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ORIGINAL RESEARCH

Prospective, Randomized, Fellow Eye-Controlled Study of Postoperative Pain and Inflammation Control with an Intracanalicular Dexamethasone 0.4 mg Ophthalmic Insert Following Small Incision Lenticule Extraction

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Purpose: To compare postoperative anterior chamber inflammation, pain, and patient preference following small incision lenticule extraction (SMILE) in eyes treated with a dexamethasone 0.4 mg intracanalicular insert (DEX) or topical prednisolone acetate (PRED).

Patients and Methods: In this prospective, randomized, fellow eye-controlled trial, 20 patients underwent same-day, bilateral SMILE. One randomly-selected eye of each patient received DEX placed immediately postoperatively, and the fellow eye received topical PRED tapered over 2 weeks. Postoperative evaluations were performed on day 1, week 1, month 1, and month 3. Primary outcomes included postoperative pain, incidence of anterior chamber cell and flare, and patient preference of steroid therapy.

Results: No eyes in either group had any clinically evident cell or flare at any postoperative time point. Mean pain scores (0–10 by subjective report) and incidence of any pain were statistically similar at all postoperative visits. Uncorrected distance visual acuity improved in all eyes, 91% of which achieved 20/25 or better. No eyes lost any lines of corrected distance visual acuity. Three eyes developed a steroid-related rise in intraocular pressure, all of which resolved with 2 of the 3 eyes requiring topical therapy. At 1 week, 1 month, and 3 months, 70%, 65%, and 53% of patients preferred DEX over PRED therapy, respectively.

Conclusion: The DEX insert was preferred by more patients and controlled postoperative inflammation and pain comparably to topical PRED in eyes undergoing SMILE. There were no statistically significant differences in visual outcomes between the two groups.

Keywords: refractive surgery, steroid, myopia, astigmatism

Introduction

Small incision lenticule extraction (SMILE) is a corneal refractive procedure performed with a femtosecond laser in which an intrastromal lenticule is dissected from its anterior and posterior stromal interfaces and removed through a small incision without the need for the creation of a flap.[1] The procedure was approved in the United States in 2016 for the correction of myopia and in 2018 for myopic astigmatism, and has been shown to be effective in correcting hyperopia and presbyopia as well.[2–4] Meta-analyses suggest SMILE results in less reduction in corneal sensitivity and less incidence of postoperative dry eye compared to femtosecond-laser assisted in situ keratomileusis (FS-LASIK), supporting its preferential use in eyes with pre-existing dryness.[5–8] The biomechanical strength of the cornea following SMILE is thought to be better preserved compared to FS-LASIK, potentially improving the safety of SMILE in patients with high refractive errors, those who engage in contact sports, or serve in active-duty military.[8,9]

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Following SMILE, the standard postoperative medication regimen includes topical antibiotic and corticosteroid eye drops multiple times per day from multiple bottles with a steroid taper. Recently, there has been a trend for cataract surgeons to move towards a drop-free postoperative experience to improve patient satisfaction and medication compliance following phacoemulsification.[10–13] A similar shift away from frequent administration of topical therapies following keratorefractive surgery would be expected to improve patients' postoperative experience.

The dexamethasone (DEX) intracanalicular insert (Dextenza, Ocular Therapeutix) is a rod-shaped insert with 0.4 mg of preservative-free dexamethasone embedded within a hydrogel matrix. The DEX insert can be placed into either the superior or inferior punctum and delivers a tapering dose of steroid to the ocular surface for 30 days before dissolving without the need for removal. Phase 3 trials demonstrated the insert's ability to control postoperative pain and inflammation following phacoemulsification cataract surgery with high patient satisfaction.[14–16]

This study compares postoperative pain, inflammation, and corticosteroid preference in patients undergoing bilateral SMILE treated with the DEX insert in one eye and topical prednisolone acetate in the fellow eye.

Patients and Methods

This prospective, randomized, fellow-eye controlled study was conducted at a single site (Clear Choice Custom LASIK Center) in 20 patients (40 eyes) with three surgeons between June 2020 and February 2021 and was performed according to guidelines established by the Declaration of Helsinki. The study protocol was approved by Salus IRB (Austin, TX), and the study was registered at ClinicalTrials.gov (NCT04380857). Written informed consent was obtained from all study participants. Patient data was anonymized and kept confidential.

Study participants were at least 18 years old and appropriate surgical candidates for SMILE as assessed by refraction and corneal tomography (Pentacam, OCULUS GmbH, Germany). Key exclusion criteria included active ocular or systemic infectious conditions, nasolacrimal duct obstruction, hypersensitivity to dexamethasone, and use of any immunosuppressant or immunomodulating therapies. Consecutive qualifying subjects were invited to participate to minimize selection bias.

