Safety of Postoperative Opioid Alternatives in Plastic Surgery: A Systematic Review

Rebecca C. O'Neill, M.D.
Kylie D. Hayes, B.S., M.B.A.
Steven P. Davison, M.D., D.D.S.

Newark, N.J.; Little Rock, Ark.; and Washington, D.C.

Summary: With the growing opioid epidemic, plastic surgeons are being encouraged to transition away from reliance on postoperative opioids. However, many plastic surgeons hesitate to use nonopioid analgesics such as nonsteroidal antiinflammatory drugs and local anesthetic blocks because of concerns about their safety, particularly bleeding. The goal of this systematic review is to assess the validity of risks associated with nonopioid analgesic alternatives. A comprehensive literature search of the PubMed and MEDLINE databases was conducted regarding the safety of opioid alternatives in plastic surgery. Inclusion and exclusion criteria yielded 34 relevant articles. A systematic review was performed because of the variation between study indications, interventions, and complications. Thirty-four articles were reviewed that analyzed the safety of ibuprofen, ketorolac, celecoxib, intravenous acetaminophen, ketamine, gabapentin, liposomal bupivacaine, and local and continuous nerve blocks after plastic surgery procedures. There were no articles that showed statistically significant bleeding associated with ibuprofen, celecoxib, or ketorolac. Similarly, acetaminophen administered intravenously, ketamine, gabapentin, and liposomal bupivacaine did not have any significant increased risk of adverse events. Nerve and infusion blocks have a low risk of pneumothorax. Limitations of this study include small sample sizes, different dosing and control groups, and more than one medication being studied. Larger studies of nonopioid analgesics would therefore be valuable and may strengthen the conclusions of this review. As a preliminary investigation, this review showed that several opioid alternatives have a potential role in postoperative analgesia. Plastic surgeons have the responsibility to lead the reduction of postoperative opioid use by further developing multimodal analgesia. (*Plast. Reconstr. Surg.* 144: 991, 2019.)

The opioid epidemic has significantly affected how physicians prescribe pain medication. Plastic surgeons are being pressured to reduce the number of opioid prescriptions they write, because of the high numbers of unused pills that have the potential to be abused or sold, further contributing to the opioid epidemic.[1] Although alternative therapies have been suggested, their use in surgical practice has yet to reduce the number of opioid prescriptions.[1,2] These medications that are reviewed in this article include ibuprofen, ketorolac, celecoxib, intravenous acetaminophen, ketamine, gabapentin, liposomal bupivacaine, and local anesthetic nerve block or continuous infusions (Table 1). Risks associated with their use, some of which may be overstated, then contribute to the hesitancy to prescribe these alternative pain medications. By investigating these risks, we aim to offer plastic surgeons an updated perspective of the safety

From Rutgers-New Jersey Medical School; University of Arkansas School for Medical Sciences; and DAVinci Plastic Surgery.
Received for publication March 18, 2018; accepted February 22, 2019.

DOI: 10.1097/PRS.0000000000006074

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

By reading this article, you are entitled to claim one (1) hour of Category 2 Patient Safety Credit. ASPS members can claim this credit by logging in to PlasticSurgery.org Dashboard, clicking "Submit CME," and completing the form.

Table 1. Safety Characteristics of Opioid Alternatives for Postoperative Analgesia

Medication	Half-Life (hr)	Contraindications	Potential Side Effects
NSAIDs	<6	Cerebrovascular bleeding, incomplete hemostasis; coagulation disorder or other anticoagulant use; known hypersensitivity; active peptic ulcer disease, recent GI bleeding/perforation, history of peptic ulcer disease or GI bleeding; advanced renal impairment; labor and delivery	Increased bleeding time; cardiovascular events; GI bleeding, ulceration, and perforation; renal injury; nausea/vomiting; hypertension; dizziness, drowsiness; elevated liver enzymes
Celecoxib	8–12	Known hypersensitivity or aspirin/NSAID hypersensitivity; during coronary artery bypass graft; sulfonamide allergy	Cardiovascular events; GI bleeding, ulceration, and perforation; hepatotoxicity; hypertension; heart failure and edema; renal toxicity and hyperkalemia
Acetaminophen (IV)	2–3	Known hypersensitivity; severe hepatic impairment or severe active liver disease	Hepatic injury; serious skin reactions; allergy and hypersensitivity
Ketamine	3	Known hypersensitivity; hypertensive urgency and emergency	Hypertension, tachycardia; diplopia, nystagmus; emergency reactions, hallucinations
Gabapentin	5–7	Known hypersensitivity	Multiorgan hypersensitivity; angioedema; somnolence/sedation, dizziness; suicidal behavior and ideation; neuropsychiatric adverse reactions; sudden and unexplained death in epileptic patients
Liposomal bupivacaine	12–24	Obstetrical paracervical block anesthesia	Central nervous system reactions; cardiovascular system reactions; allergic reactions; chondrolysis; accidental intravascular injection
Local anesthetics	1.5–5	Known hypersensitivity	Central nervous system reactions; cardiovascular system reactions; allergic reactions; neurologic reaction

NSAIDs, nonsteroidal antiinflammatory drugs; GI, gastrointestinal; IV, intravenous.

of opioid alternatives for postoperative pain that may be applied to evidence-based practice.

