Safety and Efficacy Data Supporting FDA Approval of Intracameral Phenylephrine and Ketorolac 1.0%/0.3% for Pediatric Cataract Surgery: Clinical Safety and Pupil and Pain Management

Short title: Phenylephrine and ketorolac for pediatric cataract surgery

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Abstract:

Purpose: To assess safety of phenylephrine and ketorolac (PE/K) 1.0%/0.3% compared to phenylephrine (PE) 1.0% in children ages 0-3 years undergoing cataract surgery. We also compared the effect of PE/K to PE on intraoperative pupil diameter and postoperative pain.

Setting: Multicenter study in the United States.

Design: Randomized double-masked phase 3 clinical trial. Randomization was stratified within each site according to whether an intraocular lens was implanted.

Methods: This study was powered to assess safety only. Depending on randomization, 4mL of PE/K 1.0%/0.3% or PE 1.0% were injected into the surgical irrigation solution. Safety endpoints were assessed up to 90 days postoperatively. From surgical videos, a masked central reader measured change in pupil diameter from immediately prior to incision to wound closure. Postoperative pain was measured using Alder Hey Triage Pain Score at 3, 6, 9, and 24 hours following wound closure and recorded by parent/caregiver.

Results: Seventy-two patients received masked intervention. There were no notable changes in vital signs or ophthalmological complications in either group. Mean change in pupil diameter was similar between PE/K 1.0%/0.3% and PE 1.0% (mean difference in AUC -0.071; $P = 0.599$). Postoperative ocular pain scores and overall mean scores were lower in PE/K group at all individual time points, and differences in overall mean scores were statistically significant at 6 and 24 hours ($P=0.029$ and 0.021, respectively).

Conclusions: Phenylephrine and ketorolac 1.0%/0.3% was safe for use in children and maintained mydriasis during cataract surgery. Postoperative pain levels were lower in the PE/K 1.0%/0.3% group.

Introduction

Cataract surgery poses several challenges in children, including maintaining adequate intraoperative mydriasis. This is due in part to the pupil dilator muscle being poorly developed and reduced iris stromal rigidity. During surgery the iris in children can exhibit features that resemble intraoperative floppy iris syndrome (IFIS).[1] For many years, the standard for pediatric cataract surgery pupil dilation has been topical mydriatics pre-operatively and preservative-free epinephrine in the irrigating solution intraoperatively.[2] In adults, the addition of a non-steroidal anti-inflammatory drug (NSAID) such as ketorolac to the irrigating solution has been shown to decrease intraoperative miosis as well as control pain and inflammation associated with cataract surgery.[3,4]

Different intracameral agents are currently being used during cataract surgery but only one combination agent, OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1.0%/0.3%, Omeros Corporation, Seattle, WA, USA, is approved by the Food and Drug Administration (FDA) for this use. This commercially available product containing phenylephrine (PE) 1%, an α_1-adrenergic receptor agonist, and ketorolac 0.3%, a nonselective cyclooxygenase inhibitor, is indicated for use during cataract surgery to maintain pupil size by preventing intraoperative miosis and to reduce postoperative ocular pain. Phenylephrine acts as a mydriatic agent. Ketorolac decreases prostaglandin production resulting in reduced pain and decreased potential for surgically induced miosis. Previous studies have demonstrated the safety and efficacy of phenylephrine and ketorolac (PE/K) 1.0%/0.3% in adult patients[3,5-7] and showed that it was superior to placebo or using either agent alone.

The FDA approved PE/K 1.0%/0.3% for use in adult cataract and other IOL replacement procedures in 2014. The current investigation was designed as a Phase 3 study to fulfill a pediatric study plan requested by the FDA. The study was powered to assess safety of phenylephrine and ketorolac (PE/K) 1.0%/0.3% compared to phenylephrine (PE) 1.0% in children ages birth through 3 years undergoing cataract surgery with or without IOL replacement. However, the study also looked at efficacy by comparing the effect of PE/K to PE on intraoperative pupil diameter and postoperative pain.