Eligible subjects underwent same-day, bilateral SMILE performed with the VisuMax femtosecond laser (Carl Zeiss Meditec, Inc). One eye was randomly assigned to the DEX insert, which was placed in the inferior canaliculus immediately after the SMILE procedure, and the fellow eye was assigned to topical 1% prednisolone acetate (PRED) eye drops prescribed every 2 hours on the day of surgery, 4 times daily for the first week, two times daily for the second week, and then discontinued. All eyes received standard postoperative eye drops including 0.3% ofloxacin (every 2 hours on the day of surgery and then 4 times daily for the first week) and preservative-free artificial tears as needed. Rescue therapy with topical corticosteroids was permitted if anterior chamber cell scores were 2+ or higher, flare scores 3+ or higher, or pain was graded at level 4 or higher. Patients were evaluated 1 day, 1 week, 1 month, and 3 months postoperatively.

The primary outcomes were between-group (DEX versus PRED) differences in the incidence of anterior chamber cell and flare and ocular pain scores, and patient preference for postoperative steroid therapy. Anterior chamber cell and flare were graded using the Standardization of Uveitis Nomenclature Working Group's clinical quantification scale for cell and flare.[17] Ocular pain was assessed subjectively on a 0–10 scale, with 0 being no pain and 10 being worst pain imaginable. Patient preference for steroid treatment was assessed using a 5-point scale consisting of moderately or much preferring one treatment over the other versus no preference.

Secondary outcomes were uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) at 1 week, 1 month, and 3 months postoperatively using the ETDRS chart at 4 meters, and the incidence of unscheduled patient encounters (via phone or in-person office visits). Additional data collected included intraocular pressure (IOP) using Goldmann tonometry, surgeon-rated ease of DEX insertion (easy/average/difficult), and post-insertion DEX visualization. No formal power analysis was conducted, and the sample size was set at 40 eyes based on the sample size used in several similar prior studies.[18–20] Chi-square tests were used to compare proportions and *t*-tests to compare means. The level of significance was set at 0.05.

Results

Twenty-three patients were enrolled in the study. One patient failed screening and was not randomized. Two additional patients were randomized, but the DEX insert could not be successfully placed in the assigned eye at the time of surgery. Analysis was conducted on the remaining 20 patients (40 eyes). Seventeen (85%) patients were White, 11 (55%) were women, and 9 (45%) were men. The mean age was 29.9 years (range: 20 to 37 years). The DEX insert was visualized in all 20 eyes after placement. Surgeon-rated DEX insertion was graded as easy in 12 eyes, average in 3 eyes, and difficult in 5 eyes. All subjects were seen through week 1; three were lost to follow up thereafter.

No eyes had evidence of inflammation with anterior chamber cell or flare at any time point, and no eyes required corticosteroid rescue therapy. Mean pain scores were consistently low (<1 on a 0–10 scale) and were statistically similar between DEX and PRED eyes preoperatively and at each postoperative timepoint (Figure 1). Preoperatively, two patients reported mild bilateral pain and one reported mild unilateral pain in the eye randomized to PRED. The DEX insert was preferred over topical PRED in 70% of patients (14/20) at 1 week, 64.7% of patients (11/17) at 1 month, and 52.9% (9/17) at 3 months; 10%, 17.6%, and 17.6%, respectively, preferred PRED over DEX, and 20%, 17.6%, and 29.4%, respectively, had no preference (Figure 2).

UDVA and CDVA are detailed in Table 1. At 1 week postoperatively, mean logMAR UDVA was 0.013 ± 0.183 and −0.010 ± 0.0114 in PRED and DEX eyes, respectively, which was statistically similar (P = 0.505). At 1 month postoperatively, the PRED and DEX eyes had mean UDVA of −0.026 ± 0.160 and −0.014 ± 0.181, respectively (P = 0.762). At 3 months postoperatively, the PRED and DEX eyes had mean UDVA of −0.068 ± 0.156 and −0.071 ± 0.108, respectively (P = 0.941) (Figure 3). The postoperative mean UDVA over time for both groups is shown in Figure 4. No patient lost any lines of CDVA (Figure 5). At 1 week postoperatively, mean CDVA was −0.071 ± 0.101 and −0.083 ± 0.070 in PRED and DEX eyes, respectively (P = 0.332). At 1 month postoperatively, the PRED and DEX eyes had mean CDVA of −0.114 ± 0.079 and −0.112 ± 0.087, respectively (P = 0.869). At 3 months postoperatively, the PRED and DEX eyes had mean CDVA of −0.139 ± 0.091 and −0.121 ± 0.078, respectively (P = 0.211). Mean manifest refraction spherical equivalent (MRSE) did not statistically differ between PRED and DEX eyes at 1 week, 1 month, or 3 months (P = 0.821, 0.482, and 0.369, respectively). At 3 months, 88.2% of eyes in both the PRED and DEX groups were within ± 0.5 D of intended target (Figure 6).

