Editorial

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Clobetasol propionate for post-cataract surgery pain and inflammation

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As per the WHO 2023 report, 94 million people are affected by cataracts globally[1]. Consequently, cataract extraction is the most commonly performed surgical procedure, with an estimated 20 million cases worldwide[2]. Complications are common fol lowing cataract surgery, ranging from treatable ones such as pain and inflammation to some more dangerous complications like endophthalmitis, vitreous loss, vitreous hemorrhage, and retinal detachment. However, minimally invasive procedures have been employed for cataract surgery to reduce these complications. Still, despite this, postoperative inflammation remains a concern[3,4], which, if not managed properly, can increase the chances of postoperative pain, uveitis, secondary glaucoma, and cystoid macular edema. Mohammadpour *et al*.[5] reported in a case series that out of 1500 patients who underwent cataract surgery, 126 patients developed early-onset postoperative inflammation, which causes pain, decreased vision, and patient anxiety. One of the common causes of prolonged inflammation is the lack of treatment with anti-inflammatory medication[6].

To prevent developing severe adverse effects, early treatment of pain and inflammation following cataract surgery is the main goal[7]. However, there is yet to be definite evidence from clinical trials or consensus guidelines for a standard regimen for post-cataract surgery pain and inflammation[8]. Currently, available treatment options for post-cataract surgery pain and inflamma tion include NSAIDS (Bromfenac, Indomethacin, Diclofenac, Ketorolac tromethamine, Nepafenac)[9] and corticosteroids (pre dnisolone, fluorometholone, dexamethasone, difluprednate)[10].

A prospective study by Singhal *et al*. found comparable efficacy of NSAIDs and corticosteroids in reducing inflammation[11]. A meta-analysis was conducted by Juthani *et al*., which analyzed two parameters for inflammation, namely, the number of cells in the anterior chamber and mean flare values at one week. The drugs compared were corticosteroids and NSAIDs. There was uncertainty in proving either drug's efficacy in reducing the number of cells in the anterior chamber. However, lower mean flare values were observed in the NSAIDs group, which indicated reduced intraocular inflammation[12]. An RCT by Malik *et al*. found superior efficacy of corticosteroids over NSAIDs in redu cing post-cataract surgery inflammation, while NSAIDs were superior to corticosteroids in reducing pain[13]. Kato *et al*., in their study, unveiled a significant risk associated with using ocular NSAIDs, specifically the potential for inducing ocular surface damage leading to corneal melting. However, such consequences appear to be absent when employing steroids[14]. Also, NSAIDs are associated with reduced corneal sensation, thereby delaying healing. Corticosteroids are considered the gold standard for ocular inflammation but should be used cautiously due to their side effects. However, prolonged corticosteroid use can lead to adverse effects such as elevated intraocular pressure (IOP), potentially causing progressive optic nerve damage, vision loss, and corticosteroid-induced glaucoma. The likelihood of increased IOP varies with the drug's pharmacokinetics, including tissue penetration, half-life, dosage, and treatment duration. Additionally, extended corticosteroid therapy can cause catar acts, especially posterior subcapsular cataracts. Corticosteroids with a C-20 ketone group, such as prednisolone, dexamethasone, fluorometholone, and difluprednate, are linked to cataract for mation due to their interaction with lens proteins[15].

While steroids are effective in managing pain and inflamma-tion, challenges persist in their delivery and anti-inflammatory effects. Many topical steroids, such as prednisolone, fluor-ometholone, and dexamethasone, are frequently formulated as suspension because of their limited aqueous solubility, which requires vigorous shaking before use; hence, many patients find it challenging to use[15,16].

Clobetasol propionate: mechanism of action

Clobetasol propionate, a recent FDA-approved drug for treating pain and inflammation post-cataract surgery, is an ophthalmic nanoemulsion 0.05% designed to deliver clobetasol propionate directly to the eye, effectively treating inflammation and pain associated with cataract surgery. It's a prednisolone derivative with high specificity for glucocorticoid receptors and low specificity for mineralocorticoid receptors. It exerts anti-inflammatory effects, similar to that of corticosteroids, by promoting anti-inflammatory genes and inhibiting pro-inflammatory transcription factors like NF-kappa B. This binding alters gene expression, reducing mast cell density, cytokine production, and eosinophil activation, while also inhibiting arachidonic acid metabolism. This effectively delivers the drug to the eye, treating inflammation

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and pain post-cataract surgery by these mechanisms. This formulation does not require shaking and is suitable for elderly patients[17]. The main actions of clobetasol propionate are shown in Table 1[18].

Clinical trials: CLOSE-1 and CLOSE-2

Two twin phase III multicenter, randomized, double-masked trials (CLOSE-1 and CLOSE-2) were conducted in the U.S. These trials aimed to assess the effectiveness and safety of 0.05% clobetasol propionate ophthalmic nanoemulsion compared to a placebo when applied as one drop four times daily (QID) for 14 days following routine unilateral cataract surgery. These studies received approval from the FDA and a central Institutional Review Board (IRB). A total of 427 eligible patients aged 18 years and above, who had undergone routine unilateral cataract surgery and demonstrated at least five cells in the anterior chamber (as assessed by slit lamp on postoperative day 1), were randomly allocated in a 2:1 ratio to either the clobetasol group or the placebo group. The investigational medicinal product (IMP) (clobetasol or placebo) was provided in sterile single-dose vials to be applied as one drop QID for 14 days without a tapering phase. Patients were monitored for compliance and underwent ophthalmologic assessments on days 3, 8, 15, and 29[17].

