Clinical Ophthalmology

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ORIGINAL RESEARCH

Effect Of Intracameral Phenylephrine And Ketorolac 1.0%/0.3% On Intraoperative Pain And Opioid Use During Cataract Surgery

This article was published in the following Dove Press journal:
Clinical Ophthalmology

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Purpose: To compare the effect of Omidria (phenylephrine and ketorolac 1.0%/0.3%) vs epinephrine on pain reduction and opioid usage during cataract surgery.

Patients and methods: Sixty patients at a single center underwent femtosecond laser (FLACS) or conventional phacoemulsification under topical lidocaine gel anesthesia and intracameral preservative-free lidocaine 1%. Eligible participants were prospectively assigned to receive either intracameral phenylephrine and ketorolac 1.0%/0.3% or intracameral epinephrine. All patients received standardized pre- and post-operative topical therapy. Intravenous (IV) fentanyl was administered for ocular discomfort in patients who complained of intraoperative pain. Outcome measures included both pain (measured by mean visual analog scale (VAS) pain scores from 0 (no pain) to 10 (extreme pain)) and the use of IV fentanyl during surgery. A composite endpoint identified "responders" as being patients who: (1) did not require fentanyl and (2) experienced no to minimal pain (VAS score ≤ 3).

Results: Forty-one patients were in the phenylephrine and ketorolac 1.0%/0.3% (study) group and 19 were in the epinephrine (control) group. Mean VAS pain scores were significantly (48.9%) lower in the study group than the control group (2.3 vs 4.5; $P < 0.0001$). The proportion of patients with VAS scores ≤ 3 was significantly greater in the study group (85.0%) than the control group (31.6%) ($P < 0.0001$). A smaller proportion of patients required intraoperative fentanyl in the study group compared to the control group (9.8% vs 42.1%; $P = 0.006$). For the composite endpoint, patients receiving phenylephrine and ketorolac 1.0%/0.3% were 94% less likely to require fentanyl or to have moderate-to-severe pain (pain VAS ≥ 4; OR, 0.06; 95% CI 0.02–0.24) than patients receiving epinephrine.

Conclusion: Our results suggest that the routine use of intracameral phenylephrine and ketorolac 1.0%/0.3% during cataract surgery can significantly reduce patient pain as well as the need for opioids.

Keywords: epinephrine, Omidria, ketorolac, phacoemulsification, FLACS

Introduction

The advent of small-incision phacoemulsification allowed the majority of US ophthalmologists to transition from retro- or peri-bulbar anesthesia during cataract surgery to topical anesthesia, providing easier and less invasive application, rapid onset, and reduced postoperative rehabilitation time.[1–3] Despite these advantages, topical anesthesia does not provide a completely painless procedure.[4] It may not provide adequate sensory blockade for the iris and ciliary body, leading to perioperative ocular discomfort and pain.[5] Intraoperative pain often occurs not only due

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http://doi.org/10.2147/OPTH.S229515

to direct iris manipulation and intraocular lens insertion, but also simply from movement of the iris diaphragm during intraocular fluid dynamic changes or light exposure from the operating microscope.[1] In the absence of akinesia, pain and discomfort felt by the patient can lead to sudden eye movements or squeezing, increasing the risk of intraoperative complications.[2,6] Patients requiring intravenous sedation during surgery may be less responsive to verbal command and may move during surgery increasing the risk of intraoperative complications. In addition, intraoperative pain is a major concern of patients and an important consideration when assessing satisfaction with their cataract procedures. For these reasons, proactive analgesia to prevent the onset of pain is necessary.