No intraoperative adverse events or complications were recorded. Two subjects experienced bilateral dry eye, one of which resolved within 1 month. Mean IOP was similar between DEX and PRED eyes at 1 week (P = 0.241), higher in

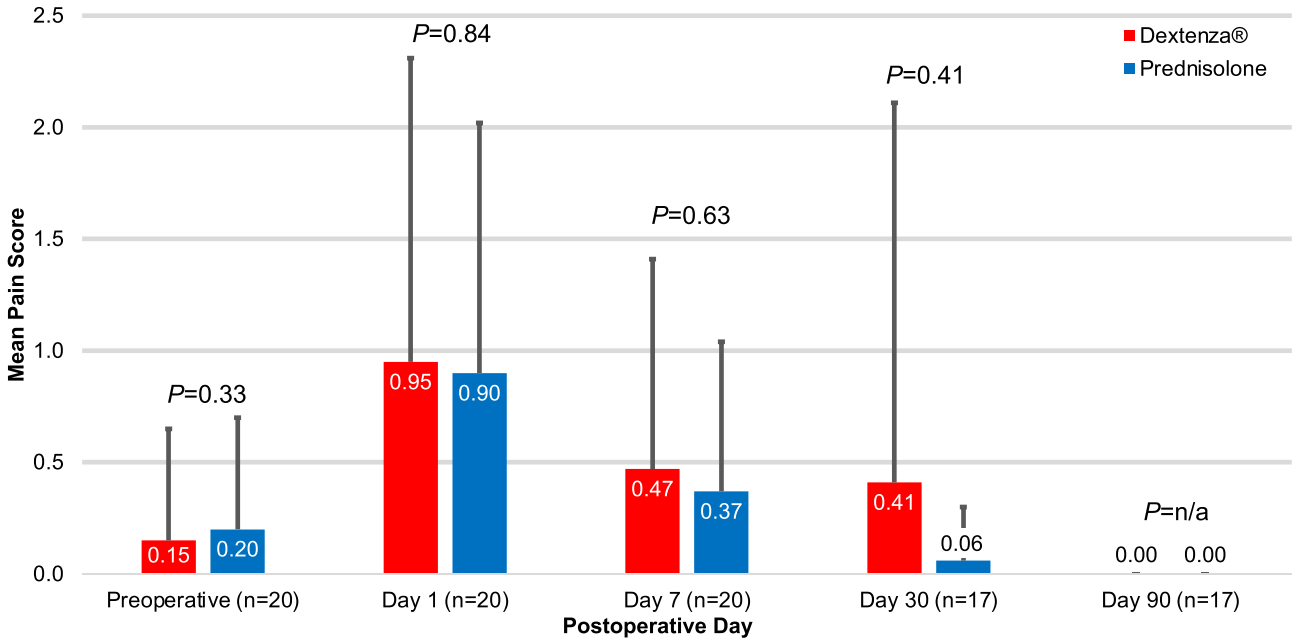

Figure 1 Mean pain scores (0–10) postoperatively after small incision lenticule extraction by treatment group.

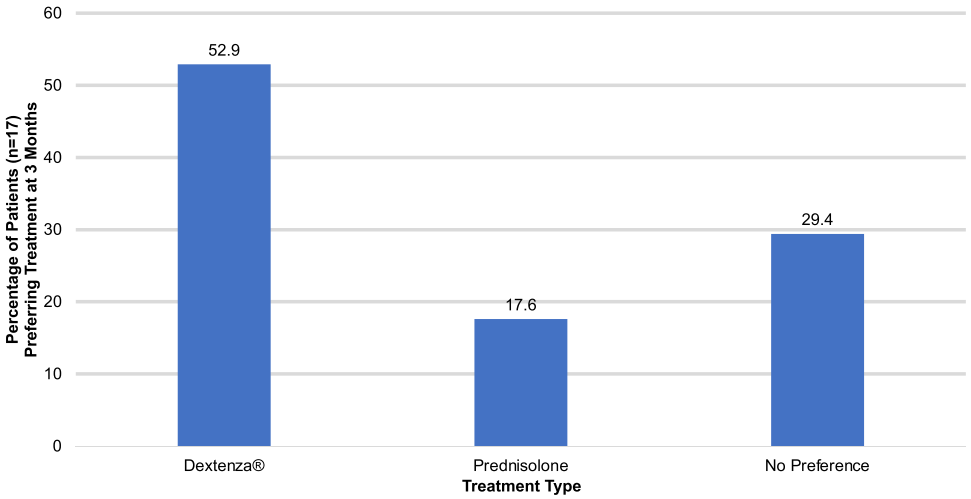

Figure 2 Patient preference for corticosteroid treatment type at month 3 (n=17).

