Acute Pain Management Following Head and Neck Surgery

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KEYWORDS

• Pain • Head and neck cancer • Free flap • Free tissue transfer • Opioid • ERAS
• Analgesia • Multimodal analgesia

KEY POINTS

- Pain management for patients with head and neck cancer is complex; opioids are uniquely hazardous due to altered upper airway anatomy and physiology.
- Several nonopioid analgesics exist for pain management of patients undergoing major head and neck surgery, including nonsteroidal anti-inflammatory drugs, acetaminophen, anticonvulsants, corticosteroids, and locoregional anesthetics.
- In addition to the safe use of multimodal analgesia (MMA), special considerations for patients undergoing head and neck free flap surgery include judicious use of steroids, and attention to donor site pain.
- Evidence for specific analgesic regimens following transoral robotic surgery is limited but should include MMA and perioperative dexamethasone if not contraindicated.

INTRODUCTION

Head and neck cancer (HNC) is diagnosed in 65,000 patients annually in the United States.[1] More than 80% of all patients with HNC experience pain before treatment and more than 40% receive opioids before treatment.[2] Despite advances in radiation and chemotherapy, surgical resection and reconstruction remains a critical component of multidisciplinary HNC management. Aside from the obvious associations with patient comfort and satisfaction, adequate pain control in patients with HNC is critically important because it is associated with microvascular free flap viability[3] and long-term psychosocial well-being.[4]

Although opioid pain medications have been the cornerstone of acute pain management for patients undergoing HNC surgery, there is renewed interest in identifying opioid-sparing analgesic for a number of reasons.[5] First, for patients with HNC

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undergoing significant alterations in their upper airway anatomy and physiology, adverse effects of opioids (eg, nausea, vomiting, respiratory depression) can be uniquely hazardous. Second, there is continued emerging evidence that multimodal analgesia (MMA) featuring opioid-sparing regimens is more effective than narcotic analgesia alone.[6,7] Finally, the concern of long-term opioid dependence is particularly significant among patients with HNC, as they are at elevated risk for short-term and long-term opioid dependence compared with the general population.[2] For patients older than 65 years who underwent primary surgical resection for any site HNC, 18% of opioid-naïve patients and 50% for patients using opioids preoperatively developed persistent postoperative opioid use (new opioid prescriptions 90–180 days postoperatively.)[8] Hand in hand with the growing attention to opioid-sparing analgesia has been the explosion of articles developing dsease-specific and procedure-specifc Enhanced Recovery After Surgery (ERAS) protocols.[9]

To help the head and neck surgeon stay abreast of ongoing controversies in managing acute postoperative pain for patients undergoing major head and neck surgery, this article (1) reviews the classes of nonopioid analgesics used for acute pain management following head and neck surgery (**Table 1**); (2) critically analyzes the evidence underlying MMA in this patient population; and (3) describes procedure-specific analgesia recommendations for unique head and neck surgical procedures.

NONOPIOID ANALGESICS

Acetaminophen

Acetaminophen has long been a safe alternative and/or adjunct in managing acute postoperative pain in patients with HNC. In a recent retrospective investigation of patients undergoing major head and neck surgery, the combination of intravenous (IV) acetaminophen with morphine patient-controlled analgesia (PCA) resulted in similar pain relief, as measured by PCA attempts and pain score, with 40% and 30% less total postoperative narcotic use in the first 8 and 24 hours, respectively, compared with standard morphine PCA.[10] Hepatic complications of appropriately dosed acetaminophen are rare. Nevertheless, liver function assessment should be considered in appropriate, high-risk patients before scheduled administration due to the prevalence of alcohol use among patients with HNC.[11] Overall, because it is an efficacious and safe medication, scheduled administration of acetaminophen should be considered following almost all major head and neck surgeries.[6,7,10,12]

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production over prolonged time periods, leading to decreased local inflammation. NSAIDs include nonselective cyclooxygenase (COX) inhibitors such as ibuprofen and ketorolac, and selective COX-2 inhibitors such as celecoxib. COX-2 inhibitors provides excellent pain control but have a lower risk of platelet dysfunction and gastrointestinal complications.[13]