First, nonsteroidal antiinflammatory drugs work primarily as cyclooxygenase inhibitors.[3] Ibuprofen and ketorolac are nonselective, reversible cyclooxygenase inhibitors whose main risks include bleeding complications, gastrointestinal ulceration, and renal dysfunction.[4] Ketorolac was considered contraindicated in plastic surgery, based largely on a 1997 study in which two of 50 plastic surgery patients experienced postoperative hemorrhages, which was not statistically significant.[4,5] Celecoxib is a selective cyclooxygenase-2 inhibitor, meaning it has minimal effect on platelets, but is still viewed as a nonsteroidal antiinflammatory drug with a bleeding risk.[1,6] In addition, a recent 10-year study disproved the belief that celecoxib has an increased risk for cardiovascular events.[7]

Next, acetaminophen is an analgesic and antipyretic medication believed to act by means of central cyclooxygenase inhibition. It is metabolized in the liver, and acetaminophen overdose is one of the main causes of acute liver failure.[8,9] Intravenous acetaminophen has recently been approved for postoperative pain management. Although oral acetaminophen may also be used, this review will focus on intravenous acetaminophen because of its recent approval and relative potential. In addition, many opioid medications contain acetaminophen, making oral use hard to compare. The efficacy and safety of postoperative intravenous acetaminophen has been demonstrated across many surgical fields, but there has been limited use in plastic surgery.[10–14]

Ketamine, an *N*-methyl-D-aspartate receptor antagonist, is an anesthetic agent with sedative, analgesic, and amnesic effects, and hypnotic and bronchodilator effects at lower doses.[15] Its well-known side effects include hallucinations, unpleasant dreams, and other psychomimetic effects.[16]

Gabapentin, an anticonvulsant, has relatively few side effects, which include somnolence, dizziness, ataxia, and fatigue.[17] Gabapentin is not recommended for patients with renal dysfunction or those taking sedative medications such as benzodiazepines.[18]

Liposomal bupivacaine is an extended-release multivesicular liposomal version of bupivacaine, which blocks axonal pain conduction.[19–21] The negative effect of liposomal properties on wound healing and the development of chondrolysis has been hypothesized, but recent studies refute this, showing no clinically evident effects.[22] Bupivacaine as a local anesthetic carries potential risks of

cardiovascular and neurologic toxicity and death, although these toxicities are associated with doses greater than 3 mg/kg, except when diluted in wetting solutions where the toxic dose is much higher.[18,19,23] In addition, liposomal bupivacaine should not be mixed with lidocaine and should not be administered earlier than 20 minutes after administered lidocaine.[21]

Nerve blocks and continuous infusion blocks have two main risks: (1) pharmaceutical and (2) because of the placement of these blocks.[24] To avoid systemic toxicity, surgeons must carefully regulate the rate and quantity of local anesthetics administered by means of continuous catheter. Furthermore, placement carries a potential risk of pneumothorax, pleural effusion, infection, nerve injury, and intravascular injection.[24–26]

The side effects of opioids are increasingly problematic, including nausea, vomiting, constipation, respiratory depression, and risk of addiction. It is time to revisit the safety of nonopioid analgesics, which will be particularly important for multimodal analgesic therapy.[1,18,27] Currently, the medications discussed in this review are part of multimodal analgesia, a regimen designed to combine different pain medications to effectively treat pain with reduced use of opioid medications. Some common regimens include intravenous acetaminophen, ketamine, gabapentin, local anesthetics, nonsteroidal antiinflammatory drugs, and lastly ketamine. This combination of medications is currently being used in evolving enhanced recovery after surgery protocols.

METHODS

A comprehensive literature search of the PubMed and MEDLINE databases was conducted to locate published studies regarding the safety of opioid alternatives in plastic surgery. Keywords used for the search protocol were "plastic surgery," AND "safety" AND each of the medications included in the study separately, including "ibuprofen," "ketorolac," "celecoxib," "intravenous acetaminophen OR Ofirmev," "ketamine," "gabapentin," "liposomal bupivacaine," "nerve block," and "continuous nerve block OR pain pump OR continuous infusion." Relevant articles were then filtered by manual assessment of title and abstract. Additional articles were located by reviewing references of previously selected articles. Any disagreements between the reviewers were discussed and resolved. Case reports were not included. Data were collected on the following parameters: type of analysis conducted, sample size, type of surgical procedure, efficacy outcomes such as postoperative pain control, opioid consumption, and pain scores, in addition to safety outcomes, including any complications, side effects, or adverse events. Articles relevant to plastic surgery procedures were prioritized. All age groups and sample sizes were included. The search was limited to studies in English with a time parameter of publication in 2008 to the present. Studies involving animal models were excluded. Because of the significant variations within the studies regarding study indications, interventions, outcomes, and complications, a quantitative meta-analysis was not appropriate and a systematic review was performed.

RESULTS

A total of 10,072 titles of potentially relevant publications were identified from the initial search. Exclusion of articles not in English, published before 2008, irrelevant to plastic surgery, animal studies, and case reports yielded 44 articles. The full texts of these articles were evaluated for discussion of nonopioid analgesic safety. Of the 44 articles, 10 were excluded for the lack of reporting complications, as this was our focus. The remaining 34 articles were included in the systematic review, summarized in Figure 1 and Table 2.[2,4,15–17,20,22,26,27–49] The specifics regarding each medication are discussed below.