Materials and Methods

This was a multicenter, randomized, double-masked, parallel-group, active-controlled Phase 3 study conducted at 17 sites in the United States. All sites received approval from an institutional review board and complied with the United States Health Insurance Portability and Accountability Act (HIPAA). A written informed consent and HIPAA authorization was obtained from the parent or legal guardian of all participating patients. This study is registered at ClinicalTrials.gov as NCT02132312, under NDA 205388.

The study population included children from 0 to 3 years of age at the time of cataract surgery. **Appendix 1** lists all inclusion and exclusion criteria. Eligible patients were randomized 1:1 to receive PE/K 1.0%/0.3% or PE 1.0%. Randomization to treatment group was stratified within each site according to whether an IOL was implanted during the surgical procedure. The randomization scheme was prepared by Pacific Northwest Statistical Consulting (Woodinville, WA, USA) and provided to the unmasked designee at each site. Depending on randomization assignment, 4 mL of either PE/K 1.0%/0.3% or PE 1.0% was injected into a 500cc bottle of balanced salt solution (BSS/BSS PLUS®,

Alcon Laboratories, Inc., Fort Worth, TX, USA) and administered as an irrigation solution during cataract extraction.

Study investigators evaluated each subject's mydriatic response to dilating drops prior to surgery. If due to inadequate mydriasis, the investigator planned to use additional (pharmacological or mechanical) techniques to obtain adequate mydriasis, the subject was withdrawn from the study. If additional means to obtain mydriasis were required after study drug administration, the subject remained in the study. Topical atropine 0.5% was allowed up to one day prior to surgery at the discretion of the investigator. On the day of surgery, one drop of atropine 0.5% was administered preoperatively. In children 6 months or younger, one drop of Cyclomydril™ (cyclopentolate hydrochloride 0.2% and PE hydrochloride 1%; Alcon Laboratories, Inc., Fort Worth, TX, USA) was administered three times at approximately 30 minutes, 15 minutes, and 5 minutes prior to the start of the surgery. For children older than six months old, one drop each of cyclopentolate hydrochloride 1% and PE 2.5% were administered at similar intervals. Postoperatively, all patients received topical ophthalmic dexamethasone 0.1% and a topical ophthalmic antibiotic to be used as prescribed by the investigator. Alternative or additional postoperative anti-inflammatory medications were prescribed if the investigator believed they were necessary to avoid inflammation-related postoperative complications. Data were collected if any additional medication was used. Patients were examined 1, 7, 28, and 90 days after surgery.

Endpoints and assessments

Safety was assessed by recording the incidence of adverse events (AE), serious adverse events (SAE), postoperative intraocular pressure (IOP), postoperative best-

corrected (age-appropriate) visual acuity (BCVA), and vital signs for 90 days postoperatively.

The primary efficacy endpoint was mean change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure). Intraoperative pupil size was determined by measuring pupil diameter from still photos captured from video recordings of the procedure. Pupil diameter measurements were performed on images from immediately prior to the initial incision and at one-minute intervals until the end of the procedure (wound closure). Pupil diameter was measured by a masked reader at a centralized location.

Another efficacy endpoint was postoperative pain experienced by the child. Pain was measured using the Alder Hey Triage Pain Score (AHTPS) at 3, 6, 9, and 24 hours following wound closure by a masked parent/caregiver and recorded in a diary. The AHTPS uses five observational and behavioral characteristics to assess pain: color, cry/voice, facial expression, movement, and posture. Each has a possible score of 0, 1, or 2, resulting in a total score ranging between 0 and 10.