DEX eyes than PRED eyes at 1 month (consistent with PRED cessation at 2 weeks) ($P = 0.006$), and similar again at 3 months ($P = 0.601$) (Figure 7). Three DEX eyes of 3 subjects experienced elevated IOP at the 1-month visit presumed related to steroid response. Two were moderate (peak IOP 25 and 26 mmHg) and one was more significant, with IOP peak of 45 mmHg and corneal stromal haze with reduced visual acuity. Two of the eyes received a brief course of topical IOP-lowering therapy; IOP in all three eyes normalized within 1 week. These adverse events resulted in a total of 9 unscheduled visits.

Discussion

In this randomized clinical trial, the DEX insert controlled postoperative pain and anterior chamber inflammation comparably to topical PRED in paired fellow eyes undergoing SMILE. At 3 months, 53% of patients preferred the DEX insert compared to only 18% who preferred topical PRED. Both treatments were safe and effective; adverse events were uncommon and not sight-threatening.

Clinically significant inflammation is uncommon after keratorefractive surgery but can adversely affect both visual outcomes and patient satisfaction. LASIK causes a transient increase in anterior chamber cell and/or flare on day 1 that

Table 1 Mean UDVA and CDVA at Postoperative Week 1, Postoperative Month 1, and Postoperative Month 3

	DEX	PRED	*P*
Postoperative week 1 (n=20)			
Mean logMAR UDVA	−0.010 ± 0.0114	0.013 ± 0.183	0.505
Mean logMAR CDVA	−0.083 ± 0.070	−0.071 ± 0.101	0.332
Postoperative month 1 (n=17)			
Mean logMAR UDVA	−0.014 ± 0.181	−0.026 ± 0.160	0.762
Mean logMAR CDVA	−0.112 ± 0.087	−0.114 ± 0.079	0.869
Postoperative month 3 (n=17)			
Mean logMAR UDVA	−0.071 ± 0.108	−0.068 ± 0.156	0.941
Mean logMAR CDVA	−0.121 ± 0.078	−0.139 ± 0.091	0.211

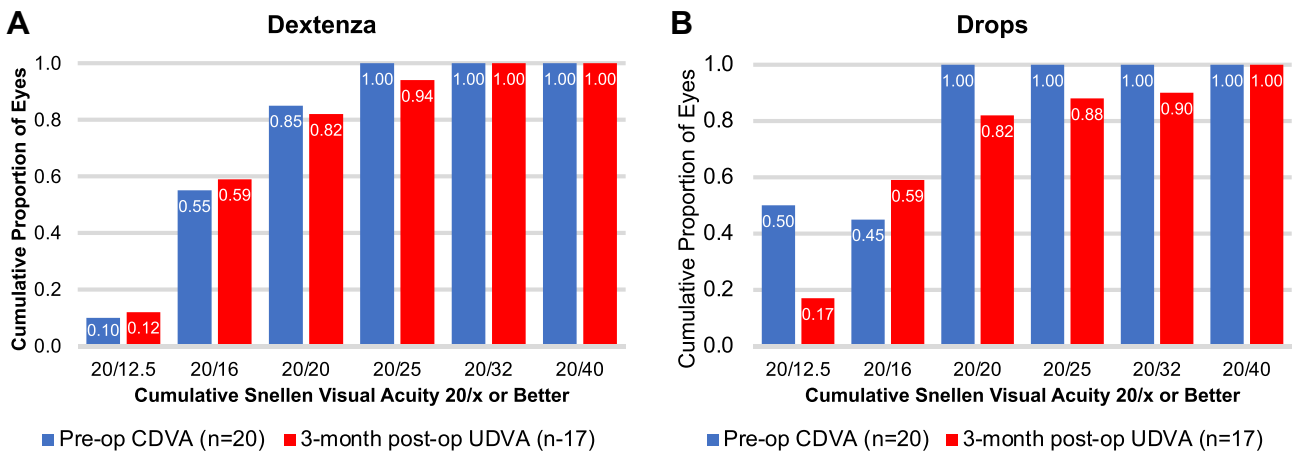

Figure 3 Uncorrected distance visual acuity (UDVA) three months postoperatively following small incision lenticule extraction in the (**A**) Dextenza (n=17) and (**B**) Drops (n=17) groups.