Ibuprofen

Kelley et al. performed a meta-analysis on four articles regarding complications following ibuprofen administration after cosmetic facial procedures, skin grafting, flap procedures, laparoscopic inguinal hernia repairs, and mastectomies.[3] Chen and Adamson performed a prospective, double-blind, randomized trial on patients who received ibuprofen after undergoing facial cosmetic surgery.[28] Both studies found that there were no statistically significant differences in bleeding or hematoma formation between patients who received ibuprofen versus patients in the control group (acetaminophen-codeine, acetaminophen alone, or ketorolac). Importantly, both studies found that ibuprofen was equally as effective as acetaminophen-codeine for postoperative pain relief.[3,28]

Ketorolac

Stephens et al. performed a systematic review of the safety of postoperative ketorolac after plastic surgery. Results showed that the risk for

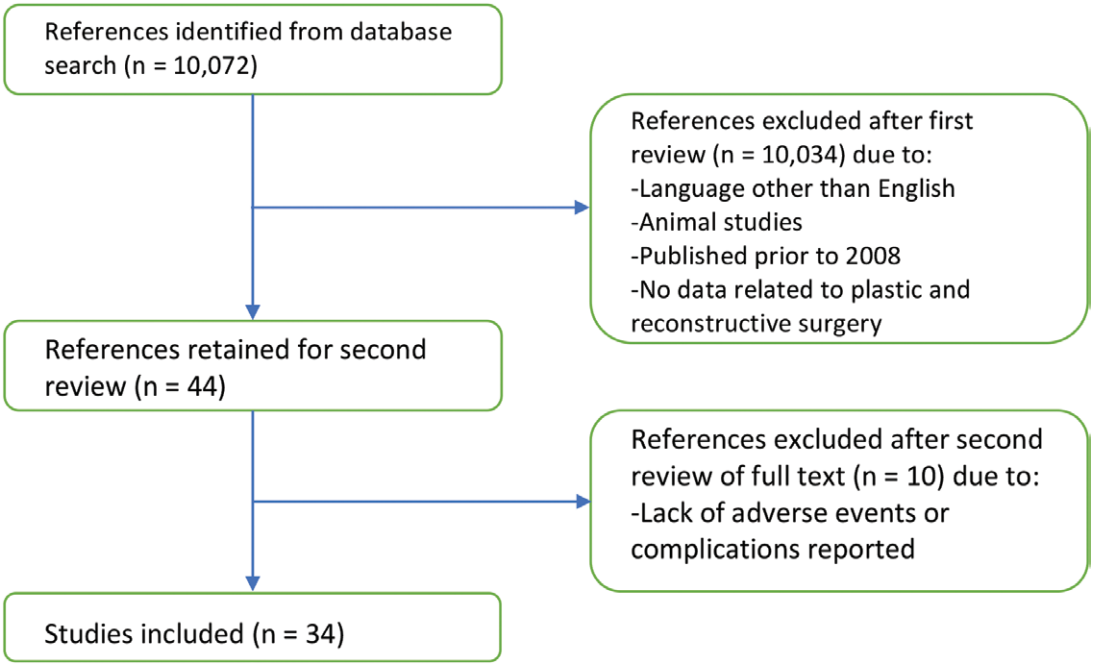

Fig. 1. Flow diagram of articles reviewed and included in the systematic review.

hematoma was not statistically significantly higher in ketorolac-treated patients overall or based on procedure. One study that showed a significant association between ketorolac and hematoma formation was confounded by the significantly higher rate of hypertension in the ketorolac-treated group.[29] Gobble et al. performed a meta-analysis of 27 studies regarding the effect of ketorolac on postoperative bleeding, finding that bleeding risk was not statistically significantly different in the ketorolac group compared to the control group.[30] Furthermore, no significant risk for hematoma or bleeding was found in separate studies evaluating ketorolac for postoperative pain management following breast and facial operations.[31–34] Importantly, the studies also found that ketorolac provided significant pain control and reduced postoperative narcotic use, with the study by Gobble et al. finding ketorolac superior to opioid controls in pain control.[29–34]

Selective Cyclooxygenase Inhibitors

Sun et al. found that postoperative celecoxib following plastic surgery procedures did not cause any statistically significant hematomas or other complications when compared to the control group. However, one patient who received celecoxib had a deep vein thrombosis, causing an extended hospitalization.[4] Similarly, Parsa et al. studied patients who received celecoxib after breast reduction surgery and found that there were no statistically significant differences between the celecoxib and control groups in terms of hematoma formation or other complications.[18] Aynehchi et al. found that patients undergoing face-lift procedures with postoperative celecoxib had statistically significantly fewer side effects, such as sedation and nausea, than the control group.[35] Furthermore, the studies found that celecoxib is effective in decreasing postoperative pain, decreasing opioid use, and enhancing rate of recovery following plastic surgery.[4,18,35]

Intravenous Acetaminophen

Wladis et al. performed a prospective study on patients who underwent orbital surgery and received postoperative intravenous acetaminophen.[36] Crisp et al. performed a randomized controlled trial of patients who received intravenous acetaminophen following vaginal reconstructive surgery.[37] In both of these studies, there were no significant complications or side effects.[36,37] Kang et al. performed a prospective study of patients who received propacetamol (a prodrug of intravenous acetaminophen) following breast surgery and found that it caused an increased risk of nausea and vomiting, but did not cause an increased risk of more serious side effects such as bleeding or hematoma formation.[38] However, Ohnesorge et al. found that patients who underwent breast surgery and received acetaminophen did not have an increased risk of nausea,

