Nonenteral Pain Management

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KEYWORDS

• Nonenteral • Analgesia • Pain • Adjuncts • Otolaryngology

KEY POINTS

- Otolaryngologic surgeries provide unique challenges to postoperative pain management as the location and nature of the surgeries may make enteral medication administration difficult or impossible.
- Several nonenteral routes of administration exist, including intravenous, transdermal, subcutaneous, and rectal.
- There are a multitude of medications that are available in nonenteral formulations, including acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, and ketamine.
- Nonenteral opioids can be delivered as intermittent intravenous boluses, patient-controlled analgesia, or transdermal patches.
- Even when limited to nonenteral medications, a multimodal approach with opioids and adjuncts can provide appropriate analgesia for the otolaryngologic patient.

INTRODUCTION

Adequate postoperative pain control in patients undergoing otolaryngologic (ENT) surgeries is a key component of their postoperative care. However, pain management in these patients poses unique challenges to their physicians given the location of the surgical site and the nature of the procedures. Postoperatively, many ENT procedures may impose certain anatomic limitations that make oral intake impossible or contraindicated, often requiring prolonged nil per os (NPO) status to protect against postsurgical bleeding or aspiration events. Given these barriers to enteral access, these patients are at greater risks for poor postoperative pain control, which could have short-term and long-term consequences. Effectively managing pain can have significant benefits in avoiding postoperative complications, such as infections, deep vein thrombosis, poor wound healing, and prolonged hospitalization,[1] while expediting successful functional recovery. The key to achieving adequate postoperative pain

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Otolaryngol Clin N Am 53 (2020) 853–863
https://doi.org/10.1016/j.otc.2020.05.014
oto.theclinics.com

lies in understanding and using various medications with nonenteral routes of administration. This article aims to review different nonenteral routes and medication groups that could be used via these routes in patients after ENT surgery with restricted enteral access to improve postoperative pain management.

ROUTES OF NONENTERAL DRUG ADMINISTRATION

Enteral drugs use the gastrointestinal (GI) tract as the primary site of absorption and is the most commonly used route for drug administration. Nonenteral routes of administration avoid the GI tract completely, often owing to limitations on oral intake, lack of enteral drug formations, or lack of a functioning GI system. Safety, efficacy, pharmacodynamics, and patient preference must be taken into account before choosing the most appropriate route of administration. In this article, we review the intravenous, subcutaneous, transdermal, and rectal routes of administration and highlight the advantages and disadvantages of each route.[2]

Intravenous

The intravenous method of administration involves injecting drugs directly into the systemic venous circulation. Many drugs have formulations that allow them to be given intravenously. It is an effective and rapid method to achieve adequate analgesic concentrations in the systemic circulation. Drugs given intravenously also have 100% bioavailability because they bypass many of the metabolic and absorptive barriers encountered through the enteral route, also known as first-pass metabolism. Patients can also be placed on infusions that allow short-term, long-term, and titratable pain control. Other advantages include decreased irritation at the site of injection, decreased cost, lower volumes needed to achieve proper analgesia, and rapid exposure of the drug to its target organs. However, clinicians should also weigh the potential disadvantages. The intravenous route of administration requires an adequate functioning cannula for access, can be labor intensive compared with other routes, is unforgiving to dosing errors, and is also prone to line infections with long-term use. Certain medications can irritate the veins and lead to phlebitis. Lastly, although intravenous medications can be an excellent option while the patient is admitted, the logistics of outpatient use make it a poor long-term option in most cases.

Subcutaneous

Subcutaneous injection is another mode of administration of analgesic medications that can be used for patients with limited enteral access. The drug is injected or implanted beneath the surface of the skin known as the cutis, a layer of skin directly below the dermis and epidermis. Subcutaneous tissue absorption is slower than intravenous owing to the reduced vasculature surface area supplying this region, while still able to obtain 100% bioavailability. Typically, 25- to 31-gauge needles are used to inject the medication, with medication volumes not exceeding 2 mL. Common injection locations include the outer area of the upper arm, abdomen, thigh, upper back, and buttocks.[3]

Transdermal

The transdermal route of administration provides an effective method to administer medications that is noninvasive and has a relatively better safety profile as compared with intravenous administration. Many medications may be administered transdermally including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, local anesthetics, and even antidepressants.