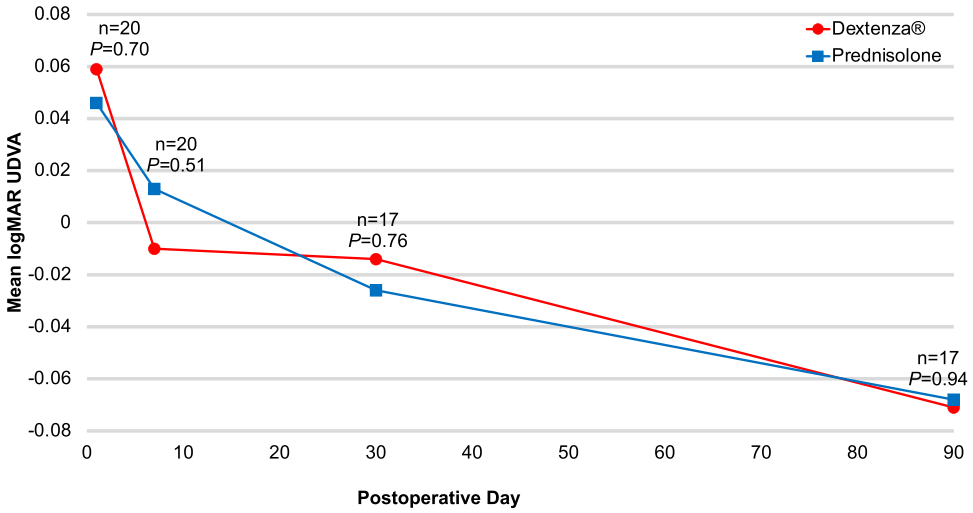

Figure 4 Mean uncorrected distance visual acuity (UDVA) postoperatively over time.

normalizes by day 7.[21–23] Inflammation is generally less common and less severe after SMILE than FS-LASIK in animal and ex-vivo human studies.[24,25] Diffuse lamellar keratitis (DLK) has a low reported incidence (0.45% to 1.6%) after SMILE.[26,27] Recognizing the adverse effects of postoperative inflammation, the American Academy of Ophthalmology's Preferred Practice Pattern for Refractive Errors and Refractive Surgery includes topical corticosteroids among the standard postoperative care following keratorefractive surgery.[28] In the current study, no eyes had clinically evident anterior chamber cell or flare, or evidence of DLK, in either treatment group.

Pain occasionally occurs after SMILE, although it is typically mild in nature. In one study of 53 eyes, 21% of eyes manifested mild pain within the first 24 hours post-procedure; no moderate or severe pain was reported, and no new reports of pain arose more than 4 hours into the first 24-hour postoperative period.[29] In the current study, half of the eyes in each group reported mild-moderate pain in the first 24 hours, half of which resolved by 1 week, and all of which resolved by month 3. The etiology of the pain in eyes in our study cannot be easily determined. Postoperative pain following keratorefractive surgery can be related to the incision, postoperative inflammation, or a well-described increase

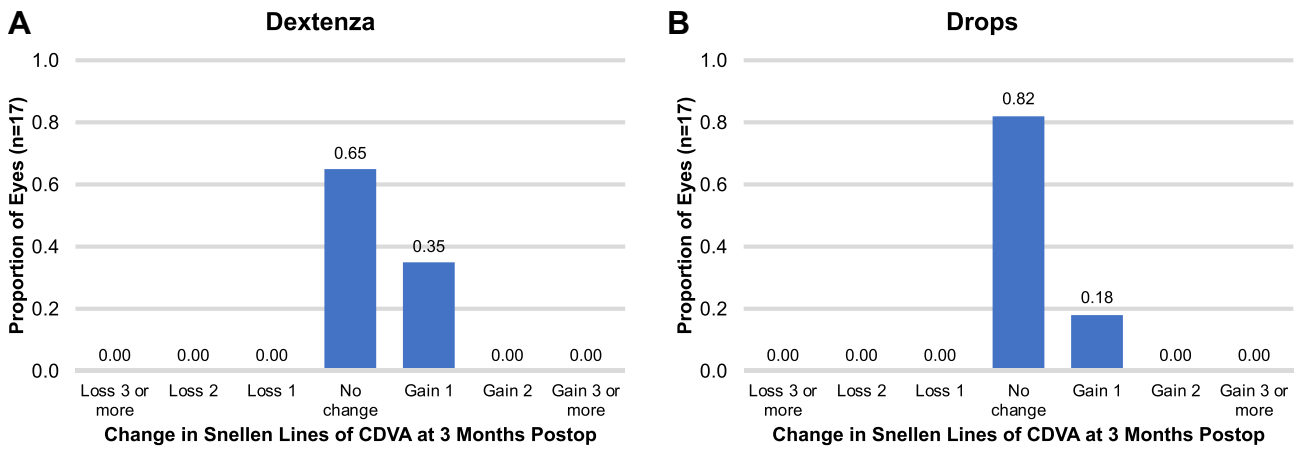

Figure 5 Change in Snellen lines of corrected distance visual acuity (CDVA) three months postoperatively following small incision lenticule extraction in the (**A**) Dextenza and (**B**) Drops groups.

