 1000	794 per 1000 (600 to 909)	OR 1.26 (0.49 to 3.27)	504 (2 RCTs)	⊕⊕⊕○ MODERATE**	
High IOP (≥21 mm Hg or a change from baseline of ≥10 mm Hg)	9 per 1000	11 per 1000 (3 to 45)	OR 1.23 (0.29 to 5.18)	883 (6 RCTs)	⊕⊕⊕○ MODERATE**	

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*One RCT has a high risk of bias, while three other RCTs have unclear risk of bias.

†Significant heterogeneity among studies ($I^2=75\%$).

‡Two RCTs have unclear risk of bias.

§Significant heterogeneity among studies ($I^2=72\%$).

¶High risk of bias in one RCT and unclear risk in another one.

**High risk of bias in one RCT which has the largest weight.

AC, anterior chamber; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IOP, intraocular pressure; RCT, randomised-controlled trial.

analysis for age (adults vs paediatric population). However, phacoemulsification versus SICS subgroup analysis could resolve this heterogeneity for AC cells clearance, but not the flare.

Limitations of the review

Included RCTs have certain limitations to be considered. First, the heterogeneity in the dosing schedule was applied either in the frequency of application of drops or the duration of postoperative treatment. Most studies started topical steroid therapy immediately after surgery for a duration ranging from 3 weeks to 4 weeks. Nevertheless, Devi *et al*¹³ did not report the dosing frequency¹³ and Gundakalle and Rekha¹⁴ did not report the duration of therapy.¹⁴ Moreover, Donnenfeld *et al* applied a

pulse-dosed regimen, starting the application of drops preoperatively before and on arrival to the surgery centre. Also, Donnenfeld reported using non-steroidal anti-inflammatory drugs (NSAIDs) drops (nepafenac 0.1%, Nevanac; Alcon Laboratories; or ketorolac tromethamine 0.4%, Acular LS; Allergan), starting 3 days before surgery and continuing for 4 weeks after surgery in combination on the recommendation of the surgeon.¹⁵ Given the anti-inflammatory activity of NSAIDs, authors should have conducted a subgroup analysis for patients on steroids only and their peers on a combined regimen. However, the analysis wasn't segregated to address this conflict. Such heterogeneity may question the reliability of the results obtained to represent the steroid effects and may

also explain the heterogeneity encountered in the results. A subgroup analysis wasn't applicable due to large variations of the dosing schedules as illustrated in [table 2](#).

Another significant limitation to consider is the method of outcome assessment. Clearing AC cells and flare is the standard way to assess the effectiveness of anti-inflammatory agents after cataract surgery. All the included trials relied on subjective assessment of the inflammatory response and none of them applied any cell/flare metres for objective assessment, raising concerns regarding the reliability of the reported outcomes. Another challenge was reporting outcomes using different scores or scales. Wilson *et al* reported most outcomes using a 3-point global inflammatory score: 0=clear, 1=improving satisfactorily and 2=not improving or worsening, or withdrawal from study, and only the 15 days outcomes were reported individually.¹⁰ Although this was assumed to be meaningful by the author, we couldn't include such data in the meta-analysis. Since this was the only trial for a paediatric population, this was a disappointing limitation.

One more limitation is the reporting of the visual acuity data. First, it wasn't reported in two out of the six included studies. Also, Donnenfeld *et al*¹⁵ reported the VA as a mean and SD, not a proportion of the included patients. The remaining trials reported VA at different time points that hindered pooling of data. Vision is the point of care for both patients and physicians and there is no justification for such studies not reporting BCVA at all assessment points. BCVA should be included in future trials.

Quality of the evidence

In general, we graded the evidence as low to moderate. This was attributed mainly due to the risk of bias in the included studies and significant heterogeneity encountered as illustrated in [table 4](#). The risk of bias was in part due to the poor reporting of trials, making it unclear to judge fundamental aspects. In addition, two of the included studies (Donnenfeld *et al*¹⁵ and Wilson *et al*) were funded by a manufacturer of one of the study agents (difluprednate). Future well-designed, larger, adequately powered and independently funded trials are essential to synthesise high-quality evidence. These trials should propose a standard dosing regimen and outcomes reporting scores or scales.

CONCLUSION

Difluprednate was superior in clearing AC cells at 1 week and 2 weeks and clearing AC flare at 2 weeks after cataract surgery. Prednisolone acetate was superior in terms of corneal clarity at 1 week after surgery. However, both agents were similarly effective and safe anti-inflammatory agents at different time points of the assessment. This was applicable for the phacoemulsification and SICS techniques in both the adult and paediatric populations. This evidence was of low-to-moderate quality, and further well-designed RCTs are needed.

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Contributors All authors drafted the protocol and the search strategies. Mahmoud Tawfik and Ahmed Basyony conducted the search and data extraction and any conflicts were resolved by discussion with Ahmed Adel. Mahmoud Tawfik conducted the statistical analysis. Ahmed Basyony and Ahmed Adel drafted the results' section. Mahmoud Tawfik wrote the discussion section. All authors revised the manuscript.

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