

Pain control and reduction of opioid use associated with intracameral phenylephrine 1.0%–ketorolac 0.3% administered during cataract surgery



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Purpose: To compare pain and the need for the opioid fentanyl use associated with the administration of phenylephrine 1.0%–ketorolac 0.3% (P/K) with those of epinephrine administration during cataract surgery.

Setting: Ambulatory surgery center.

Design: Single-center, prospective, randomized, double-masked, self-controlled trial.

Methods: Patients undergoing bilateral, topical anesthetic cataract surgery were randomized to receive either intracameral P/K or epinephrine in their balanced salt solution for the first eye and the other for the second eye, 2 weeks later. Fentanyl was used to manage intraoperative pain. The primary end point was the need for fentanyl administration intraoperatively. Secondary outcomes included pain measurements; surgery duration; effective phacoemulsification time; pupil size; and complications.

Results: 112 eyes of 56 patients were enrolled. Significantly fewer eyes in the P/K group (7 [12.5%]) than in the epinephrine group (19 [33.9%]; $P = .013$) required intraoperative fentanyl administration. Mean pain scores were lower in the P/K group than those in the control group at all timepoints. For patients with no pain to mild pain (pain scores ≤ 3), 85.7% ($n = 48$) of the P/K group and 58.9% ($n = 33$) of the epinephrine group met this benchmark ($P = .003$) intraoperatively. The combined outcome, the number of patients not receiving intravenous fentanyl and experiencing no pain to mild pain, was significantly higher in the study (82.1%, $n = 46$) than in the control group (58.9%, $n = 33$; $P = .013$).

Conclusions: P/K administration significantly reduced pain and the need for fentanyl use. Using P/K is a practical way for cataract surgeons to provide better patient care and reduce the need for intraoperative opioids.

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Data from the Centers for Medicare and Medicaid Services show cataract extraction to be the most common surgical procedure for Medicare beneficiaries.¹ According to the Centers for Medicare and Medicaid Services National Summary Data File, 3.2 million cataract surgeries were performed in 2018 and 3.4 million in 2019 in this patient population.²

Cataract surgery has a low complication rate, and patients have the expectation of rapid visual rehabilitation and a comfortable, pain-free procedure. Cataract surgery can be performed with topical anesthesia or with peribulbar or retrobulbar injection of anesthetics. The latter requires the injection of anesthetics around the eye and can be associated with complications including perforation of the globe and extraocular muscle palsy. In addition, these patients need to wear a patch after the surgery,

delaying their visual rehabilitation and use of postoperative medications. Topical anesthesia is widely used, but pain is the most commonly reported adverse event, with up to 35% of patients experiencing moderate to severe pain during surgery or in the first few hours postoperatively.^{3–5} Experiencing intraoperative pain with topical anesthesia is associated with patient movement, squeezing of the eye, and general lack of cooperation, which can increase the risk for surgical complications. In addition, patients view comfort during surgery almost as importantly as their visual rehabilitation. The associated pain and discomfort are often treated with analgesic medications, including intraoperative or postoperative opioid drugs. With the current opioid crisis in the United States, public health initiatives have mobilized the medical community to reduce or avoid treatment with opioids

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since even low exposure has been shown to have associated risks, including a risk for future opioid use.⁶ These risks are even more pronounced in the elderly population.⁷

Despite technological and procedural advances in ophthalmic surgery, the prescription rate for opioids after ophthalmic procedures, including cataract surgery, has been paradoxically increasing. Recently, Kolomeyer et al. evaluated 2 407 962 incisional ocular surgery claims over a 16-year period from a large insurance claims database.⁸ Of interest was the rate of opioid prescriptions filled from 1 day preoperatively to 7 days postoperatively for each ophthalmic subspecialty. Of these surgeries, 45 776 patients were prescribed an opioid (1.90%). Cataract surgery had the highest number of opioid prescriptions written (19 494), although the lowest rate of prescriptions filled per surgery at 0.95%. Of the approximately 20 000 opioid prescriptions written for postcataract surgery pain and discomfort, 77% of these patients also received a topical nonsteroidal anti-inflammatory drug (NSAID) and/or steroid preoperatively and/or postoperatively.⁸ This indicates that these topical treatments may not sufficiently address patients' postoperative pain.