The use of intracameral preservative-free lidocaine 1% is one such strategy that is commonly employed by cataract surgeons.[5] While lidocaine may decrease perception of tissue touch and discomfort from the microscope light,[7,8] there is evidence to suggest that it does not provide added pain relief during phacoemulsification.[4,8–10]

While surgeons might consider cataract surgery a relatively "low-pain" procedure, as many as 35% of the patients undergoing cataract surgery report moderate-to-severe postoperative pain.[11] To manage intraoperative pain and to mitigate postoperative pain, opioids such as fentanyl are commonly employed by anesthesiologists monitoring patients during cataract surgery. Opioids increase patient comfort and sedation, offering better pain relief and improved patient satisfaction.[12,13] However, opioids have side effects and risks, including excessive restlessness, movement during the procedure, nausea, vomiting, respiratory depression, pruritus, and confusion.[5,13] Many surgeons and facilities use an intravenous combination of midazolam and fentanyl as part of the anesthetic regimen for patients undergoing cataract surgery. Although the doses of fentanyl may be lower in cataract surgery than in other surgical procedures, cataract surgery patients are generally elderly, and elderly patients are more sensitive to the effects of opioids,[14] often further exacerbated by repeated exposure to opioids resulting from multiple temporally related procedures (eg, orthopedic, cardiovascular).

With the current opioid addiction crisis in the United States, there is a strong impetus to reduce or avoid opioid exposure in medical settings, because even low exposure to opioids intraoperatively has been shown to be associated with an increase in risk of later opioid use. A study conducted by Alam et al[15] examined the risk of long-term opioid use in patients who received an opioid prescription following low-risk surgical procedures. Cataract surgery patients who received an opioid prescription were found to be 1.6 times more likely to be using opioids long term than those patients who were not prescribed an opioid. The prescription rate for opioids following cataract surgery is unexpectedly high, with approximately 20,000 opioid prescriptions written annually. Seventy-seven percent of these patients also received an NSAID and/or steroid pre- and/or post-surgery, indicating that topical treatments did not adequately address postoperative pain.[16] Given the growing awareness and concerns regarding opioids and opioid use disorder, there is a need to determine alternate strategies to improve analgesia during cataract surgery.

Omidria® (Omeros Corporation, Seattle, WA, USA) is a combination drug product containing a mydriatic agent (phenylephrine 1%) and an NSAID (ketorolac 0.3%) that is added to the irrigating solution for continuous intracameral administration during cataract surgery.[17] Its efficacy has been established in controlled clinical studies for preventing intraoperative miosis and reducing postoperative ocular pain.[18–25] Due to its anti-inflammatory and mydriatic properties, phenylephrine and ketorolac 1.0%/0.3% also has the potential to prevent ocular pain during surgery, although this has not previously been previously studied. In the FDA clinical trials involving over 800 patients, compared to the control group, phenylephrine and ketorolac 1.0%/0.3% provided both a >50% increase in pain-free patients and a 30% decrease in the proportion of patients who required analgesics.[18] The present study was aimed at evaluating the efficacy of phenylephrine and ketorolac 1.0%/0.3% in reducing pain and opioid usage during cataract surgery.

Materials And Methods

Patients

This prospective, single-masked, comparative study enrolled 60 patients who were scheduled to undergo femtosecond laser-assisted cataract surgery (FLACS) or conventional phacoemulsification under topical anesthesia at Island Eye Surgicenter (Westbury, NY, USA). The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki. The risks, benefits, and alternatives to cataract surgery and all associated medications were explained to all patients prior to surgery and written informed consent was obtained. The procedures and collection of information were all conducted consistent with routine care at the investigator's facility,

and Advarra Institutional Review Board (Columbia, MD) determined that the research project is exempt from IRB oversight.

Exclusion criteria included potentially confounding factors, namely hypersensitivity to study medication; recent use of opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) other than the topical ophthalmic NSAIDs used for 3 days preoperatively to help maintain intraoperative mydriasis; use of preoperative phenylephrine (other than for the screening ophthalmological examination), corticosteroids (topical, inhaled, or oral), or ocular mast cell stabilizers within 7 days before surgery; use of monoamine oxidase inhibitors within 21 days before surgery; use of depot corticosteroids within 30 days prior to surgery; repeated use of pilocarpine within 6 months prior to surgery; history of α1-adrenergic antagonist use (eg, tamsulosin); intraocular non-laser surgery in the study eye within 3 months; or intraocular laser surgery in the study eye within 30 days of surgery.