A major barrier to widespread use of NSAIDs is concern for postoperative hemorrhage, which can be acutely fatal when occurring in the neck or upper airway. However, a recent retrospective cohort study showed that a regimen including scheduled celecoxib 200 mg twice per day for a minimum of 5 days and ketorolac pro re nata (PRN) for up to 3 days was not associated with an increased risk of bleeding in patients with HNC undergoing free flap reconstruction.[6] A retrospective cohort study of postoperative ketorolac in patients undergoing major head and neck surgeries also found no increased risk of bleeding and favorable free flap outcomes.[14]

Table 1
Recommended dosing and considerations of opioid-sparing analgesic medications

Analgesic Class	Analgesic Name	Dosing	Special Considerations
Acetaminophen	Acetaminophen or paracetamol	Preop • 650 mg – 1000 mg once Intraop • 1000 mg IV once Postop • 650 mg Q 6 h–950 mg Q 8 h	Up to 4 g per 24 h Consider hepatic dosing in patients with reduced liver function
NSAIDs	Celecoxib	Preop • 200 mg once Postop • 200 mg BID	Continue for 5 d post-discharge Consider renal dosing or omission in patients with CKD or decreased GFR
	Ketorolac	Postop Ketorolac 15 mg–30 mg IV Q 6 h PRN[a]	For up to 3 d maximum Consider renal dosing or omission in patients with CKD or decreased GFR
Anticonvulsants	Gabapentin	Preop • 1000 mg–1200 mg once Postop • 100 mg–900 mg TID as tolerated	Up-titration based on side effects Consider renal dosing or omission in patients with CKD or decreased GFR
	Pregabalin	Preop • 100 mg once Postop • 50 mg–300 mg BID as tolerated	Up-titration based on side effects Consider renal dosing or omission in patients with CKD or decreased GFR
Corticosteroids	Dexamethasone	Intraop • 10 mg IV once[b] Postop • 8 mg IV Q 8 h up to 4 d[b]	Consider dose or duration reduction in patients with diabetes mellitus

Abbreviations: BID, twice a day; CKD, chronic kidney disease; GFR, glomerular filtration rate; Intraop, intraoperative; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; postop, postoperative; preop, preoperative; PRN, pro re nata; Q, every; TID, 3 times a day.
[a] Consider 15 mg dose for patient appearing frail or elderly.
[b] For TORS patients.

It is also important to note that NSAIDs have other long-established risks, including renal dysfunction. As such, the use of ketorolac should be limited to 72 hours.[15] Although the renal complications due to NSAID use are rare in healthy individuals, patients with HNC have additional risk factors including hypovolemia and prior kidney injury from nephrotoxic chemotherapy agents.

Anticonvulsants

Anticonvulsants are defined by their ability to suppress seizures, although several of them are known to also modulate pain pathways. The routine control of neuropathic

and postoperative pain remains limited to gabapentinoids, which include gabapentin and pregabalin.[16]

A double-blinded, randomized controlled trial (RCT) comparing gabapentin 300 mg twice daily with placebo in 110 patients undergoing large head and neck mucosal operations showed that gabapentin use resulted in decreased pain during rest, coughing, and swallowing, as well as less nausea and vomiting.[17] In a retrospective study of patients with HNC, the median dose of 2700 mg/d of gabapentin resulted in only 10% of patients requiring additional narcotics postoperatively.[18]

The side-effect profile of gabapentin is mild for most patients with dose-limiting side effects related to sedation and dizziness. Various dosing titration regimens have been proposed to avoid these, most conservative titration regiments begin at 300 mg/d and increase according to tolerance.[19]

Pregabalin has also been used for treatment of radiotherapy-related neuropathic pain in patients with HNC[20] and following head and neck–related surgery[21] with good efficacy and similar tolerance to gabapentin. However, evidence for the routine use of pregabalin in the perioperative setting compared with gabapentin is relatively lacking.