Statistical analysis

The planned sample size of 30 patients per study arm provided a probability of 95% for observing at least one occurrence of an AE with an incidence rate of at least 10% in the study population. An as-treated safety endpoint analysis was performed and included all randomized patients, regrouping them according to actual treatment received. The safety data, including AEs, IOP values, distance BCVA measurements, vital signs, concomitant medications, and reasons for withdrawal from the study, were descriptively summarized by treatment group. Adverse events were coded according to preferred

term and system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA, Version 14.1) AE coding dictionary.

An intent-to-treat analysis was used for efficacy. All randomized patients who received treatment were included and analyzed for this purpose. Changes in pupil diameter over time were summarized using descriptive statistics by treatment group and time point (every minute). The mean change in pupil diameter during surgery was calculated as the area-under-the curve (AUC) divided by the surgery time minus the baseline pupil diameter for each patient. Summary statistics of the mean AUC change from baseline were provided by stratum and treatment group. A generalized Cochran-Mantel-Haenszel (CMH) test was used to compare the two treatment groups. The mean AUC postoperative pain score was also compared between the treatment groups using the generalized CMH test.

Results

Patient characteristics and disposition

Thirteen of 17 study sites recruited patients (**Appendix 2**). Of 83 patients screened, 78 were randomized (5 were screen failures). Thirty-seven eyes received primary IOL implantation (PE/K 1.0%/0.3% n=18; PE 1.0% n=19). Forty-one eyes were left aphakic at the time of cataract surgery (PE/K 1.0%/0.3% n=19; PE 1.0% n=22). After randomization, 4 patients in the PE/K 1.0%/0.3% group and 2 patients in the PE 1.0% group were ineligible to receive assigned intervention (**eFigure 1**). These six patients were not included in the analysis. Seventy-two patients received masked intervention in this intent-to-treat population (PE/K 1.0%/0.3%: n = 33, PE 1.0%: n = 39) and were used for efficacy analysis. One patient was randomized to study drug PE/K 1.0%/0.3%,

but received PE 1.0%, so the as-treated population in the safety analysis included 32 patients in the PE/K 1.0%/0.3% group and 40 in the PE 1.0% group. There were three patients who were randomized, received study treatment, and completed their primary efficacy assessments, but were then lost to follow up (PE/K 1.0%/0.3% group: 2, PE 1.0% group: 1) (**eFigure 1**). Demographic characteristics are shown in **eTable 1**.

Safety

Overall, PE/K 1.0%/0.3% was well tolerated by patients in this study. All AEs were described in **eTable 2.** The most frequently observed AEs were anterior chamber opacity, elevated IOP, pyrexia, conjunctival hemorrhage, bronchiolitis, and immunization reaction. There were no appreciable differences in the safety profile of study drug PE/K 1.0%/0.3% compared to PE 1.0%. One patient in the PE/K 1.0%/0.3% treatment group experienced an AE (persistent inflammatory pupillary membrane) considered possibly treatment-related by the investigator.

There were no notable changes in vital signs (blood pressure, respiratory rate, heart rate, and temperature), and no treatment-related ophthalmological findings (iris/pupil, lens status, eyelid erythema and edema, conjunctival erythema and edema, corneal staining/erosion and edema, visual acuity, ocular inflammation, anterior chamber cell count and grade, IOP, fundus findings) in ether group.

Efficacy

Pupil diameter data were available for 31/33 patients in the PE/K 1.0%/0.3% group and 32/39 patients in the PE 1.0% group. **Table 1** describes pupil diameter in each group. Change in pupil diameter was similar between the PE/K 1.0%/0.3% and PE 1.0% (CMH weighted mean difference in AUC -0.071; $P = 0.599$). Intraoperative change in pupil

diameter from baseline is shown graphically in **eFigure 2**. A sensitivity analysis of the mean AUC pupil diameter change from baseline was performed by excluding two patients whose pupil diameter data were potentially not accurate due to video issues: one patient in the PE/K 1.0%/0.3% group was excluded because the ruler image was not captured as a continuous file with the surgical procedure and one patient in the PE 1.0% was excluded because iris hooks were used during the surgical procedure. The CMH weighted mean difference (standard error) between the two treatment groups was -0.064 (0.133) (*P* = 0.64). The result was similar to the initial result when all patients were included.