The most obvious benefit of transdermal opioids is that it allows a total bypass of the GI tract when either there is a problem with absorption or, for the purposes of ENT surgeries, the GI tract may be unavailable. Transdermal release of opioids provides a steady concentration of the drug in the plasma, thus avoiding large fluctuations and providing a consistent level of analgesia. Other benefits include simplicity of administration, potential for long-term outpatient use, and improved quality of life.[4]

Rectal

The final route of administration we briefly discuss is the rectal route, which may also be considered when enteral administration is contraindicated. There are many different medications that have rectal formulations including laxatives, acetaminophen, NSAIDs, antiemetics, benzodiazepines, and opioids. The benefits of the rectal route of administration include allowing for delivery of medications that have poor stability or solubility that would be unable to tolerate the physiologic environment of the stomach and GI tract, low cost of rectal formulation of most medications, and ease of administration that does not require a health care provider. However, patient discomfort and/or refusal of rectal administration limits their practical use in the perioperative setting.[5]

ACETAMINOPHEN

Acetaminophen is a common, effective, and safe medication used as an over-the-counter pain reliever for daily life, but also plays an important role in multimodal analgesia in the perioperative setting. Unlike NSAIDs, another very common over-the-counter analgesic, acetaminophen does not interfere with platelet function or cause adverse reactions in patients with asthma or peptic ulcer disease. Although the mechanism of action is not entirely clear, it is thought to selectively inhibit cyclooxygenase in the central nervous system, although this inhibition is absent in the peripheral nervous system and stomach, accounting for its decreased incidence of ulcers and platelet interference. It has been proposed that the analgesic effects of acetaminophen come from agonism on the cannabinoid receptors, leading to increased levels of endogenous cannabinoids and results in analgesia and a sense of well-being.[5,6] Acetaminophen is available for various routes of administration including oral, intravenous, and rectal. The uptake of acetaminophen is the greatest via the intravenous route with very little absorption occurring via the GI tract. However, some studies suggest that there is not increased bioavailability with intravenous use compared with oral. One review article analyzed 6 randomized clinical trials and found that the bioavailability of 1000 mg of oral acetaminophen was 89% and concluded that there is no clear indication for intravenous acetaminophen over oral when a patient has a normally functioning GI tract. However, the intravenous formulation has a much faster onset of action and results in higher plasma concentrations of the drug, resulting in greater patient satisfaction and perceived pain relief as compared with oral administration. This review article found that intravenous acetaminophen decreased pain by 50% in 37% of patients and decreased opioid use by 30% at 4 hours and 16% at 6 hours.[7] A Cochrane review of 20 randomized, double-blind, placebo-controlled clinical trials found that the number needed to treat to achieve 50% pain relief after a single 1000-mg dose of acetaminophen as compared with placebo was 4.6 demonstrating acetaminophen's superiority to placebo and effectiveness as a stand-alone analgesic. Not only can acetaminophen be used alone, but when combined with other analgesics, such as opioids, a greater analgesic effect can be achieved. This same Cochrane Review showed that, in patients with moderate to severe acute postoperative pain, oral oxycodone at doses of more than 5 mg had greater