Table 2. Summary of Included Studies

Intervention and References	Type of Study (Sample Size)	Indication	Safety Outcome
Ibuprofen			
Kelley et al., 2016[3]	Meta-analysis ($n = 186$)	Various specialty surgery	No statistically significant increase in bleeding
Chen and Adamson, 2009[28]	Prospective trial ($n = 18$)	Facial plastic surgery	No statistically significant increase in bruising/bleeding
Ketorolac			
Stephens et al., 2015[29]	Systematic review ($n = 483$)	Various plastic surgery	No statistically significant increase in hematoma formation
Gobble et al., 2014[30]	Meta-analysis ($n = 1304$)	Various specialty surgery	No statistically significant increase in bleeding complications
Tan et al., 2017[31]	Retrospective study ($n = 47$)	Breast augmentation	No bleeding complications
Mahabir et al., 2008[32]	Prospective trial ($n = 23$)	Breast augmentation	No clinically significant hematoma formations
Afonso et al., 2017[33]	Retrospective study ($n = 42$)	Breast reconstruction	No statistically significant increase in any complications, including bleeding
Torgerson et al., 2008[34]	Prospective trial ($n = 115$)	Facial plastic surgery	No hematoma-type complications
Selective COX inhibitors			
Sun et al., 2008[4]	Prospective trial ($n = 80$)	Various plastic surgery	No statistically significant increase in hematoma formation
Parsa et al., 2017[17]	Retrospective study ($n = 44$)	Breast reduction	No statistically significant increase in any complications, including hematoma formation
Aynehchi et al., 2014[35]	Retrospective study ($n = 50$)	Face-lift surgery	Statistically significant decrease in postoperative complications
IV acetaminophen			
Wladis et al., 2016[36]	Prospective trial ($n = 50$)	Orbital surgery	No postoperative complications
Crisp et al., 2017[37]	Prospective trial ($n = 47$)	Vaginal reconstruction	No statistically significant increase in any complications
Kang et al., 2015[38]	Prospective trial ($n = 111$)	Breast surgery	No bleeding complications
Ohnesorge et al., 2009[39]	Prospective trial ($n = 27$)	Breast reconstruction	No statistically significant increase in bleeding complications
Ketamine			
Kayyal et al., 2014[41]	Retrospective study ($n = 8$)	Facial plastic surgery	No statistically significant increase in any complications
El Mourad et al., 2018[40]	Prospective trial ($n = 30$)	Facial plastic surgery	No statistically significant increase in any complications
Demir and Yuzkat, 2018[15]	Prospective trial ($n = 70$)	Facial plastic surgery	No statistically significant increase in any complications
Low and Gan, 2014[16]	Meta-analysis ($n = 3129$)	Various specialty surgery	No statistically significant increase in any complications, including psychomimetic effects
Gabapentin			
Hah et al., 2017[42]	Prospective trial ($n = 208$)	Various specialty surgery	Statistically significant increase in constipation, impaired coordination, rash
Arumugam et al., 2016[43]	Meta-analysis ($n = 895$)	Various specialty surgery	Statistically significant increase in somnolence
Tinsbloom et al., 2017[44]	Prospective trial ($n = 23$)	Various plastic surgery	No statistically significant increase in any complications
Low and Gan, 2014[16]	Systematic review ($n = 1400$)	Various plastic surgery	Well tolerated, some transient symptoms such as somnolence
Liposomal bupivacaine			
Jablonka et al., 2017[45]	Retrospective study ($n = 62$)	Breast reconstruction	No statistically significant increase in any complications, including hematoma formation
Vyas et al., 2016[20]	Systematic review ($n = 405$)	Various specialty surgery	No statistically significant increase in any complications, including hematoma formation
Baxter et al., 2013[22]	Systematic review ($n = 823$)	Various specialty surgery	No statistically significant increase in any complications, including hematoma formation
LA nerve block			
Shah et al., 2015[27]	Retrospective study ($n = 89$)	Breast reconstruction	One case of pneumothorax, resolved without intervention
Tahiri et al., 2011[46]	Meta-analysis ($n = 618$)	Breast surgery	Two cases of pneumothorax, one case of pleural puncture without pneumothorax
Hivelin et al., 2011[47]	Prospective trial ($n = 15$)	Breast reconstruction	No postoperative complications
LA continuous infusion			
Smith et al., 2008[48]	Retrospective study ($n = 100$)	Abdominal plastic surgery	No statistically significant increase in any complications, including seroma formation
Colpaert et al., 2008[26]	Retrospective study ($n = 92$)	Breast reconstruction	One case of air entrapment
Chavez-Abraham et al., 2011[49]	Retrospective study ($n = 690$)	Various plastic surgery	One case of unilateral infection, 3 cases of catheter ruptures
Heller et al., 2008[26]	Prospective trial ($n = 23$)	Breast reconstruction	No postoperative complications
O'Donoghue et al., 2008[24]	Retrospective study ($n = 18$)	Breast reconstruction	No postoperative complications

COX, cyclooxygenase; IV, intravenous; LA, local anesthetic.