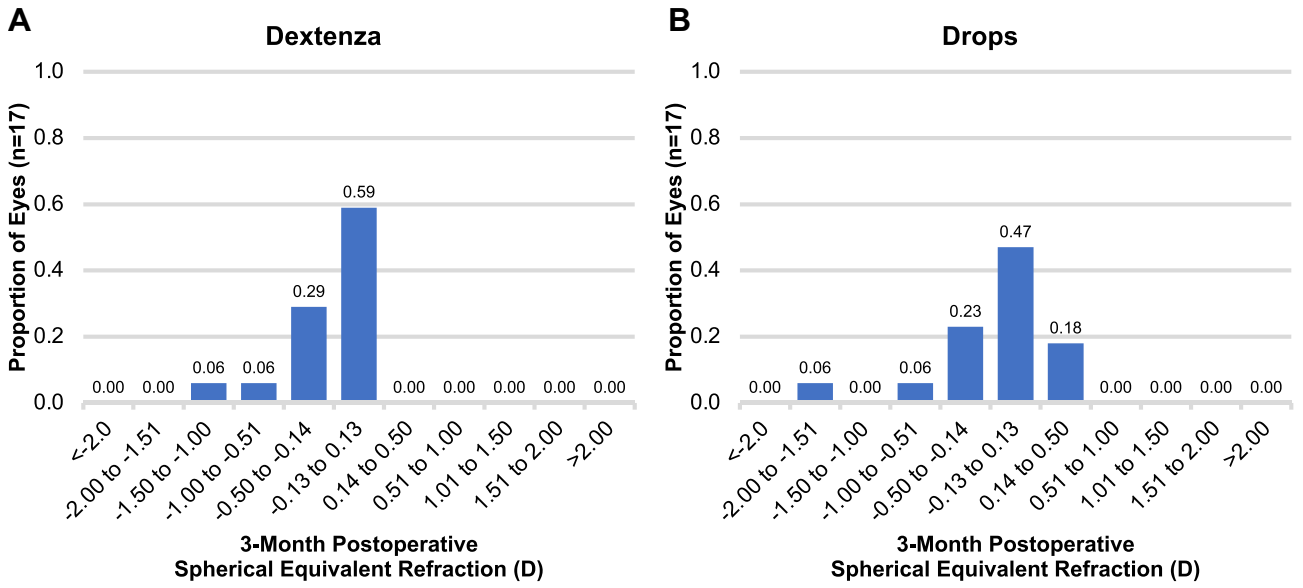

Figure 6 Manifest spherical equivalent refractive accuracy three months postoperatively following small incision lenticule extraction in the (**A**) Dextenza and (**B**) Drops groups.

in the prevalence and severity of dry eye symptoms. Dry eye symptoms are a significant contributor to patient dissatisfaction with keratorefractive surgery, accounting for 20–30% in published series of dissatisfied patients.[30,31] A meta-analysis found that SMILE is less likely to cause or aggravate dry eye symptoms compared to FS-LASIK, presumably attributable to avoidance of flap creation and attendant corneal denervation.[6,32]

Visual outcomes were comparable between treatment groups in this study and were excellent as evidenced at 3 months (Figures 3, 5, 6, 8, 9, and 10). No eyes lost any lines of CDVA. At 3 months, 82.4% of eyes in both groups achieved UDVA of 20/20 or better with 88.2% of eyes with MRSE within ±0.5 D. These outcomes are consistent with prior studies of SMILE.[33,34]

IOP elevations occurred in 3 eyes at 1 month and were presumed related to steroid response. Two eyes were treated with topical IOP-lowering therapy that quickly restored IOP control, while the third eye's IOP normalized without therapy. In phase 3 studies of DEX for control of postoperative inflammation and pain following cataract surgery, IOP elevations were reported in 4.4–7.4% of dexamethasone eyes.[14,15] Steroid responses may be more common in myopic

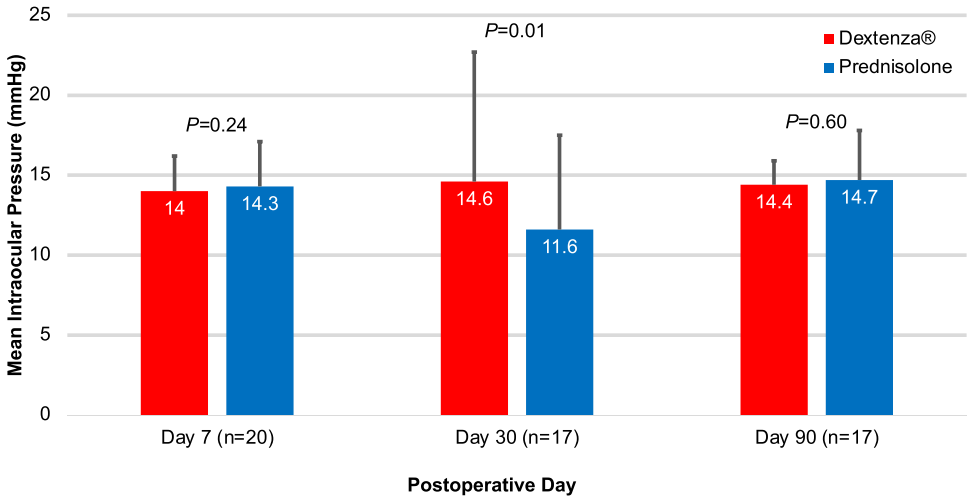

Figure 7 Mean intraocular pressure (mmHg) postoperatively over time by treatment group.