Patients were also excluded if they had any connective tissue disorder (eg, lupus, rheumatoid arthritis, fibromyalgia); abnormal blood pressure on the day of surgery; narrow-angle or unstable glaucoma; glaucoma being treated with prostaglandins or prostaglandin analogues; history of iritis or trauma with iris damage in the study eye; pseudoexfoliation syndrome in either eye; uncontrolled chronic eye disease; active corneal pathology or scarring; extraocular/intraocular inflammation; active bacterial or viral infection in either eye; or dementia or any major psychiatric disease that could have impaired memory or cognitive function.

Eligible study participants were prospectively assigned to either the study group receiving intracameral phenylephrine and ketorolac 1.0%/0.3% or the control group receiving intracameral epinephrine, based on each patient's respective type of insurance coverage (ie, phenylephrine and ketorolac 1.0%/0.3% was not used in patients whose insurance plans did not reimburse for it). In both groups, the intracameral medications were added to the irrigating solution. Patients were masked as to their respective treatment groups.

Surgical Technique

All procedures were performed by a single surgeon (EDD). All patients in both treatment groups received the following standardized preoperative topical treatment: ofloxacin 0.3% antibiotic (four times daily for 3 days), bromfenac 0.07% (once daily for 3 days), and mydriatics (one drop of phenylephrine 2.5% and one drop of tropicamide 1% at approximately 30 mins, 15 mins, and 5 mins prior to surgery). All subjects received preoperative topical lidocaine gel for anesthesia, administered 2–3 times 15 mins before surgery. At the start of the surgery, all patients received 0.5 mL of intracameral preservative-free lidocaine 1%.

In the study group, the patients received continuous intracameral administration of phenylephrine and ketorolac 1.0%/0.3% in the irrigating solution. In the control group, patients received intracameral epinephrine (1 mg/mL), added to the irrigation solution. Both Healon (1% sodium hyaluronate) and Healon EndoCoat (3% sodium hyaluronate) ophthalmic viscosurgical device (OVD; Johnson & Johnson Vision, Jacksonville, FL, USA) were used for all patients during surgery.

FLACS was performed in 34 patients and conventional phacoemulsification in 26 patients. Clear-corneal phacoemulsification was performed in all cataract surgical procedures in the study. During surgery intravenous (IV) fentanyl was administered by an anesthesiologist as additional analgesia for ocular discomfort for patients who complained of intraoperative pain. Postoperative treatment for all patients included standardized antibiotic and steroid drops.

Outcome Measures

The outcome measures were (1) pain experienced during the surgery, as measured by mean visual analog scale (VAS) pain scores ranging from 0 (no pain) to 10 (extreme pain) assessed 10 mins postoperatively in the recovery room and (2) the use of IV fentanyl during surgery. A composite endpoint was defined as a combination of these two related outcome measures, wherein a "responder" was defined as a patient who: (1) did not require fentanyl, an opioid, during surgery and (2) experienced no pain to mild pain (Pain VAS score ≤ 3).

Statistical Analyses

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). VAS pain scores were analyzed using an independent *t*-test. Categorical data were analyzed using Fisher's exact test. All *P* values were two-sided and were considered statistically significant when less than 0.05.

Results

Sixty patients were included in the study, 41 of whom were treated with phenylephrine and ketorolac 1.0%/

0.3% (study group) and 19 of whom were treated with epinephrine (control group). Both groups were comparable in terms of age, gender, type of surgery (ie, FLACS vs conventional phacoemulsification), dominant/non-dominant eye, cataract severity grade, and intraocular pressure (IOP) (Table 1).

Mean VAS pain scores were found to be significantly (48.9%) lower in the study group than the control group (2.3 vs 4.5; $P < 0.0001$) (Figure 1). The distribution of pain VAS scores for patients in the study and control groups is summarized in Figure 2A. The proportion of patients with no to minimal pain (VAS score ≤ 3) was significantly greater in the study group (85.0%) than in the control group (31.6%) ($P < 0.0001$) (Figure 2B). The odds of a patient in the study group having no to minimal pain (VAS score ≤ 3) are 12.3 times (significantly) higher (odds ratio (OR), 12.3; 95% CI 3.3–45.0) than a patient in the control group.