vomiting, or sedation. However, eight patients dropped out because of side effects; notably, two patients in the study experienced postoperative bleeding requiring surgical reoperation, one of whom received postoperative intravenous acetaminophen.[39] Importantly, each study found that intravenous acetaminophen decreases postoperative opioid use, with the exception of the study by Crisp et al. of vaginal reconstruction patients, which showed no significant decrease in pain score versus placebo.[36–39]

Ketamine

Two prospective clinical trials and one retrospective trial found that ketamine did not cause any significantly increased risk of side effects or complications compared to the control group.[15,40,41] In a meta-analysis by Low and Gan, multiple individual articles found an increased risk of psychomimetic effects in the ketamine group, but the overall statistical analysis found that ketamine does not increase the risk of psychomimetic effects.[16] Importantly, all four studies found that ketamine use reduces the opioid requirement and decreases pain scores compared with the control group.[15,16,40,41]

Gabapentin

Hah et al. performed a randomized, double-blind, placebo-controlled study of perioperative gabapentin for patients undergoing surgery, including breast reconstruction, and found a statistically significant increased risk of constipation, impaired coordination, and rash.[42] Arumugam et al. performed a meta-analysis of 17 studies investigating postoperative gabapentin and found a statistically significant increase in somnolence.[43] Similarly, Low and Gan performed a systematic review of postoperative gabapentin and found that they were well tolerated overall, with somnolence and dizziness as the most common side effects.[16] In contrast, Tinsbloom et al. performed a prospective trial of preoperative gabapentin and acetaminophen in patients undergoing plastic surgery and did not find any statistically significant increased risk of any side effects.[44] Interestingly, none of these studies found any risk of bleeding or hematoma formation associated with gabapentin. Furthermore, these studies show that gabapentin can be as effective as acetaminophen for pain control and may also decrease opioid use.[16,42–44]

Liposomal Bupivacaine

Jablonka et al. performed a retrospective analysis of patients who received intraoperative transversus abdominis plane block injections with liposomal bupivacaine during breast reconstruction surgery.[45] Vyas et al. and Baxter et al. performed systematic reviews of liposomal bupivacaine in various fields including plastic surgery.[20,22] In each of these studies, there were no statistically significant differences in any adverse effects, including hematoma formation or flap loss, between the liposomal bupivacaine group when compared to the control group. In addition, these studies found that liposomal bupivacaine is effective in reducing postoperative opioid use and in producing long-acting pain relief.[20,22,45]

Local Anesthetic Nerve Block

Shah et al. performed a retrospective study on patients who underwent bilateral or unilateral breast reconstruction with thoracic intercostal nerve blocks using Marcaine (Pfizer, Inc., New York, N.Y.) with epinephrine. There was one case of a pneumothorax that resolved spontaneously in a patient who underwent a simultaneous port placement.[27] Tahiri et al. performed a meta-analysis of 11 studies on thoracic paravertebral blocks during breast surgery, with the studies using either lidocaine, ropivacaine, or bupivacaine. The most common complications were hypotension and bradycardia. In addition, two of the 618 cases were complicated by pneumothorax, with one additional instance of pleural puncture without pneumothorax.[46] Hivelin et al. performed a prospective study of patients who received a ropivacaine transversus abdominis plane block after breast reconstruction surgery. Each transversus abdominis plane block was placed under ultrasound guidance and, interestingly, none of the transversus abdominis plane block patients experienced any postoperative complications.[47] In these studies, local anesthetic nerve blocks were shown to significantly reduce opioid consumption and decrease pain scores.[27,46,47]

Local Anesthetic Continuous Infusion

Smith et al. performed a retrospective analysis of patients who received a continuous infusion local anesthetic pain pump during abdominal plastic surgery procedures and did not find an increased risk for complications, such as seroma formation.[48] Colpaert et al. and Chavez-Abraham studied patients who received postoperative continuous local anesthetic infusions after breast or abdominal operations.[26,49] The study by Colpaert et al. and Chavez-Abraham et al. had one recorded complication, which was air entrapment attributed

to the patient's lateral positioning.[26] In the study by Chavez-Abraham et al., one patient developed a unilateral infection and three experienced catheter rupture related to home removal.[49] Heller et al. and O'Donoghue et al. performed studies on continuous bupivacaine infusion pumps in the setting of transverse rectus abdominis musculocutaneous flap procedures and latissimus dorsi breast reconstruction.[24,25] Both of these studies found that none of the patients experienced any complications related to the continuous infusion pump or local anesthetic toxicity.[24,25] In addition, these studies also found that continuous infusions with local anesthetics were effective for postoperative pain management and significantly reduce postoperative narcotic use.[24–26,48,49]

DISCUSSION

This systematic review analyzes the efficacy and safety of several nonopioid analgesic medications. Notably, aspirin was not included in this review because of its unequivocal bleeding effects. When used as an anticoagulant, it gives a 20 percent risk reduction for thromboembolism. In contrast, the bleeding risks of nonsteroidal antiinflammatory drugs are, based on this review, quite exaggerated. Furthermore, without a doubt of their efficacy, nonsteroidal antiinflammatory drugs are an excellent choice for pain control. Specifically, a retrospective study published in November of 2018 found that hematoma was not associated with ketorolac use in reduction mammoplasty patients, further supporting the findings of this systematic review.[50] Similarly, intravenous acetaminophen is both a safe and an effective method of postoperative pain control. Although it is more expensive than oral acetaminophen at an average of $150 per patient, other surgical fields have found associated reductions in hospital costs and readmission rates.[51,52]