When looking at the overall trend in opioid prescriptions across ophthalmic subspecialties from 2000 through 2016, the odds of having an opioid prescription filled in 2014 to 2016 was 3 times higher than in 2000 to 2001.⁸ In a retrospective study assessing 4 low-risk, short-stay surgeries including cataract surgery, patients undergoing cataract surgery who received a postoperative prescription for an opioid were 60% more likely to use opioids long-term compared with those not prescribed an opioid.⁹ Ung et al. evaluated the rate and risk factors for new persistent opioid use after ophthalmic surgery.¹⁰ Of 327 379 opioid naïve patients 14 841 (4.5%) had an initial perioperative opioid prescription; 3.4% of these patients continued to use opioids after ophthalmic surgery compared with 0.6% of patients not receiving perioperative opioids. Initial perioperative opioid prescription fill was independently associated with a 6.21-increased rate of new persistent opioid use.

The increased concern regarding the social effect of opioids and opioid use disorder, along with evidence suggesting topical medications are insufficient for controlling pain associated with cataract surgery, demonstrates a need for alternative strategies to manage pain in cataract surgery patients.

Omidria (phenylephrine 1.0%–ketorolac 0.3% [P/K]; Omeros Corporation) is the U.S. Food and Drug Administration–approved drug for use during cataract surgery or intraocular lens (IOL) replacement to maintain pupil size and to reduce postoperative pain. P/K is added to the irrigating solution for continuous intracameral administration during cataract surgery, and clinical studies have demonstrated its efficacy in preventing intraoperative miosis and reducing postoperative pain.^{11–20} The anti-inflammatory properties of P/K are primarily

responsible for its pain-limiting effects. In clinical trials involving more than 800 patients, the use of P/K resulted in both a greater than 50% increase in pain-free patients and a 30% decrease in the proportion of patients who used analgesics on the day of surgery compared with the control group.¹³

A previous study assessing intraoperative pain and the need for opioid use during cataract surgery in patients treated with P/K ($n = 41$) compared with the control group, which received epinephrine ($n = 19$). In that study, the use of P/K was associated with a statistically significant reduction in both pain and the need for intraoperative fentanyl use.²¹ These results led to this current study in which, rather than using a separate patient control group, patients undergoing bilateral sequential cataract surgery served as their own control group, each receiving P/K in one eye and epinephrine in the other eye.

The primary aim of this study was the same as that of the earlier study—to assess the effect of P/K use during cataract surgery on the need for intraoperative opioids and perioperative pain. Opioid requirement and patient-reported pain during surgery were captured, as were patient-reported pain and discomfort at 10 minutes and 1 day postoperatively.

METHODS

This single-center, prospective, randomized, double-masked, self-controlled, clinical trial enrolled 112 eyes of 56 adult patients who underwent bilateral sequential cataract surgery under topical lidocaine gel anesthesia. The study was approved by Advarra Institutional Review Board. In accordance with standard clinical protocols, the risks for, benefits of, and alternatives to cataract surgery were explained to each patient, and informed consent was obtained. This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice, in accordance with the latest Health Insurance Portability and Accountability Act regulatory standards.

Initial eligibility was determined based on patients' insurance coverage of P/K. Patients had to be aged 50 to 80 years and scheduled for cataract surgery in both eyes. Prior to surgery on the first eye, eligible patients were randomized to receive either P/K or epinephrine during the initial cataract surgery. The other treatment was then used for cataract surgery on the second eye, performed 2 weeks after the first procedure. For all procedures, P/K or epinephrine was administered as part of the intracameral irrigation. The surgeon, anesthesiologist, and patient were masked to the study intervention. Patients were excluded from the trial if undergoing unilateral cataract surgery or fell outside the specified age range.