The number of patients requiring intraoperative fentanyl analgesia was significantly lower in the study group compared to the control group (9.8% vs 42.1%; $P = 0.006$) (Figure 2C). The relative risk for a patient requiring intraoperative fentanyl analgesia was 76.8% lower in the study group versus the control group. Stated differently, the odds of a patient in the study group not requiring intraoperative fentanyl analgesia are 6.7 times higher than a patient in the control group (OR, 6.7; 95% CI 1.7–26.6).

For the composite endpoint, the relative risk reduction for a patient requiring intraoperative fentanyl analgesia and having moderate-to-severe pain (pain VAS ≥ 4) was 79.6% in the study group versus the control group ($P < 0.0001$). Patients receiving phenylephrine and ketorolac 1.0%/0.3% in the irrigating solution during cataract surgery are 94% less likely to require fentanyl or to have moderate-to-severe pain (pain VAS ≥ 4; OR, 0.06; 95% CI 0.02–0.24) than patients receiving irrigating solution with epinephrine (Figure 2D).

Discussion

Advances in surgical techniques and technology have elevated patients' expectations for cataract surgery, including high precision in refractive and astigmatic outcomes, low tolerance for complications,[26,27] and anticipation of little to no pain.[28] Effective analgesia strategies during cataract surgery help reduce patients' anxiety and improve their intraoperative cooperation, allowing the surgeon to focus on obtaining optimal surgical and refractive outcomes.[3,29] Autonomic pain reflexes can cause physiological and behavioral changes. In addition to the changes pain can cause on the cardiovascular, immune, and other body systems, pain can also have psychological impact. If a patient experiences intraoperative pain, it can affect their health-seeking behavior, making them hesitant to seek medical care for future health issues.[30] For these reasons,

Table 1 Preoperative And Operative Characteristics Of Study Subjects

Characteristics	Study Group	Control Group	*P* Value
	Mean±SD	Mean±SD	
Age (years)	72.1±8.8	73.5±7.2	0.562
Duration of surgery (minutes)	7.9±1.6	9.1±2.0	0.011
Intraocular pressure (mmHg)	16.3±1.9	15.6±2.2	0.208
Cataract severity grade (0-4)	1.8±0.7	2.1±0.7	0.169
	Number of patients n (%)		
Gender			0.759
Males	19 (46.3)	8 (42.1)	
Females	22 (53.7)	11 (57.9)	
Type of surgery			0.896
FLACS	23 (56.1)	11 (57.9)	
Conventional phacoemulsification	18 (43.9)	8 (42.1)	
Surgical eye			0.630
Dominant eye	21 (51.2)	11 (57.9)	
Non-dominant eye	20 (48.8)	8 (42.1)	

Note: Statistical significance: $P < 0.05$.
Abbreviations: FLACS, femtosecond laser-assisted cataract surgery; mmHg, millimeter of mercury.

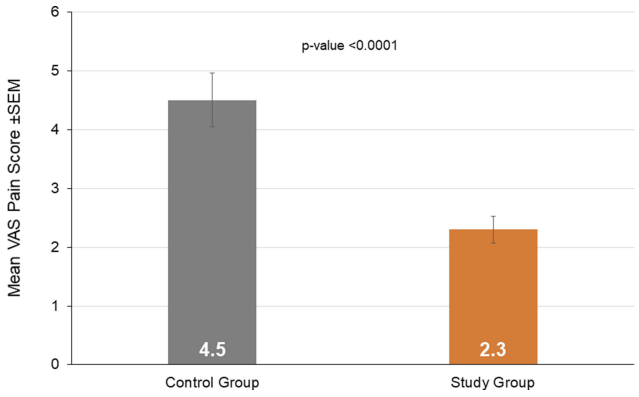

Figure 1 Mean VAS pain scores by control and study groups. The control group received intracameral epinephrine in the irrigating solution during cataract surgery. The study group received intracameral phenylephrine and ketorolac 1%/0.3%.
Abbreviation: VAS, visual analog scale.

pain management during clear-corneal phacoemulsification is vital.