efficacy and longer lasting analgesia when combined with acetaminophen.[8] Owing to its low side effect profile, efficacy, and ability to be given nonenterally, acetaminophen is a useful perioperative analgesic for ENT surgeries.[9]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are among the most common and effective nonopioid analgesic medications used not only over the counter, but also in the perioperative setting. There are many different types of nonselective NSAIDs including salicylates, proprionic acids, pyrazoles, acetic acids, oxicams, fenamates, and napthyl-alkanones, which all act by reversibly inhibiting cyclooxygenase 1 and 2, which is responsible for prostaglandin synthesis. Arachidonic acid is released from tissues as a result of damage, which is subsequently metabolized into prostaglandins that then lower the pain threshold and cause pain. The mechanism of action of NSAIDs is due to the inhibition of cyclooxygenase and, therefore, decreased prostaglandin synthesis.[9,10] NSAIDs also have a variety of routes of administration, including oral, intravenous, and transdermal, and have been used as local infiltration as the site of wounds or surgical incisions and even intranasally.[10] Intravenous ketorolac is the most common nonparenteral NSAID used postoperatively and intranasal ketorolac has recently been approved for use and has been shown to have effective analgesia in the postoperative setting.[11] The maximum dose of intravenous ketorolac is 30 mg every 6 hours for a maximum of 5 days. This dose should be decreased to 15 mg in patients age 65 or older. NSAIDs have been clearly shown to have superior analgesic effects as compared with acetaminophen in dental surgery with one review article demonstrating 8 studies that found NSAIDs were superior to acetaminophen in regards to pain scores postoperatively.[12] One systemic review found that NSAIDs, when given postoperatively, were effective in decreasing opioid requirements by 20% to 35% and also decreased the side effects of opioids, such as nausea, vomiting, and sedation.[11,13] Despite their effectiveness, NSAIDs do not come without risks. Chronic use of NSAIDs can commonly cause gastric ulcers and interfere with platelet inhibition, which is associated with a higher bleeding risk. However, short-term use of NSAIDs in the perioperative setting in terms of platelet inhibition and increased bleeding risk is less well-studied. Decreased prostaglandin synthesis may also be associated with impaired bone healing and acute renal injury. Cyclooxygenase-2 specific inhibitors, such as celecoxib, have a lower side effect profile, because the specificity of these drugs have little to no effect on platelet aggregation and the GI tract. They also offer similar analgesic profiles to nonspecific NSAIDs.[9–11] However, their role in the postoperative period, and especially for ENT surgeries, is limited because currently all available formulas in the United States are oral medications. Parecoxib has been approved in Europe and is available in the intravenous formulation; however, it has not been approved by the US Food and Drug Administration. NSAIDs are an effective analgesic class in the postoperative setting for ENT, especially dental surgeries.

OPIOIDS

ENT patients with significant acute postoperative pain or with chronic pain from an anatomic defect or malignancy would likely benefit from the use of opioid medications for analgesia. Opioid agonists such as hydrocodone, oxycodone, morphine, and many others act primarily at the mu-opioid receptor to provide analgesic effects. Although many opioids are administered orally, there are intravenous, intramuscular, intranasal, transdermal, and neuraxial formulations[14] available for patients who are physically unable to take the medications by mouth. In this discussion, we focus on intravenous and

transdermal options, which are more commonly used and more pertinent to the otolaryngology patient population. As a word of caution, the recommendations provided do not account for specific patient comorbidities and may not be appropriate for patients with complex pain pathology, such as patients with a history of high-dose opioid use, opioid abuse disorder, or central pain disorders. In managing patients with a history of chronic pain, it is imperative to involve their outpatient chronic pain physicians and develop individualized pain management plans. Furthermore, in the inpatient setting, patients with high opioid requirements at baseline may benefit from consultations with the acute pain service, supportive care service, or similar services within the hospital that have experience managing patients with complicated pain.

In the postoperative setting, intravenous delivery of opioid medications is one of the most common methods of pain management. Especially in patients with difficulties with swallowing or with residual effects of anesthesia putting them at risk for aspiration, the intravenous route can provide analgesia reliably, quickly, and effectively. Intermittent boluses of opioid agonists such as morphine, hydromorphone, or fentanyl can be requested by the patient and delivered by the nursing staff. However, intermittent boluses typically require a significant dose of opioid per bolus as well as a greater demand on the nursing staff to both deliver the medication and to monitor for sedation and respiratory depression. This strategy is typically most appropriate in the postanesthesia care unit where close monitoring by the nursing staff is standard. Reliance on intermittent opioid boluses on the inpatient units, where there is typically a lack of continuous pulse oximetry and higher patient-to-nurse ratios, may lead to inadequate analgesia or greater adverse events.