All patients were seen in the authors' private office for a preoperative visit during which eligibility criteria were reviewed and written informed consent was obtained. Data including medical history, medications, medication allergies, and demographics were also collected. Patients were randomized 1:1 as to which drug would be added to the irrigating solution for their first cataract procedure.

As part of a standardized preoperative and intraoperative medication regimen, patients received a once-a-day topical NSAID (bromfenac 0.07% or nepafenac 0.3% for 3 days prior to surgery), a mydriatic cocktail (topical tropicamide 1.0%, cyclopentolate 1.0%, and phenylephrine 2.5%) on the day of surgery, topical lidocaine gel 10 minutes preoperatively, intracameral 1% nonpreserved lidocaine at the start of surgery, and 2 mg

intravenous midazolam at the beginning of the surgery. Either P/K or epinephrine was added to the irrigating solution for each patient, following the randomization schedule. Fentanyl was used for intraoperative pain control based on the surgeon's and anesthesiologist's clinical judgment and the patients' request for pain medication.

During surgery, pupil size was measured at the beginning of surgery and at the time of IOL placement. Pain level was assessed intraoperatively by the operating room nurse, asking patients to verbally grade their pain on a scale from zero to 10. In addition, the need for fentanyl during surgery, the total duration of surgery, the phacoemulsification time and power, and any complications were recorded.

Ten minutes postoperatively, patients were again asked to assess their pain level using visual analog scale (VAS) score, and complications were recorded. A standardized postoperative medication regimen was initiated postoperatively: topical bromfenac 0.07% once daily for 4 weeks; topical prednisolone acetate 1% 4 times daily for 1 week, 3 times daily for 1 week, and then twice daily for 1 week; and topical ofloxacin 0.3% 4 times daily for 10 days. Patients returned for a 1-day postoperative follow-up visit after each of the 2 cataract procedures, during which they were asked again to grade their pain on a VAS. Complications were also recorded.

The overall study objective was to compare pain control and the need for opioid use during cataract surgery associated with the intracameral use of either P/K or epinephrine. The primary outcome measure was the proportion of procedures requiring opioid medication (ie, need for fentanyl) to control pain during surgery. The secondary outcome variables included the following: (1) level of pain experienced during the surgery using a VAS pain score, as assessed by an individual masked observer intraoperatively, 10 minutes postoperatively in the postoperative care room, and 1-day postoperatively; (2) mean total duration of surgery in minutes; (3) effective phacoemulsification time in minutes, as recorded by the phacoemulsification machine; (4) pupil size in millimeters at the start of surgery (measured manually); (5) pupil size in millimeters at the time of IOL insertion (measured manually); and (6) incidence of complications.

Statistical analysis was performed using SAS software, v. 9.4 (SAS Institute). VAS pain scores were compared using a *t* test based on the assumption that carryover effects were equal. Categorical data were analyzed using logistic regression analysis or Fisher exact test. All *P* values were evaluated as 2-sided, and a *P* value less than 0.05 was considered statistically significant.

RESULTS

This study enrolled 112 eyes of 56 patients (23 men [41.1%]; 33 women [58.9%]) undergoing bilateral cataract surgery.

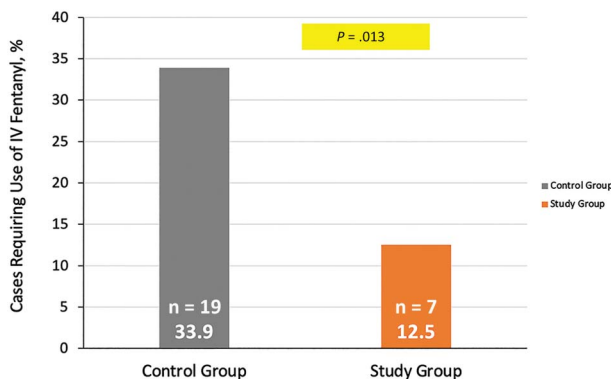


Figure 1. Proportion of patients requiring intravenous fentanyl for cataract surgery

Twenty-eight patients received epinephrine for the first eye, followed 2 weeks later by P/K in the second eye; the other half of patients received P/K in the first eye, followed by epinephrine in the second. The mean age of the 56 study patients was 70.1 (SD = 7.09) years. All enrolled patients completed the study.