In line with previous studies[12,14], the primary efficacy endpoint was the proportion of patients achieving an anterior chamber cell (ACC) grade of '0' on day 8 to assess inflammation. The ACC grade was evaluated by the investigator using the standard clinical slit-lamp examination results, utilizing the Standardization of Uveitis Nomenclature (SUN) grading system (Table 2). These clinical grading systems depend on subjective assessments made via the slit lamp and typically employ non-linear and non-continuous scales (https://classic.clinicaltrials.gov/ProvidedDocs/01/NCT04246801/Prot_000.pdf). The secondary efficacy endpoint was the proportion of patients reporting a visual analogue scale (VAS) pain score of '0' on day 8 to evaluate perceived pain. In the clobetasol group, 37.8% achieved the primary efficacy endpoint, which was the absence of cells in the anterior chamber on day 8, compared to 18.1% in the placebo group ($P < 0.0001$). Additionally, 54.7% of clobetasol-treated patients achieved the secondary efficacy endpoint, defined as a VAS pain score of 0 on day 8, while 36.5% of patients in the placebo group reached this endpoint ($P = 0.0005$)[17].

Analysis of adverse events (AEs) revealed that 3.9% of clobetasol patients and 5.5% of placebo patients reported at least one IMP-related AE, with only one being severe (cystoid macular edema) in the clobetasol group. Additionally, only one patient in each group experienced a moderate increase in intraocular pressure related to the IMP[17].

Table 2

Grading scheme for anterior chamber cells

Grade	Cells in field
0	0
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	> 50

Another multicentre, evaluator-blinded randomized controlled trial (RCT), CLOSE-3, is currently in the recruitment phase. This trial checks the efficacy and safety of clobetasol propionate 0.05% nanoemulsion against prednisolone acetate 1% suspension after cataract surgery in the pediatric population (0–3 years). In contrast to CLOSE-1 and CLOSE-2 trials, this trial measures pain by assessing a change in the face, legs, activity, cry, consolability (FLACC) behavioral scale score (https://clinicaltrials.gov/study/NCT05724446). Currently, no documents are available for this study.

Conclusion

Clobetasol propionate has demonstrated improved efficacy in reducing inflammation and pain associated with cataract surgery. It has been recognized as safe and efficacious, with favorable patient tolerance levels, as demonstrated by CLOSE-1 and CLOSE-2 trials. Clobetasol propionate has garnered considerable attention as a highly promising anti-inflammatory compound, owing to its extensive therapeutic applications in global medical practice over several decades. The availability of clobetasol propionate products in the United States (U.S.) and internationally was investigated by searching the national medicine registries of 13 countries and regions[19]. In the United States, clobetasol propionate is offered in various topical formulations and is classified as a fifth-generation corticosteroid utilized to treat oral lichen planus (OLP), psoriasis, and other dermatological conditions responsive to steroids. Nonetheless, adverse effects such as skin atrophy, allergic contact dermatitis, steroidal acne, Cushing's syndrome, hypopigmentation, and skin irritation have been reported[20]. In addition, a retrospective analysis by Wang *et al*. found that clobetasol propionate was associated with cataracts (0.55%) and glaucoma (0.63%) when it was used for topical treatment of psoriasis. However, the incidence was much lower compared to other drugs used for psoriasis[21]. Not enough information is available on the efficacy and safety of clobetasol propionate in treating ocular manifestations. However, two case reports, one on three pediatric patients and one on five adult

Table 1

Mechanism of action of clobetasol propionate

Anti-inflammatory	Vasoconstrictor	Antimitotic
Increases production of phospholipase A2 inhibitory proteins, lipocortin	Inhibits synthesis of inducible nitric oxide	Inhibits mitosis in epidermal cells
Inhibits activator protein A and nuclear factor kappa B, resulting in reduced levels of interleukin 2, 6, and 8	Inhibits degranulation of mast cells	Inhibits levels of pro-inflammatory cytokines
Inhibits production of cyclooxygenase 2	Decrease levels of pro-inflammatory cytokines	Direct modulation of mast cell numbers
Modulate mast cell numbers		

patients, have demonstrated that clobetasol propionate is effica cious in treating periocular capillary hemangioma with no ocular side effects[22,23]. A recent trial[17] has demonstrated that clobeta sol propionate exhibits a reduced risk of adverse effects, crucial for optimal post-surgery recovery. Its favorable safety profile, characterized by notably low severity of adverse events, particularly the rare occurrence of severe complications like cystoid macular edema, underscores its overall tolerability. Moreover, the formulation's convenience, eliminating the need for shaking, offers a practical advantage, especially for elderly patients, potentially improving treatment compliance and out comes. While these findings highlight its promising potential, further comparative trials are warranted to ascertain its efficacy and safety relative to other corticosteroids, enhancing clinical understanding and guiding treatment decisions.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contribution

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Transparency statement: M.S.D. affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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