Topical anesthesia, due to its ease of administration, non-invasive nature, quicker visual recovery, preservation of ocular motility, and avoidance of temporary cosmetic derangement, has become the standard of care for clear-corneal phacoemulsification.[1] However, patients may experience greater anxiety and discomfort during surgery with topical agents because those agents only anesthetize superficial trigeminal nerve endings, leading to inadequate sensory blockade for the iris and ciliary body.[1,5] Lidocaine, a common adjunct to topical anesthesia, is often injected into the anterior chamber to provide more complete sensory blockade for the iris and ciliary body.[5,31]

In studies assessing pain management, typically either the treatment is held constant and pain assessed or the reported pain is held constant while assessing the amount of medication required. In this study, both pain level and medication use (in this case, fentanyl) were assessed. Despite allowing both variables to float unrestricted, use of phenylephrine and ketorolac 1.0%/0.3% led to nearly an 80% reduction in the need for fentanyl while concurrently decreasing VAS pain scores by approximately 50%.

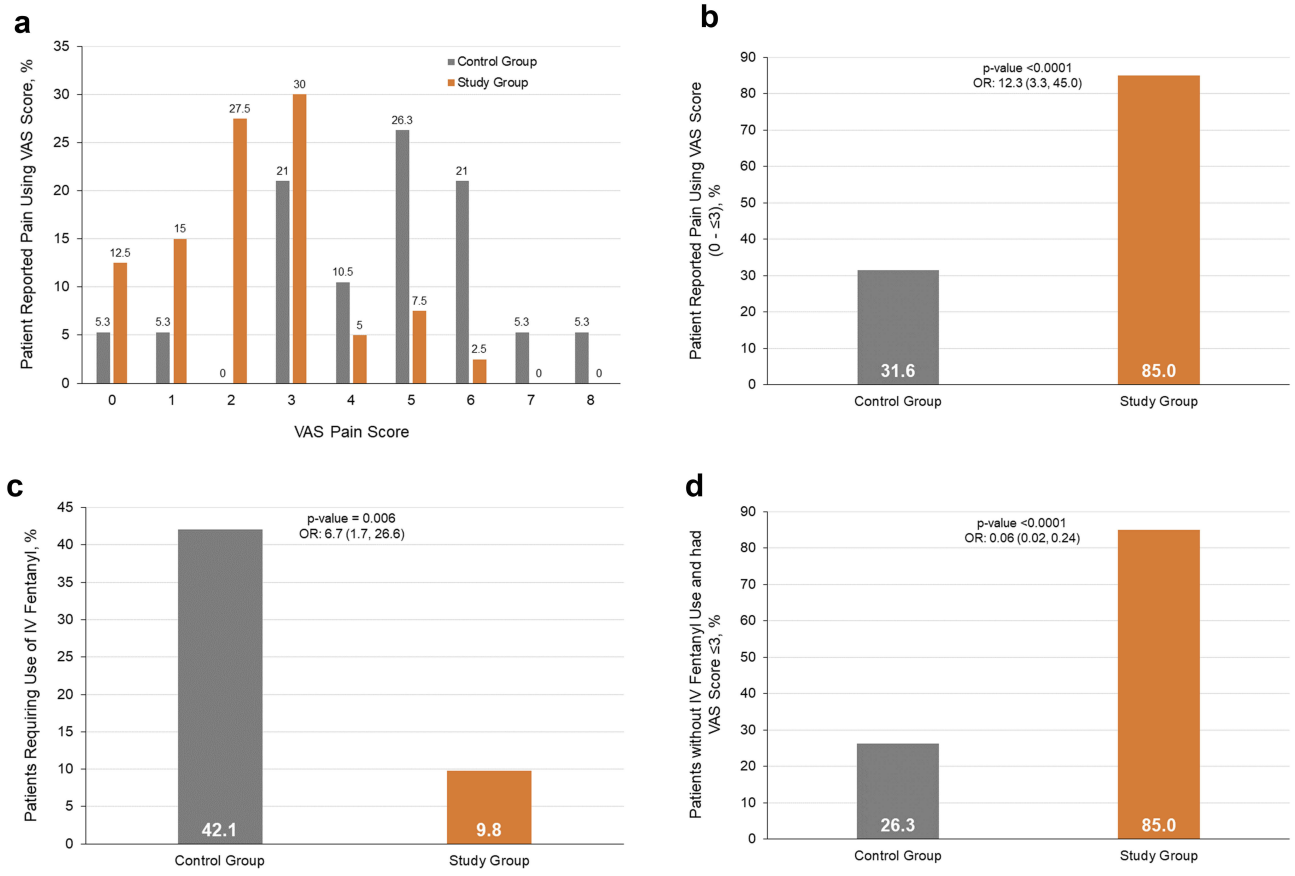

Figure 2 (**A–D**) Comparison of pain and fentanyl use between the control (epinephrine) and study (phenylephrine and ketorolac 1%/0.3%) groups. (**A**) Proportion of patients by VAS pain scores (0–10); (**B**) Proportion of patients with no pain to mild pain (VAS scores 0–3); (**C**) Proportion of patients requiring intravenous fentanyl for cataract surgery; (**D**) Proportion of patients not receiving intravenous fentanyl for cataract surgery with VAS scores 0–3 (no pain to mild pain).
Abbreviations: VAS, visual analog scale; IV, intravenous.

The decreased levels of pain during cataract surgery observed in this study might be attributed to ketorolac-mediated reduction in the levels of prostaglandins (PGs) intraoperatively. Trauma to ocular tissues, even during uneventful cataract surgery, is known to release PGs that can cause pain and inflammation. The mechanism involves activation of phospholipase A_2, the precursor for arachidonic acid metabolites. Arachidonic acid metabolites act as a substrate for the cyclo-oxygenase (COX) pathways, leading to the production of PGE and PGF in aqueous humor.[32] The effects of endogenous PGs are miosis during surgery, intra- and post-operative pain and inflammation, conjunctival hyperemia, and changes in IOP.[32] The build-up of PGs in the anterior chamber as surgery progresses may explain why pain during cataract surgery is observed more frequently during the later stages of the procedure.[33]