Next, ketamine appears to be an effective and safe medication for pain control, with most patients not experiencing any psychomimetic effects. However, similar to intravenous acetaminophen, is it only useful when the patient has venous access. The safety of gabapentin has also been established, without evidence of consistent efficacy following plastic surgery procedures. Next, liposomal bupivacaine was also demonstrated to be a safe and effective means of pain control, with its liposomal characteristics ideal for longer term analgesia. Despite growing evidence supporting its use, liposomal bupivacaine may not reach its use potential for a different reason: cost. One treatment with liposomal bupivacaine costs approximately $285. Hospital studies show a favorable cost-to-benefit analysis, including shorter length of hospital stays; this expense may still limit use among private practice plastic surgeons.[53–59]

Lastly, local anesthetic nerve blocks and continuous infusions have a small but definite risk of pneumothorax, with deeper thoracic nerve blocks carrying greater risk than those placed in the abdomen. Although patients who experienced a pneumothorax recovered, it is a valid risk that should be taken seriously. Fortunately, based on this review, placement with ultrasound guidance or by an experienced practitioner minimizes this risk. In addition, one alternative to interpleural nerve blocks is the T3 to T4 block, which is more superficial and may lead to decreased risk of pneumothorax complications. An adverse event identified for continuous infusion catheters was ruptures during home removal, reinforcing the need for removal by a medical professional. There was only one reported case of infection with continuous infusion catheters, suggesting a lower risk than previously perceived.

The authors confidently advocate for the increased use of nonopioid analgesics, despite the limitations to this review, with the small sample size present in several of the reviewed studies. Data from two trials were each represented in two of the systematic reviews included in this article, meaning these data were overrepresented. The different control groups, administrations, and medication dosages make it difficult to compare and analyze individual study results. The inclusion criteria were created to reduce bias, but there are inherent limitations in systematic reviews that arise because of selection and publication biases. Positive results regarding medication efficacy and safety may be preferentially published over those without significant or positive findings. To minimize these limitations and further endorse the safety of nonopioid analgesics, larger studies in plastic surgery may be necessary.

CONCLUSIONS

The current opioid crisis has demanded an investigation into opioid alternatives. One possible outcome of this investigation is to use multimodal analgesics as first-line agents, and saving opioids for breakthrough pain. The multimodal pain regimen is a hot topic that is gaining popularity. The medications discussed in this review are all potential candidates for multimodal analgesia and can contribute to the reduction of opioid use,

prompting the examination of their safety and efficacy. Based on our practice experience and this review, we suggest the following postoperative pain control regimen:

1. Preoperative intravenous acetaminophen or ketamine administration for patients following plastic surgery procedures.
2. Superficial T3 to T4 perforator blocks, transversus abdominis plane blocks with long-acting liposomal bupivacaine *or* continuous infusion catheter therapy
3. Ibuprofen, ketorolac, or cyclooxygenase inhibitors (celecoxib) as a proactive, integral portion of postoperative pain management.
4. Addition of gabapentin for longer postoperative recovery or nerve regeneration.
5. Systematic decrease of opioid dose, duration, and refill.

Plastic surgeons are often trailblazers in the field of surgery. It is our duty to spearhead the campaign to decrease opioid use by applying and further developing postoperative multimodal analgesia, specifically by using the nonopioid medications that may have more reward than risk.

Rebecca C. O'Neill, M.D.
29 Shira Lane
Manalapan, N.J. 07726
rco38@njms.rutgers.edu