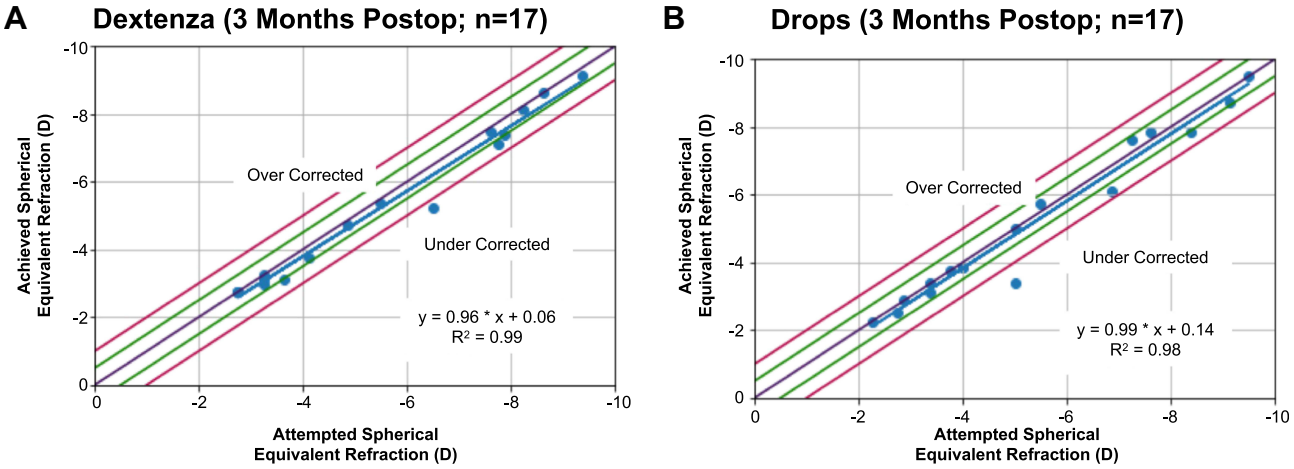

Figure 8 Attempted versus achieved manifest spherical equivalent refraction three months postoperatively following small incision lenticule extraction in the (**A**) Dextenza and (**B**) Drops groups.

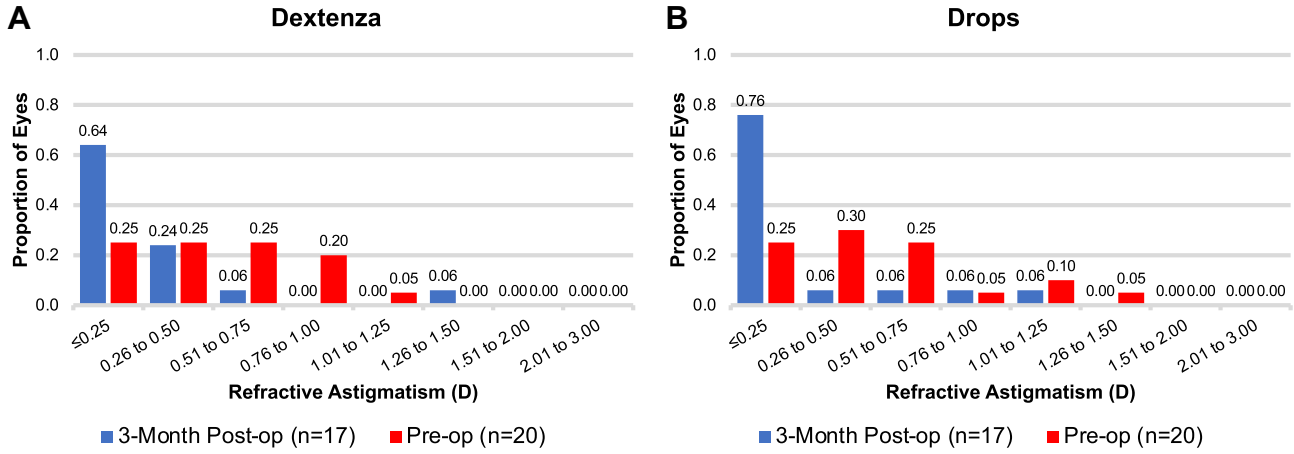

Figure 9 Refractive astigmatism three months postoperatively following small incision lenticule extraction in the (**A**) Dextenza and (**B**) Drops groups.