Summary of postoperative ocular pain, measured by the Alder Hey Triage pain score at 3, 6, 9, and 24 hours after surgery is presented in **Table 2**. The time-weighted average pain scores for 24 hours, estimated by AUC, were similar between the PE/K 1.0%/0.3% and the PE 1.0% (CMH weighted mean difference AUC of -0.214, *P* = 0.287). Patients in both treatment groups have comparable overall average postoperative ocular Adler Hey Triage total pain scores; the average scores were low, at less than one for the 3, 6, 9, and 24 hour timepoints after surgery for both groups (PE/K 1.0%/0.3% and PE 1.0%), on a 10-point scale (**Table 3** and **e-Figure 3**). Mean pain scores were significantly lower in the PE/K 1.0%/0.3% group as compared to the PE 1.0% group at 6 and 24 hours *(P*=0.029 and 0.021, respectively). One patient randomized to PE 1.0% did not have pain data collected due to a site-level misunderstanding about whether patients with protocol deviations should be included in the collection of endpoint data.

Discussion

Herein, we present results from the clinical study performed to support US FDA approval of OMIDRIA® (PE/K 1.0%/0.3%) for pediatric use. We compared the effect of PE/K 1.0%/0.3% to that of PE 1.0%. This study was not a placebo-controlled study as many pediatric surgeons use epinephrine in the irrigation solution as their standard practice. During the planning of this randomized trial, the US FDA rejected using epinephrine as the active control, perhaps because it is considered an off-label use of epinephrine. Instead, the FDA approved the use of PE 1.0% (one of the ingredients of the study drug) as the active control. Preservative-free, bisulfite-free PE is not commercially available in the United States, so the sponsor provided both the study drug (PE/K 1.0%/0.3%) and the active control (PE 1.0%).

The most frequently observed AEs are all anticipated events following pediatric cataract surgery or common events in this population. Overall, the safety of PE/K 1.0%/0.3% is consistent with that reported in previous clinical studies and in studies of intracameral mydriatic agents, PE, and ketorolac.[3,5-8] The study was powered to detect common AEs and was not powered for efficacy. Based on the safety demonstrated in this randomized trial and FDA's determination that efficacy in children could be extrapolated from clinical efficacy data in adults, PE/K 1.0%/0.3% is now FDA approved for children.

Change in pupil diameter was comparable between study drug PE/K 1.0%/0.3% and PE 1.0%. One conclusion pediatric eye surgeons may draw from this study is that a PE-containing irrigating fluid is adequate for maintaining mydriasis in young children. The study, though, was not powered to detect a difference in efficacy between the two treatment arms. A previously published study, however, demonstrates that PE/K

1.0%/0.3% was nearly four times more effective than PE 1.0% in maintaining pupil diameter at 6 mm or greater during cataract surgery in adults (*P*=0.0216)[3]. Also relevant to the iris in children, a prospective, double-masked, controlled study using PE/K 1.0%/0.3% in adult cataract surgery prevented IFIS.[9]