For inpatient floor patients, a patient-controlled analgesia (PCA) device can provide immediate analgesia, at lower bolus doses, without requiring an increased nursing workload.[15,16] A PCA device for intravenous medications, most commonly opioids, involves the use of a microprocessor-controlled infusion pump[15] that delivers a preset amount of medication when activated by the patient. The medications used in PCAs are commonly pure mu-opioid agonist such as morphine, hydromorphone, and fentanyl, given their relatively rapid onset of action, high efficacy, and intermediate duration of action.[14]

The advantages of PCA use for postoperative pain management include patient autonomy, medication dosing as frequently as every 6 minutes and a consistent level of analgesia by avoiding peaks and troughs in medication plasma concentration.[15] By design, the PCA is intended to be activated by the patient, to decrease the risk of another individual overmedicating an already sedated patient. With increased sophistication of PCA devices, there is detailed tracking of opioid usage and may be real-time monitoring of end-tidal carbon dioxide as a proxy for adequate ventilation. The primary disadvantage of PCA usage is the lack of analgesic coverage while the patient is asleep, given the short to intermediate duration of action of the medications, which may result in uncontrolled pain once the patient awakens.[14]

PCA use is not appropriate for every patient, making it important to evaluate each individual for potential limitations. In particular, PCA use requires the patient to be cooperative with the ability to follow instructions, which can be difficult for young children, mentally delayed adults, patients with dementia or delirium, and those with a physical disability that would prevent manual activation of the PCA button. Even in able-bodied adults, an understanding of the duration of action of the medications and the lock-out interval is important for managing expectations and overall success of the pain management plan.

There are several important variables that determine how opioids are delivered by a PCA device. The most common parameters are demand dose, lock-out interval, and 1-hour maximum dose. Descriptions of these parameters are summarized in **Table 1**,

Table 1
Parameters, descriptions, and ranges related to PCA for various opioids

Parameter	Descriptions	Range
Initial loading dose	One-time dose at the time the PCA is started	Morphine: 1–3 mg Hydromorphone: 0.25–1 mg Fentanyl: 25–50 μg
Demand dose	Drug-specific amount delivered at the lock-out interval	Morphine: 0.5–2.5 mg Hydromorphone 0.1–0.5 mg Fentanyl: 5–25 μg
Lock-out interval	Minimum time between demand doses	5–20 min
1-Hour maximum dose	Maximum dose of medication that can be delivered within 1 h	Typically, total calculated by demand dose × doses per hour
Basal rate	Continuous infusion, delivered without patient activation. Consider for opioid tolerant patients	Depends on chronic opioid usage
Nursing bolus	Intermittent doses that can only be administered by nursing staff, to allow patient to "catch up"	Typical 2–3× demand dose, every 2–4 h

along with commonly used values to which they are set based on cited publications and various institutional protocols including Emory University and MD Anderson Cancer Center.[14,15,17] It is typically prudent to start at a lower dose before uptitrating the settings based on the patient's response. For example, a typical starting hydromorphone PCA order set includes a demand dose of 0.2 mg, every 6 minutes, with a 1-hour maximum dose of 2 mg. If the patient has a tolerance to opioids, they may require a higher regimen, with the goal of eventually weaning the PCA and transitioning to an oral regimen before patient discharge. In some instances, if their chronic opioid use is greater than 60 mg oral morphine equivalents, a continuous rate on the PCA or a separate long-acting medication can be added to the regimen to provide a basal analgesic effect. However, a continuous basal rate may detract from the safety of PCA. Without a continuous basal rate, if a patient becomes overly sedated, the patient stops pushing the demand button and stops receiving further opioid. With a continuous basal rate, a sedated patient would continue to receive opioid. Therefore, caution is recommended with continuous basal rate infusions.

One intravenous option for a long-acting opioid is methadone, a synthetic mu-receptor agonist, serotonin reuptake inhibitor, and N-methyl-D-aspartate (NMDA) receptor antagonist.[14,18] It has a variable half-life that is likely due to several factors, including lipophilicity and distribution, and results in a biphasic elimination pattern. Owing to an alpha elimination of 8 to 12 hours, methadone can provide analgesia for 6 to 8 hours after administration, and the beta elimination period of 30 to 60 hours allows for prevention of opioid withdrawal for greater than 24 hours.[14,18] As a result, methadone for analgesia should be dosed every 8 hours, whereas methadone for maintenance therapy for opioid or heroin addiction is dosed daily. For patients on chronic oral methadone therapy, conversion to intravenous has traditionally been a 2:1 ratio, although some providers have found a 1:0.7 ratio[19] to be more appropriate. However, with these patients it is highly recommended that the primary service obtain assistance from the acute pain service regarding an appropriate regimen so as to