To reduce pain, then, it is beneficial to decrease the amount of PG present in the aqueous humor. Prostaglandin synthesis can be reduced either by inhibiting phospholipase A_2, which further inhibits the release of arachidonic acid, or by inhibiting the conversion of arachidonic acid to prostaglandins via the COX pathway.[34] Ketorolac (present in phenylephrine and ketorolac 1.0%/0.3%) inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), resulting in decreased prostaglandin production and, therefore, potentially less pain.[18,21] Due to the continuous administration of phenylephrine and ketorolac 1.0%/0.3% in the irrigation solution, intraocular tissues are exposed to a constant concentration of its active components, irrespective of the duration of the surgical procedure.[17] This constant exposure of ocular tissues to ketorolac is thought to continually prevent the release of PGs.

In addition to PG release, patients may also perceive pain as a result of surgical manipulation of ocular tissue, movement of the iris diaphragm during intraocular fluid dynamic changes, light from the operating microscope, and intraocular lens insertion.[1] Although pupil diameter was not assessed in this study, superior maintenance of appropriate mydriasis and prevention of miosis throughout cataract surgery in the group of patients receiving phenylephrine and ketorolac 1.0%/0.3% most likely occurred relative to the group receiving epinephrine alone, as has been shown in multiple published studies.[21–24] The phenylephrine and ketorolac 1.0%/0.3% may also have provided a more adequate working area within the pupil for intraocular manipulation, thereby decreasing the likelihood of pain perception due to tissue touch/manipulation.[19,21]

While intraoperative pain alleviation is primarily the collective result of appropriate selection of preoperative analgesics/anesthetics, excellent surgical technique, and a relaxed environment for the patient,[1] other factors related to intraoperative pain during cataract surgery have been identified. These include age, gender, eye dominance, type of surgery, severity of cataract, and higher baseline IOP. These factors were assessed, and, with the exception of surgical duration, all were similar between the phenylephrine and ketorolac 1.0%/0.3% and the epinephrine control groups (Table 1). Consistent with findings in multiple other published studies,[22,24] mean surgical time in the phenylephrine and ketorolac 1.0%/0.3% group was 13% faster than in the epinephrine control group (7.9 mins vs 9.1 mins; $P = 0.011$). Shorter surgical duration likely means that the procedures performed with phenylephrine and ketorolac 1.0%/0.3%, in general, allowed better visualization and/or required less manipulation than those performed with epinephrine. As a result, the phenylephrine and ketorolac 1.0%/0.3%-treated eyes likely incurred less trauma, causing less prostaglandin release and, therefore, less inflammation and pain.