The AUC pain score over 24 hours following surgery was lower in the PE/K 1.0%/0.3% group as compared to the PE 1.0% group, but the difference was not statistically significant (CMH weighted mean difference AUC of -0.214, *P* = 0.287). Due to small sample size, the study was not powered to detect a difference in pain score between the treatment groups; however, a trend was seen, with mean scores significantly lower in the PE/K 1.0%/0.3% group as compared to the PE 1.0% group at 6 and 24 hours (*P*=0.029 and 0.021, respectively**)**. Average pain score and highest pain score were also lower in the PE/K 1.0%/0.3% group as compared to PE 1.0% alone. This trend can also be seen at 3, 6, 9, and 24 hours in **eFigure 3**. Future studies using larger sample size in children are needed to compare respective overall postoperative pain scores of PE/K 1.0%/0.3% and PE 1.0%. Rating pain in an infant who has just had general anesthesia is difficult since there may be many sources of discomfort in the postoperative period that are not related to the eye.[10] In adult studies, adding PE/K 1.0%/0.3% to the irrigating solution was beneficial, both with respect to pain and to mydriasis maintenance during surgery.[3, 5-7] Prior to FDA approval of PE/K 1.0%/0.3%), cataract surgeons did not administer ketorolac intracamerally. Based on this study, ketorolac used intracamerally appears safe for use in young children. Despite the present pediatric study not having been adequately powered to assess efficacy, statistically significant reductions in pain were seen at 6 and 24 hours postoperatively.

To assess whether PE/K 1.0%/0.03% could deliver in children undergoing cataract surgery, as already demonstrated in adults, pain reduction throughout the entire early postoperative period as well as maintenance of mydriasis, an adequately powered study would be required.

The alternative for pediatric cataract surgeons is preservative-free, bisulfite-free epinephrine. Walter and co-workers reviewed 100 cataract surgeries using PE/K 1.0%/0.3% in the BSS irrigating solution to a matched group of 100 cataract surgeries using epinephrine. Pupil expansion devices were required less often (2 versus 12) in the PE/K 1.0%/0.3% group than in the epinephrine group.[7] Other studies have shown similar superiority of PE/K over epinephrine in adult cataract surgeries.[11-12] PE/K has also been shown, compared to epinephrine, to reduce by multi-fold the incidence of cystoid macular edema while eliminating the need for perioperative steroids.[13-14] In addition, use of epinephrine may be a less desirable option since it is off-label and has had supply shortages in the past. Off-label preservative-free PE is also used in cataract surgery to support pupil dilation. With the risk of compounded medications resulting in an incorrect dose and the potential for systemic and ocular AE[15-19], there is benefit in using an FDA-approved medication like PE/K 1.0%/0.3%, particularly in the pediatric population.

In conclusion, this study found that PE/K 1.0%/0.3% was safe for use in children ages 0-3 years, maintained mydriasis during pediatric cataract surgery with or without IOL implantation, and decreased pain postoperatively. The potential benefit of PE/K 1.0%/0.3% more broadly on postoperative pain and inflammation in children requires further study.

What was known:

- Adequate preoperative mydriasis is a requirement for safe and efficient pediatric cataract surgery.
- Phenylephrine and ketorolac 1.0%/0.3%, when added to the irrigation solution and delivered intracamerally during cataract surgery in adults, maintains pupil size and reduced postoperative pain.
- Phenylephrine and ketorolac 1.0%/0.3% is safe and efficacious in adult cataract surgery.

What this paper adds:

- Phenylephrine and ketorolac 1.0%/0.3% when added to the irrigation solution and delivered during pediatric cataract surgery was safe.
- Phenylephrine and ketorolac 1.0%/0.3% maintained mydriasis during pediatric cataract surgery.
- Postoperative pain level was lower when using phenylephrine and ketorolac 1.0%/0.3% as compared with phenylephrine 1% alone.

Legend for tables

Table 1. Pupil size at beginning and end of the surgical procedure

Table 2. Postoperative Alder Hey Triage Pain Score (full analysis set population)

Table 3. Summary of postoperative Alder Hey Triage Pain score

Legend for figures

e-Figure 1. Patient enrollment and randomization

e-Figure 2. Intraoperative pupil diameter change from baseline.

e-Figure 3. Postoperative Alder Hey Triage Pain Score

Legend for e-table

e-Table 1. Demographic characteristics

e-Table 2. Subject incidence of treatment-emergent adverse events by preferred term (safety population)

Legend for appendix

Appendix 1. Inclusion and exclusion criteria

Appendix 2. Investigators

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