REFERENCES

1. Demsey D, Carr NJ, Clarke H, Vipler S. Managing opioid addiction risk in plastic surgery during the perioperative period. *Plast Reconstr Surg.* 2017;140:613e–619e.
2. Janis JE, Joshi GP. Introduction to "current concepts in pain management in plastic surgery". *Plast Reconstr Surg.* 2014;134(Suppl 2):6S–7S.
3. Kelley BP, Bennett KG, Chung KC, Kozlow JH. Ibuprofen may not increase bleeding risk in plastic surgery: A systematic review and meta-analysis. *Plast Reconstr Surg.* 2016;137:1309–1316.
4. Sun T, Sacan O, White PF, Coleman J, Rohrich RJ, Kenkel JM. Perioperative versus postoperative celecoxib on patient outcomes after major plastic surgery procedures. *Anesth Analg.* 2008;106:950–958, table of contents.
5. Marín-Bertolín S, De Andrés J, González-Martínez R, Valia Vera JC, Amorrortu-Velayos J. A controlled, randomized, double-blind study of ketorolac for postoperative analgesia after plastic surgery. *Ann Plast Surg.* 1997;38:478–484.
6. Gupta A, Jakobsson J. Acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 selective inhibitors: An update. *Plast Reconstr Surg.* 2014;134(Suppl 2):24S–31S.
7. Nissen SE, Yeomans ND, Solomon DH, et al.; PRECISION Trial Investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med.* 2016;375:2519–2529.
8. O'Malley PA. Intravenous acetaminophen: Progress in relief of pain? Implications for clinical nurse specialist practice. *Clin Nurse Spec.* 2013;27:179–181.
9. Schwartz SB, Rauch D. Intravenous acetaminophen: An alternative to opioids for pain management? *Hosp Pediatr.* 2013;3:294–296.
10. Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: A systematic review and meta-analysis. *Pain* 2013;154:677–689.
11. Sanzone AG. Use of nonopioid analgesics and the impact on patient outcomes. *J Orthop Trauma* 2016;30(Suppl 1):S12–S15.
12. Liang L, Cai Y, Li A, Ma C. The efficacy of intravenous acetaminophen for pain control following total knee and hip arthroplasty. *Medicine* 2017;96:1–10.
13. Altenau B, Crisp CC, Devaiah CG, Lambers DS. Randomized controlled trial of intravenous acetaminophen for postcesarean delivery pain control. *Am J Obstet Gynecol.* 2017;217:362.e1–362.e6.
14. Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. *Pain Pract.* 2011;11:290–296.
15. Demir CY, Yuzkat N. Prevention of emergence agitation with ketamine in rhinoplasty. *Aesthetic Plast Surg.* 2018;42:847–853.
16. Low YH, Gan TJ. NMDA receptor antagonists, gabapentinoids, α-2 agonists, and dexamethasone and other non-opioid adjuvants: Do they have a role in plastic surgery? *Plast Reconstr Surg.* 2014;134(Suppl 2):69S–82S.
17. Parsa AA, Sprouse-Blum AS, Jackowe DJ, Lee M, Oyama J, Parsa FD. Combined preoperative use of celecoxib and gabapentin in the management of postoperative pain. *Aesthetic Plast Surg.* 2009;33:98–103.
18. Parsa FD, Cheng J, Stephan B, et al. Bilateral breast reduction without opioid analgesics: A comparative study. *Aesthet Surg J.* 2017;37:892–899.
19. Harmatz A. Local anesthetics: Uses and toxicities. *Surg Clin North Am.* 2009;89:587–598.
20. Vyas KS, Rajendran S, Morrison SD, et al. Systematic review of liposomal bupivacaine (Exparel) for postoperative analgesia. *Plast Reconstr Surg.* 2016;138:748e–756e.
21. Pacira Pharmaceuticals, Inc. Exparel: Opioid free. Available at: https://www.exparel.com/hcp/pharmacokinetics. Accessed February 2018.
22. Baxter R, Bramlett K, Onel E, Daniels S. Impact of local administration of liposome bupivacaine for postsurgical analgesia on wound healing: A review of data from ten prospective, controlled clinical studies. *Clin Ther.* 2013;35:312–320.e5.
23. Pace MM, Chatterjee A, Merrill DG, Stotland MA, Ridgway EB. Local anesthetics in liposuction: Considerations for new practice advisory guidelines to improve patient safety. *Plast Reconstr Surg.* 2013;131:820e–826e.
24. O'Donoghue JM, Bahia H, Bunsell RP, Regan PJ. Intrapleural bupivacaine in latissimus dorsi breast reconstruction. *Ann Plast Surg.* 2008;61:252–255.
25. Heller L, Kowalski AM, Wei C, Butler CE. Prospective, randomized, double-blind trial of local anesthetic infusion and intravenous narcotic patient-controlled anesthesia pump for pain management after free TRAM flap breast reconstruction. *Plast Reconstr Surg.* 2008;122:1010–1018.
26. Colpaert SD, Smith PD, Caddy CM. Interpleural analgesia in breast reconstruction. *Scand J Plast Reconstr Surg Hand Surg.* 2008;42:32–37.
27. Shah A, Rowlands M, Krishnan N, Patel A, Ott-Young A. Thoracic intercostal nerve blocks reduce opioid