Insufficient pain management during surgery may cause the patient to experience moderate-to-severe pain.[30] Therefore, IV opioids are used as an adjuvant to decrease pain in patients who find the intraoperative pain unbearable.[12,35] However, opioid use carries risks of both adverse events and side effects related to its mechanism of action.[36] It may cause excessive restlessness, sudden movement, and airway obstruction, leading to intraoperative complications.[5] With modern presbyopia-correcting IOLs, excellent centration is vital to achieving optimal function. For the patient to fixate on the microscope light as part of the centration process, patient cooperation is required, which may be compromised with opioid-induced sedation.[37] Intraoperative opioid use may also cause postoperative nausea and vomiting, respiratory and circulatory depression, pruritus, and confusion.[16] Of public health importance is the potential for long-term use of opioids and the development of opioid use disorder in elderly cataract surgery patients. This patient population is at high risk for these opioid concerns, which may have implications not only to the health of individual patients but also to the healthcare system and to society.

In this study, even though all patients received standard preoperative topical mydriatics together with topical (lidocaine gel 2%) and intracameral (preservative-free lidocaine 1%) anesthetics, phenylephrine and ketorolac 1.0%/0.3% not only decreased fentanyl requirements but concurrently reduced pain. The proportion of phenylephrine and ketorolac 1.0%/0.3%-treated patients requiring additional opioid

analgesics (fentanyl) was more than four-fold lower than in the epinephrine-treated control group, and the relative risk that the study group patients would require intraoperative fentanyl analgesia was 77% lower than for control patients. Furthermore, the odds of a patient in the study group being pain-free or having only minimal pain are 12 times higher (OR, 12.3; 95% CI 3.3–45.0) than a control patient. The study's composite endpoint showed a similarly compelling difference: patients receiving phenylephrine and ketorolac 1.0%/0.3% were 94% less likely to require fentanyl or to experience moderate-to-severe pain (Pain VAS ≥ 4; OR, 0.06; 95% CI 0.02–0.24) compared to those who received the control drug epinephrine.

We did not perform intraoperative verbal assessment of pain scores, which is believed to be more accurate than postoperative VAS assessment.[7] However, because most patients did not request additional IV analgesia intraoperatively, we feel that the postoperative VAS assessment at 10 mins in the recovery room was an accurate representation of intraoperative pain.

Collectively, the results of the study suggest that, while IV opioid sedation might still be needed as a supplement to topical anesthesia in some patients (eg, those with high levels of anxiety), routine use of continuous intracameral phenylephrine and ketorolac 1.0%/0.3% can significantly reduce the need for opioids in patients undergoing cataract surgery. Fentanyl is a mainstay of anesthesia during cataract surgery and despite other attempts at pain management, approximately 20,000 prescriptions for postoperative opioids are administered annually following cataract surgery. The ability of phenylephrine and ketorolac 1.0%/0.3% to reduce pain and the need for fentanyl should be a welcome advance for cataract surgery patients, a population already at risk for increased exposure to and dependence on opioids.

Conclusion

We found that the intraoperative delivery of phenylephrine and ketorolac 1.0%/0.3% resulted in a nearly 80% reduction in the need for intraoperative opioid analgesics during cataract surgery while decreasing mean VAS pain scores by approximately 50%, significantly reducing the risk of moderate-to-severe pain. Future studies may help confirm these findings.

Acknowledgment

This study was part funded by an unrestricted grant from Omeros Corporation.

Disclosure

Dr. Donnenfeld holds an equity interest in and is a consultant for Omeros Corporation. The authors report no other conflicts of interest in this work.

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