For the primary end point, the number of patients or eyes requiring intraoperative fentanyl analgesia was significantly lower in the P/K group (7 [12.5%]) than that in the epinephrine control group (n = 19, 33.9%; *P* = .013) (Figure 1). The relative risk for a patient requiring intraoperative fentanyl analgesia was 63.1% lower in the P/K study group vs the control group. Stated differently, the odds of a patient in the epinephrine group requiring intraoperative fentanyl analgesia were 3.6 times higher than those of a patient in the P/K group (odds ratio, 3.6; 95% CI, 1.36-9.4).

The mean VAS pain scores intraoperatively were significantly (56.7%) lower in the P/K group than in the control group (1.3 vs 3.0; *P* < .001), as were the mean VAS pain scores at 10 minutes (0.9 vs 2.1; *P* < .001) and 1 day (0.2 vs 0.6; *P* < .001) postoperatively, representing pain score reductions of 57.1% and 66.7%, respectively, in the P/K group (Figure 2).

Intraoperatively, the number of patients with no pain to mild pain, defined as pain scores ≤ 3 , was 48 (85.7%) in the P/K group compared with 33 (58.9%) in the epinephrine control group (*P* = .003). At 10-minutes postoperatively, the number of reports of no pain to mild pain in the P/K group was 53 (94.6%) compared with 41 (73.2%) in the control group (*P* = .004). There was no statistically significant difference between the groups at the 1-day visit (Figure 3).

The number of patients not receiving intravenous fentanyl and patients experiencing no pain to mild pain (VAS ≤ 3) intraoperatively was significantly higher in the study group (46, 82.1%) than that in the control group (33, 58.9%; *P* = .013) (Figure 4).

The total operating room time for the P/K group was significantly (*P* = .004) shorter (6.9 minutes [SD = 1.2]) than for the control group (7.6 minutes [SD = 1.3]). However, the phacoemulsification time was not statistically

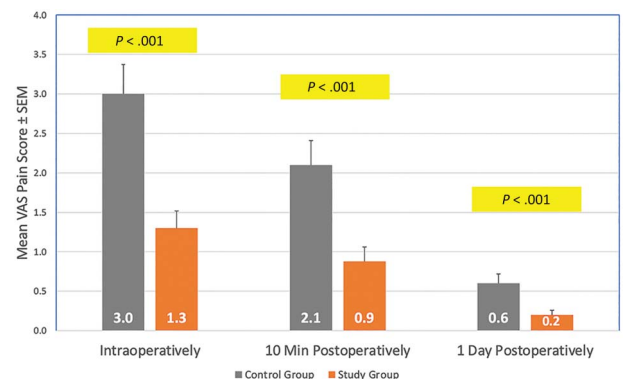


Figure 2. Mean VAS pain scores intraoperatively, 10 minutes postoperatively, and 1 day postoperatively. VAS = visual analog scale

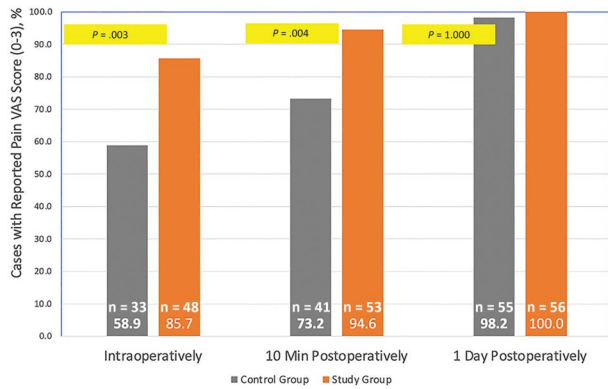


Figure 3. Cases with no pain to mild pain (VAS scores 0 to 3) intraoperatively, 10 minutes postoperatively, and 1 day postoperatively. VAS = visual analog scale

different between the 2 groups (36.3 and 34.9 seconds, respectively; $P = .710$).