consumption and length of stay in patients undergoing implant-based breast reconstruction. *Plast Reconstr Surg.* 2015;136:584e–591e.
28. Chen T, Adamson PA. Comparison of ibuprofen and acetaminophen with codeine following cosmetic facial surgery. *J Otolaryngol Head Neck Surg.* 2009;38:580–586.
29. Stephens DM, Richards BG, Schleicher WF, Zins JE, Langstein HN. Is ketorolac safe to use in plastic surgery? A critical review. *Aesthet Surg J.* 2015;35:462–466.
30. Gobble RM, Hoang HL, Kachniarz B, Orgill DP. Ketorolac does not increase perioperative bleeding: A meta-analysis of randomized controlled trials. *Plast Reconstr Surg.* 2014;133:741–755.
31. Tan P, Martin MS, Shank N, et al. A comparison of 4 analgesic regimens for acute postoperative pain control in breast augmentation patients. *Ann Plast Surg.* 2017;78(Suppl 5):S299–S304.
32. Mahabir RC, Peterson BD, Williamson JS, Valnicek SM, Williamson DG, East WE. Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients: Part II. 10-day follow-up. *Plast Reconstr Surg.* 2008;121:638–643.
33. Afonso A, Oskar S, Tan KS, et al. Is enhanced recovery the new standard of care in microsurgical breast reconstruction? *Plast Reconstr Surg.* 2017;139:1053–1061.
34. Torgerson C, Yoskovitch A, Cole AF, Conrad K. Postoperative pain management with ketorolac in facial plastic surgery patients. *J Otolaryngol Head Neck Surg.* 2008;37:888–893.
35. Aynehchi BB, Cerrati EW, Rosenberg DB. The efficacy of oral celecoxib for acute postoperative pain in face-lift surgery. *JAMA Facial Plast Surg.* 2014;16:306–309.
36. Wladis EJ, Kattato DF, De A. Intravenous acetaminophen in orbital surgery. *Ophthalmic Plast Reconstr Surg.* 2016;32:211–213.
37. Crisp CC, Khan M, Lambers DL, et al. The effect of intravenous acetaminophen on postoperative pain and narcotic consumption after vaginal reconstructive surgery: A double-blind randomized placebo-controlled trial. *Female Pelvic Med Reconstr Surg.* 2017;23:80–85.
38. Kang JE, Park SK, Song IK, Lee JH, Kim JT, Kim HS. Comparison of the efficacy and safety of different doses of propacetamol for postoperative pain control after breast surgery. *Pain Manag Nurs.* 2015;16:367–371.
39. Ohnesorge H, Bein B, Hanss R, et al. Paracetamol versus metamizol in the treatment of postoperative pain after breast surgery: A randomized, controlled trial. *Eur J Anaesthesiol.* 2009;26:648–653.
40. El Mourad MB, Amer AF. Effects of adding dexamethasone or ketamine to bupivacaine for ultrasound-guided thoracic paravertebral block in patients undergoing modified radical mastectomy: A prospective randomized controlled study. *Indian J Anaesth.* 2018;62:285–291.
41. Kayyal TA, Wolfswinkel EM, Weathers WM, et al. Treatment effects of dexmedetomidine and ketamine on postoperative analgesia after cleft palate repair. *Craniomaxillofac Trauma Reconstr.* 2014;7:131–138.
42. Hah J, Mackey SC, Schmidt P, et al. Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: A randomized clinical trial. *JAMA Surg.* 2017;153:303–311.
43. Arumugam S, Lau CS, Chamberlain RS. Use of preoperative gabapentin significantly reduces postoperative opioid consumption: A meta-analysis. *J Pain Res.* 2016;9:631–640.
44. Tinsbloom B, Muckler VC, Stoeckel WT, Whitehurst RL, Morgan B. Evaluating the implementation of a preemptive, multimodal analgesia protocol in a plastic surgery office. *Plast Surg Nurs.* 2017;37:137–143.
45. Jablonka EM, Lamelas AM, Kim JN, et al. Transversus abdominis plane blocks with single-dose liposomal bupivacaine in conjunction with a nonnarcotic pain regimen help reduce length of stay following abdominally based microsurgical breast reconstruction. *Plast Reconstr Surg.* 2017;140:240–251.
46. Tahiri Y, Tran DQ, Bouteaud J, et al. General anaesthesia versus thoracic paravertebral block for breast surgery: A meta-analysis. *J Plast Reconstr Aesthet Surg.* 2011;64:1261–1269.
47. Hivelin M, Wyniecki A, Plaud B, Marty J, Lantieri L. Ultrasound-guided bilateral transversus abdominis plane block for postoperative analgesia after breast reconstruction by DIEP flap. *Plast Reconstr Surg.* 2011;128:44–55.
48. Smith MM, Hovsepian RV, Markarian MK, et al. Continuous-infusion local anesthetic pain pump use and seroma formation with abdominal procedures: Is there a correlation? *Plast Reconstr Surg.* 2008;122:1425–1430.
49. Chavez-Abraham V, Barr JS, Zwiebel PC. The efficacy of a lidocaine-infused pain pump for postoperative analgesia following elective augmentation mammaplasty or abdominoplasty. *Aesthetic Plast Surg.* 2011;35:463–469.
50. Firriolo JM, Nuzzi LC, Schmidtberg LC, Labow BI. Perioperative ketorolac use and postoperative hematoma formation in reduction mammaplasty: A single-surgeon experience of 500 consecutive cases. *Plast Reconstr Surg.* 2018;142:632e–638e.
51. Hansen RN, Pham AT, Lovelace B, Balaban S, Wan GJ. Comparative analysis of inpatient costs for obstetrics and gynecology surgery patients treated with IV acetaminophen and IV opioids versus IV opioid-only analgesia for postoperative pain. *Ann Pharmacother.* 2017;51:834–839.
52. Mont M, Lovelace B, Pham A, et al. Intravenous acetaminophen may be associated with reduced odds of 30-day readmission after total knee arthroplasty. *J Knee Surg.* 2019;32:414–420.
53. Kirkness CS, Asche CV, Ren J, Kim M, Rainville EC. Cost-benefit evaluation of liposomal bupivacaine in the management of patients undergoing total knee arthroplasty. *Am J Health Syst Pharm.* 2016;73:e247–e254.
54. Clarke R, Derry S, Moore RA. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2014;5:CD004309.
55. Ribotsky BM, Berkowitz KD, Montague JR. Local anesthetics: Is there an advantage to mixing solutions? *J Am Podiatr Med Assoc.* 1996;86:487–491.
56. Mahabir RC, Peterson BD, Williamson JS, Valnicek SM, Williamson DG, East WE. Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients. *Plast Reconstr Surg.* 2004;114:1910–1916.
57. Hsia HC. On beyond lidocaine: Reconsidering local anesthetics in tumescent liposuction. A critical review. *Ann Plast Surg.* 2016;77(Suppl 1):S66–S69.
58. Paik AM, Daniali LN, Lee ES, Hsia HC. Local anesthetic use in tumescent liposuction: An American Society of Plastic Surgeons survey. *Ann Plast Surg.* 2015;74:145–151.
59. Swanson E. Prospective study of lidocaine, bupivacaine, and epinephrine levels and blood loss in patients undergoing liposuction and abdominoplasty. *Plast Reconstr Surg.* 2012;130:702–722.