Corticosteroids

The efficacy of corticosteroids for pain control has been established for other procedures in otolaryngology,[22] with additional benefits including decreased nausea and swelling (including both airway structures and tissue surrounding microvascular free flap anastomosis). However, steroid use carries considerable risks, including hyperglycemia, psychosis, fluid and electrolyte imbalance, infection, and poor wound healing. A double-blind RCT investigating postoperative dexamethasone versus placebo in 93 patients following HNC resection with free flap reconstruction showed an increase in major complications including wound breakdown/necrosis, infection, venous thrombosis, and postoperative bleeding in the steroid group relative to control.[23]

Local and Regional Analgesia

Support for the routine use of local and regional analgesia for pain following major head and neck procedures remains limited, although protocols for delivering preoperative mandibular nerve blocks with ropivacaine[24] and for parotidectomy have been shown to decrease pain.[25] The utility of these techniques has yet to be used for more extensive head and neck surgeries, however. The continuous infusion of medication to surrounding airway structures and/or free flap pedicles poses obvious risks that warrant careful consideration.

MULTIMODAL ANALGESIA AND ENHANCED RECOVERY AFTER SURGERY

Established in 2010, the ERAS Society aims to optimize all aspects of perioperative care.[26] ERAS protocols improve surgical outcomes. Head and neck oncology recently joined this community.[27,28] According to the ERAS Society, optimal perioperative pain control for major HNC surgery should include the use of an opioid-sparing, multimodal approach consisting of NSAIDs, acetaminophen, gabapentin, local anesthetics, corticosteroids (when appropriate), and opioids for breakthrough pain. With high-level evidence, these are strong recommendations by the ERAS Society.[28] In addition, preemptive analgesia (ie, administered before any noxious stimuli) has become an important aspect of ERAS protocols and is beneficial before major head and neck surgery.[5,6,29]

A recent retrospective cohort study evaluated MMA in the context of the ERAS protocols for head and neck surgery with free tissue transfer.[6] Traditional analgesia in the control group consisted of acetaminophen, hydrocodone-acetaminophen combination, or IV morphine PRN. Study patients received preoperative oral acetaminophen and gabapentin, as well as intraoperative IV acetaminophen. This was followed by postoperative acetaminophen and gabapentin every 8 hours, celecoxib every 12 hours, and ketorolac every 6 hours as needed (for up to 3 days), and IV fentanyl for breakthrough pain. Patients treated with MMA required a median of 10 morphine equivalent doses (MED) compared with 89.6 in the control group over the first 72 hours. Although there were no differences in ambulation, intensive care unit (ICU) or hospital length of stay, or complications (including bleeding), there was a remarkable reduction is discharge opioids. The MMA group was discharged with a median of 0 MEDs compared with 300 in the control group. Discharge medications otherwise included a 5-day course of celecoxib and gabapentin. Although this study population included a select group of patients (excluding those with ongoing opioid use from outside sources, and patients with renal and hepatic failure), it suggests that patients with HNC can achieve great pain control with MMA, significantly reducing the amount of opioids in both the inpatient and outpatient settings without increasing complications.

In concert with MMA, head and neck surgeons should use opioids for breakthrough pain, providing the lowest possible dose that achieves desired pain control. It is recommended that prescribers use institutionally developed prescribing guidelines, procedure-specific recommendations, and promote a culture of opioid stewardship.[5] A sample MMA pathway, provided by Cramer and colleagues[5] based on ERAS principles is depicted in **Fig. 1**.

PROCEDURE-SPECIFIC RECOMMENDATIONS

Transoral Robotic Surgery

Transoral robotic surgery (TORS) has emerged as an important tool for the treatment of oropharyngeal and supraglottic tumors. Strategies to ensure optimal postoperative pain following TORS is critical, as inadequate analgesia can result in unplanned hospital readmissions and increase the risk of bleeding.[30] Unfortunately, evidence-based analgesia regimens following TORS remain lacking. Multiple studies support the use of perioperative steroids in patients undergoing traditional tonsillectomy to reduce pain.[22] Some institutions including ours, have extrapolated from these data and now routinely prescribe perioperative steroids to patients undergoing TORS.[31] One study investigated the effects of an extended perioperative course of corticosteroids for improving pain control following TORS.[32] All patients in the study received a single intraoperative dose of 10-mg dexamethasone and were then randomized to further receive 8-mg every 8 hours, or a placebo, for up to 4 days after surgery. The steroid group reported a sharper decline of visual analog scale (VAS) pain scores over 1 to 3 postoperative days, decreased length of stay by 1 day, and accelerated ability for consumption of solid food at 1- and 3-week follow-up, with no difference in complications.