The mean pupil size at the start of surgery was not statistically different between the P/K and epinephrine control groups (8.01 vs 7.98, $P = .870$). However, when measured at the time of IOL insertion, the P/K group had a mean pupil size of 7.2 mm, whereas the control group had a mean of 6.5 mm ($P < .001$). The mean reduction from baseline in pupil size at this timepoint was 0.8 mm in the P/K group and 1.5 mm in the epinephrine group ($P < .001$).

The only complication noted was elevated intraocular pressure (IOP). Ten patients had IOP ≥ 30 mm Hg at the 1-day postoperative visit for a rate of 6.4%. Of these patients, 3 (5.4%) were in the P/K group, and 7 (12.5%) were in the epinephrine group. This difference was not statistically significant ($P = .321$). No patient had elevated IOP after the first day, and there were no complications due to the elevated IOP.

DISCUSSION

Cataract surgery techniques and technologies have become more advanced, particularly in recent years with evolving topical and intracameral anesthesia including the routine use of topical NSAIDs, accommodative and adjustable IOLs, femtosecond laser, and heads-up displays.^{22–26} Because of these improvements, cataract surgery has become a convenient and safer outpatient procedure. Patients expect a pain-free procedure and generally do not tolerate discomfort. Yet, despite these procedural and technological improvements, there remains a significant proportion of patients who experience moderate to severe intraoperative or postoperative pain associated with cataract surgery.²⁷

This study demonstrated that patients treated with P/K had a statistically significant lower use of the opioid fentanyl intraoperatively while also experiencing significantly less pain than those treated with epinephrine. Pain reduction was significantly greater with administration of P/K vs epinephrine at all timepoints evaluated: intraoperatively, immediately postoperatively, and 1-day postoperatively (Figure 2). The pain reduction findings are

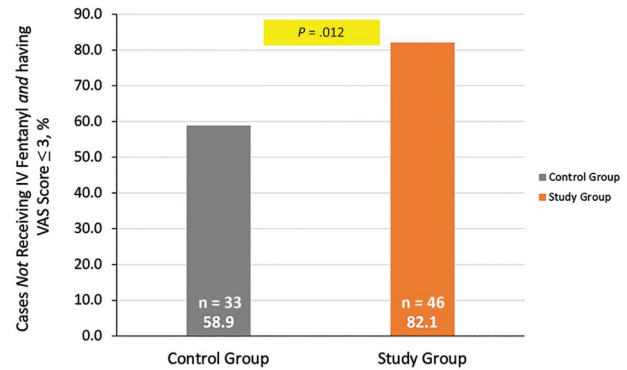


Figure 4. Proportion of cases not receiving intravenous fentanyl for cataract surgery and having pain (VAS scores ≤ 3). VAS = visual analog scale

consistent with a large number of other studies, and the reduction in fentanyl use is similar to the results of a previous cataract surgery study examining the same endpoint.^{12–21}

In the 2 phase 3 clinical trials leading to the U.S. Food and Drug Administration approval of P/K, patients either received P/K or placebo intracamerally in the irrigation solution during cataract surgery. These studies found a significant reduction in postoperative ocular pain measured using VAS. Over the first 12 hours, the VAS pain scores of the treatment group were more than 50% lower than those in the placebo group.¹² There was also significantly lower use of oral analgesics on the day of surgery in the treatment group compared with the placebo group. When looking at patients who had no pain at all timepoints measured, the P/K group had a significantly higher proportion than did the placebo group (104/403 [25.8%] vs 69/403 [17.1%], respectively; $P = .0027$). Assessment of patients who had moderate to severe pain at any timepoint found the proportion to be significantly lower in the treatment group (29/403 [7.2%] vs 57/403 [14.1%], respectively; $P = .0014$).¹³ Collectively, these results correlate closely with the findings of this study.