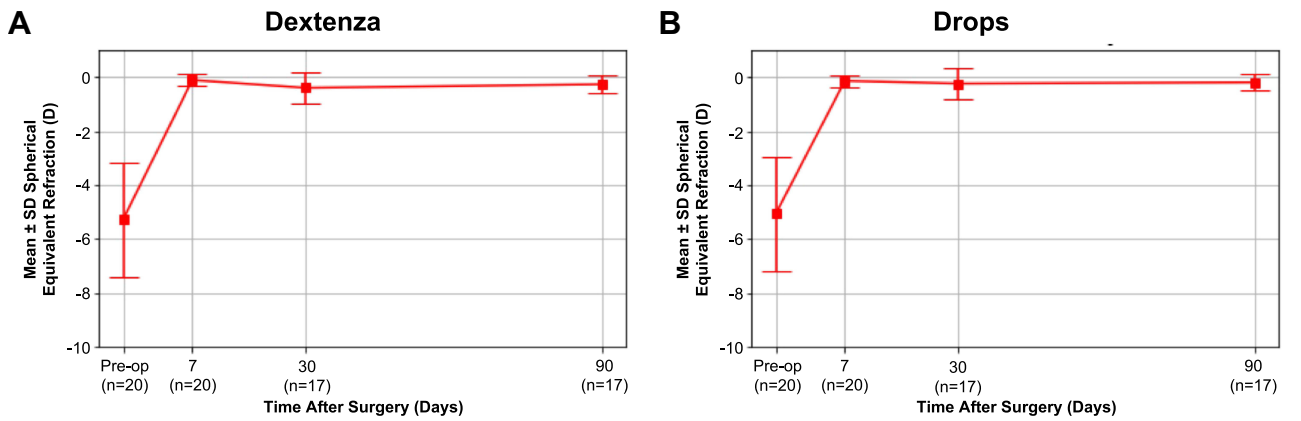

Figure 10 Stability of spherical equivalent refraction after small incision lenticule extraction in the (**A**) Dextenza and (**B**) Drops groups.

eyes.[35] A statistically significant difference in mean IOP between groups was seen at 1 month, but this was attributable to a reduction in mean IOP in the PRED group and not a rise in mean IOP in the DEX group. Future applications of the DEX insert in conjunction with SMILE could decrease the dose to reduce steroid response.

This study demonstrates that postoperative inflammation and pain following SMILE can be controlled without the need for patient-administered topical corticosteroid eye drop therapy. The DEX insert can eliminate the risk of nonadherence with topical steroid therapy. Half of patients administer fewer than half of their postoperative antibiotic and steroid eye drops after cataract surgery.[36] Even though SMILE patients are still responsible for administering topical antibiotics, there is a benefit to simplifying the postoperative medical regimen by eliminating the steroid taper. Regimen complexity is associated with poorer adherence, which increases the risk of inflammation, pain, delayed visual recovery, and patient dissatisfaction.[37–39] Minimizing the frequency of eye drop instillation also reduces hand-face contact, an important consideration in the COVID-19 era, particularly given that about 30% of patients report not washing hands when instilling postoperative eye drops after anterior segment surgery.[40]

The key strength of this study is its prospective, randomized design. Assessments and outcomes were standardized, and all subjects experienced both treatments, serving as their own controls and giving them the ideal opportunity to identify their preferred treatment. Limitations included the relatively small sample size, although our sample size was consistent with similar studies in the recent literature.[18–20] In addition, validated tests or questionnaires were not used for analysis of ocular pain and steroid preference, which were primary endpoints. Because validated tests were not used, full understanding of the implications of statistical tests is difficult. Moreover, the possibility of cross effects of a drug in both eyes should be considered; however, effects are expected to be minimal for drugs with low penetration into the blood-brain barrier and low systemic absorption.

In summary, the DEX insert controls postoperative inflammation and pain comparably to topical PRED in eyes undergoing SMILE, with similar visual outcomes achieved in both groups and with more patients preferring the DEX insert (53%) over PRED (18%). The DEX insert may reduce the postoperative medication burden, which may improve adherence and reduce the risk of adverse outcomes.

Data Sharing Statement

The data generated and analyzed for this study is not publicly available but may be requested from the corresponding author, Kathleen Jee.

Ethics Approval and Informed Consent

The study protocol was approved by Salus IRB (Austin, TX), and the study was registered at ClinicalTrials.gov (NCT04380857). Written informed consent was obtained from all study participants.

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Disclosure

The authors report no conflicts of interest in this work.

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