Pain control regimens for TORS should otherwise include MMA including acetaminophen and gabapentin as with other HNC surgery. The incorporation of NSAIDs in pain management following TORS remains controversial due to the theoretic increased risk of bleeding. However, an increased risk of bleeding has not been demonstrated following traditional tonsillectomy.[33] In addition, Scott and colleagues describe the use of NSAIDS following TORS[31] without an increase in adverse events.

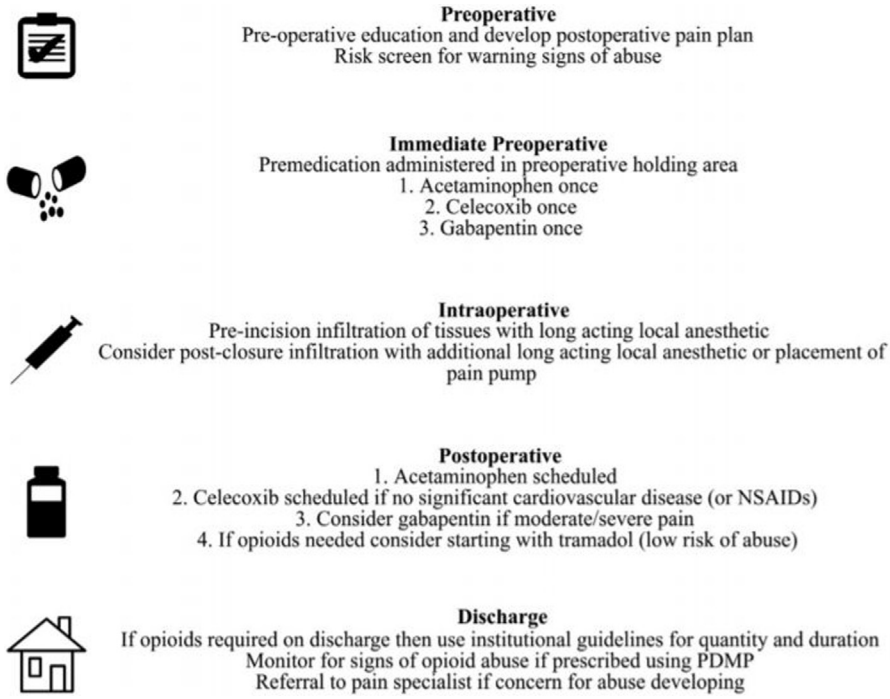

Fig. 1. Sample multimodal analgesia pathway developed using ERAS principles for head and neck surgery. PDMP, prescription drug monitoring program. (*From* Cramer JD, Wisler B, Gouveia CJ. Opioid Stewardship in Otolaryngology: State of the Art Review. Otolaryngol Head Neck Surg. 2018;158(5):817-827; with permission.)

Free Flap Reconstruction

Major head and neck surgery with free flap reconstruction is complex and generates multiple surgical sites. Several MMA regimens have been described (**Table 2**). NSAIDs are an integral part of MMA for major head and neck surgery, although there is a concern that that celecoxib may increase the risk of microvascular complications.[34] However, preclinical studies have shown that celecoxib has no significant negative effects on free tissue transfer survival or healing in a rat model.[35] Furthermore, a retrospective cohort study of 51 patients undergoing free flap surgery who received 200 mg of celecoxib twice daily for a minimum of 5 days starting on postoperative day 1 showed no increased risk of free flap complications compared with retrospective controls who did not receive celecoxib. However, patients receiving celecoxib required less opioids.[15] Another retrospective cohort study examined 65 patients with HNC undergoing free flap reconstruction and found no increase in the rate of adverse effects in the celecoxib and ketorolac receiving groups, but showed a significant decrease in mean MED in the NSAID group.[6]

Gabapentin has also been used in the preemptive analgesic setting for patients with HNC with free flap reconstruction and, similar to postoperative use, has been shown to reduce postoperative pain and nausea, with subsequent decrease in postoperative analgesic and antiemetic usage.[29] Preemptive and postoperative use of gabapentinoids have been used in several MMA regimens for patients with HNC free flap reconstruction with great efficacy.[6,29] Dosing as high as 2700 mg per day (900 mg 3 times a

Table 2
Opioid-sparing analgesic regimens for patients undergoing head and neck free flap surgery