A randomized, active control, double-masked pediatric study yielded similar results in which Alder Hey Triage Pain Scale scores were significantly lower in the study group (P/K) compared with the control group (phenylephrine 1.0%). Furthermore, although the study was not powered to detect a difference, statistically significantly lower mean pain scores were seen at both 6 hours ($P = .029$) and 1 day ($P = .021$) postoperatively.²⁸

Consistent with other studies examining pain reduction with P/K use, in this study, the administration of P/K significantly reduced pain while decreasing patients' need for pain medication, especially fentanyl.

A previous published study conducted by the authors compared the same 2 therapies: 41 patients receiving P/K and 19 patients receiving epinephrine. Again looking at mean pain scores, the P/K group had 48.9% lower scores than the control group (2.3 vs 4.5; $P < .0001$).²⁰ When assessing patients who experienced no pain to mild pain

(VAS scores ≤ 3), a significantly greater proportion of the P/K group achieved this benchmark (85.0% vs 31.6%, $P < .0001$) compared with the epinephrine control group.²¹ This study also looked at the proportion of patients receiving intraoperative fentanyl, showing just 9.8% of the P/K group compared with 42.1% of the epinephrine group needing the opioid ($P = .006$). Across all aforementioned studies, the patients treated with P/K, although with reduced need for opioids and other pain medications, concurrently had pain scores that were 50% to more than 66% lower than the comparator arms.^{12,21,28}

Although postoperative opioid prescribing varies among practitioners, the use of P/K has also been shown to reduce the number of opioids prescribed postoperatively after cataract surgery. A retrospective analysis of IBM MarketScan's Medicare and Commercial databases of individuals aged older than 65 years undergoing cataract surgery from 2013 through mid-2019 identified 218 672 patients, of whom, 5145 receiving P/K were prescribed significantly fewer opioids postoperatively than were those patients who did not receive P/K (20 vs 45 pills, respectively, $P = .015$). This decrease in the number of opioids prescribed is even more meaningful given that the P/K-treated patients had significantly more preoperative comorbidities and risk factors for surgery (46.6% vs 31.3%, $P < .001$) than did those patients not treated with P/K.²⁹

Individuals aged between 50 and 80 years are particularly susceptible to opioid misuse and abuse, and this group overlaps with the typical cataract surgery patient population.^{7,30} In addition, surgery itself is a risk factor for opioid use disorder, with postoperative pain being a significant contributor. Despite cataract surgery techniques becoming more refined, many ambulatory surgery centers must use fentanyl as part of standard intraoperative pain relief and monitored anesthesia care. Fentanyl is not without risk and can cause intraoperative respiratory depression and prolonged recovery postoperatively.^{31,32} By using P/K as part of cataract surgery protocols, both intraoperative and postoperative pain are minimized, and the need for intraoperative fentanyl use is significantly decreased, potentially lowering the risk for ongoing issues with opioid medications.

The primary limitation of this study is that it was a single-center investigation. This limitation, however, is substantially mitigated by the design requiring patients to act as their own control group. A second limitation could be that it did not assess postoperative opioid use, but the consistently lower pain scores in the P/K group compared with the epinephrine control group should reasonably reflect the need for postoperative pain management drugs.

With the current opioid crisis, reducing the use of intraoperative opioids should be supported. The use of P/K is a pragmatic way that cataract surgeons can not only provide better care to their patients but also help minimize the need for intraoperative opioid use, especially in this vulnerable elderly population.

WHAT WAS KNOWN

- Phenylephrine/ketorolac 1.0%/0.3% (P/K) is the U.S. Food and Drug Administration–approved drug for both maintaining pupil size by preventing intraoperative miosis and reducing postoperative pain.
- The United States is in the midst of a significant opioid crisis.
- The elderly cataract surgery patient population is particularly at risk for opioid misuse and abuse.

WHAT THIS PAPER ADDS

- This study confirms the findings of previous clinical research, demonstrating that the use of P/K during cataract surgery decreases pain scores intraoperatively and at 10 minutes and 1 day postoperatively while reducing the need for perioperative fentanyl use.
- Taken collectively, the data demonstrated that P/K is a viable nonopioid alternative for the management of both intraoperative and early postoperative pain. This finding may lead to decreased use of intraoperative opioids.

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