Author, Year	Study Design	Sample Size, n (Treatment Group)	Analgesic Regimen (Comparison Group Regimen)	Pain Outcomes	Other Outcomes
Carpenter et al,[15] 2018	Retrospective cohort	102 (51)	Postop • Celecoxib 200 mg BID $\geq$ 5 d • Opioids PRN (Historical control group which did not receive celecoxib)	• Decrease of MME by 14/d.	• No difference in complications (flap failure, hematoma, SSI)
Eggerstedt et al,[6] 2019	Retrospective cohort	65 (28)	Preop • Acetaminophen 975 mg • Gabapentin 900 mg Intraop • Acetaminophen 1000 mg IV Postop • Acetaminophen 950 mg Q 8 h • Gabapentin 300 mg Q 8 h • Celecoxib 200 mg Q 12 h • Ketorolac 15 mg IV Q 6 h PRN $\leq$ 3 d • Fentanyl ORN (Historical control group which received standard opioid-based regimen)	• Decrease in MED over 72 h (10 vs 89.6) • Decrease in mean pain score by DVPRS (2.05 vs 3.66) • Decrease in discharge MED (0 vs 300)	• No difference in LOS, ICU stay, postop bleeding, return to OR, ED visits, or readmissions
Schleiffarth et al,[14] 2014	Retrospective cohort	138 (2)	Postop • Ketorolac 30 mg IV Q 6 h $\times$ 5 d[a] (Control group received either 325 mg aspirin or no NSAID per surgeon preference)	• No difference MED/d (48.9 vs 46.6) over 7 d • Higher mean pain score (3.1 vs 2.4 by VAS)	• No difference in postoperative transfusion, flap failure, or return to OR

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Table 2
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Author, Year	Study Design	Sample Size, n (Treatment Group)	Analgesic Regimen (Comparison Group Regimen)	Pain Outcomes	Other Outcomes
Chiu et al,[29] 2012	Nonrandomized open labeled trial	50 (25)	Preop • Gabapentin 1200 mg (Control group received no preemptive analgesia)	• Decrease in pain score (1.2 vs 1.7 by VAS) over first 24 h • Decrease in mean morphine use (3.5 vs 11.4)	• Decreased antiemetic use in first 24 h, (0 vs 12.2 mg metoclopramide), no change in LOS or flap failure
Kainulainen et al,[23] 2017; Kainulainen et al,[37] 2018	Prospected, randomized, double-blind trial	93 (51)	Preop • dexamethasone 10 mg IV Postop • Acetaminophen 1 g × 3 doses • Oxycodone PRN • Dexamethasone 10 mg IV Q 8 h on POD1, Q 12 h on POD2, × 1 dose on POD3 (Control group did not receive preop or postop dexamethasone)	• Decrease in total oxycodone administered (81.2 vs 112.1)	• Increased major complications[b], insulin use and lactate levels in steroid group, no change in PONV, LOS, or ICU stay

Abbreviations: BID, twice a day; DVPRS, defense and veterans pain rating score; ED, emergency department; ICU, intensive care unit; Intraop, intraoperative; IV, intravenous; LOS, length of stay; MED, morphine equivalent dose; MME, morphine milligram equivalents; OR, operating room; ORN, osteoradionecrosis; POD, postoperative day; PONV, postoperative nausea and vomiting; Postop, postoperative; Preop, preoperative; PRN, pro re nata; Q, every; SSI, surgical site infection; VAS, visual analog scale.

[a] 15 mg IV Q 6 h for elderly patients and those appearing frail, not recommended use for more than 3 d.

[b] Major complications included flap loss, venous thrombosis, wound necrosis/fistula, infection, postop bleeding, later tracheostomy, and pneumothorax.

Data from Refs.[6,14,15,23,29,37]

day), with no specific up-titration regimen has been described. Despite this, titration should be considered in patients with lower extremity donor sites to limit potential dizziness and prevent increased risk of falls.

There is less robust evidence to support the routine use of corticosteroids for pain control in patients undergoing head and neck free flap surgery. A retrospective cohort study analyzing the routine use of preoperative dexamethasone for large HNC surgeries with free flap reconstruction found a reduction in inflammatory markers and improved hemodynamic stability with no increase in complications.[36] However, these retrospective findings differ from a prospective, double-blind RCT evaluating perioperative dexamethasone use following HNC surgery with free flaps. In this RCT, although dexamethasone was associated with a small reduction in oxycodone administration (81.2 mg vs 112.14 mg over 5 days), it was also associated with an increased risk of major complications (wound breakdown/necrosis, infection, venous thrombosis, and postoperative bleeding.)[23,37] As such, although corticosteroid use following major head and neck surgery with free tissue transfer can improve pain control, the increase in adverse events argue against routine administration.

Head and neck free flap reconstruction surgery introduces an additional donor site, and thus an additional source of acute postoperative pain to be managed. The use of local anesthetic infusions is an increasingly popular method of donor site analgesia following free tissue transfer. A prospective study of patients undergoing fibula free flap surgery for head and neck defects demonstrated that injecting a bolus of Chirocaine (0.125% wt/vol; 20 mL) through a catheter into the fibular donor site at the end of surgery and 8, 16, and 24 hours postoperatively is associated with improved pain control and reduced opioid requirements.[38] At our institution, we routinely uses a continuous infusion of 0.2% ropivacaine at the fibula and anterolateral thigh free tissue donor sites through the ON-Q SELECT-A-FLOW, **Fig. 2**.

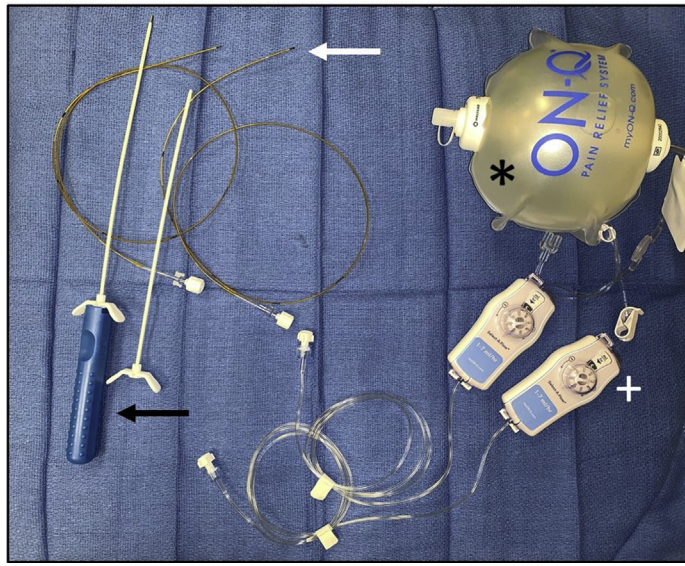

Fig. 2. ON-Q SELECT-A-FLOW system (Halyard Health, Alpharetta, GA) for continuous infusion of 0.2% ropivacaine at donor sites. White arrow = indwelling perforated catheter, black arrow = tunneler and introducer sheath, asterisk = medication containing reservoir, plus = SELECT-A-FLOW adjustment.

SUMMARY AND CLINICAL RECOMMENDATIONS

In conclusion, for the management of acute postoperative pain following major head and neck surgery, we recommend an MMA regimen including preemptive analgesia and postoperative acetaminophen, NSAIDs, gabapentinoids, and locoregional anesthetics as suggested by ERAS. Although the most comprehensive MMA regimens focus on safe and efficacious pain control in patients with HNC undergoing free flaps, we feel that extrapolating these regimens is appropriate for patients who undergo regional, local, or less complex reconstructions as well. **Fig. 1** (from Cramer and colleagues[5]), sets forth an MMA pathway that, based on current evidence, is safe for routine use in patients with HNC, with special considerations as detailed previously. We hope that more procedure-specific MMA regimens arise from ongoing research, particularly for the TORS patient population to address the paucity of reliable and effective opioid-sparing protocols for these patients.

Although opioids will continue to have a role in management of cancer pain, chronic pain, and acute postoperative pain, there is growing literature that provides insight to the prescribing patterns and direction on amount of these rescue analgesics for head and neck procedures.[39] Continued progress in developing optimal combinations, dosages, durations of perioperative analgesia medications, both opioid and nonopioid, is warranted and further exploration of topical, local, and regional anesthesia is still required.

DISCLOSURE

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