minimize respiratory depression and monitoring for QTc changes on the electrocardiogram. Even for patients naïve to methadone, several double-blinded randomized controlled trials have found intraoperative methadone use to be associated with reduced postoperative opioid requirements, decreased pain scores, and patient perception of pain management in cardiac surgeries[20] and spinal fusion.[21] This finding suggests that methadone can be a viable medication in the management of postoperative pain, possibly in other specialties including otolaryngology, although more research is needed to determine appropriate dosing, rate of respiratory depression, and whether there is a decrease in chronic postsurgical pain.[22]

One alternative to the use of a long-acting opioid such as methadone is to use an opioid that can be continuously delivered via a transdermal patch. Of the options on the market currently, two of the most commonly used are buprenorphine patches and fentanyl patches. Buprenorphine is a partial agonist at the mu opioid receptor, with a ceiling effect on respiratory depression but not on its analgesic properties.[23] At higher doses, buprenorphine has traditionally been used for treatment of and maintenance therapy for opioid use disorder. Recent research including a metanalysis of randomized controlled trials has shown that buprenorphine can provide noninferior analgesia for acute pain compared with traditional opioids.[24] In the transdermal formulation, branded as Butrans,[25] buprenorphine is a nonenteral option for postsurgical patients. Available doses for buprenorphine transdermal patches are 7.5 μg, 10 μg, 15 μg, and 20 μg/h patches, to be worn for 7 days before replacing.[25] However, even at the highest dose, the analgesic effect is limited and may not be appropriate for patients requiring more than 80 mg of oral morphine equivalents per day.[25]

Fentanyl is a high potency mu opioid agonist[26] that can be found in a transdermal patch and has been used for management of acute and chronic pain. Fentanyl patches have doses ranging from 12 μg/h up to 100 μg/h, which is equivalent to 30 to 240 mg of oral morphine equivalents per days, approximately, according to the Medicare opioid conversion table.[27] As a result, fentanyl patches can provide significantly higher opioid effects as compared with buprenorphine patches. Owing to its pharmacokinetics, the analgesic effect may be delayed by up to 12 hours after the initiation of the patch and the patch should be changed every 72 hours.[4] Owing to the delayed onset, fentanyl patches may be difficult to titrate in response to fluctuating acute postoperative surgical pain, but can provide the basal opioid level for opioid-tolerant patients.[4] It is important to be aware that skin temperature impacts the rate of absorption, meaning that febrile patients or those using external heating apparatuses may have increased levels of fentanyl.[4] Fentanyl patches also contain significantly higher amounts of drug product than what is delivered to the patient, so patches should never be tampered with or cut and used patches should be disposed of responsibly. Fentanyl can also be found in intranasal, buccal, and sublingual formations, although these avenues are used less frequently.

KETAMINE

The use of ketamine in multimodal analgesia in the postoperative setting has been rapidly gaining popularity owing to its efficacy and low side effect profile. Ketamine was first developed in 1970 and functions as an NMDA receptor antagonist, which blocks nociceptive and inflammatory pain transmission.[28] During tissue injury, glutamate is released from the dorsal horn of the spinal cord and upregulates the release of proinflammatory cytokines via binding of the NMDA receptor which leads to acute pain and ultimately central sensitization, opioid-induced hyperalgesia, and opioid tolerance. By acting as an NMDA receptor antagonist, ketamine has a role not only

Table 2
Mechanism of action and common dosages of several nonopioid medications and nonintravenous opioid formulations

Medication	Analgesic Mechanism of Action	Common Dosages
Acetaminophen	Selectively inhibits cyclooxygenase in CNS Agonism of cannabinoid receptors	IV: 1000 mg every 8 h PR: 650 mg every 4–6 h
NSAIDs	Nonselective: reversibly inhibit cyclooxygenase 1 and 2 Selective: selectively inhibit cyclooxygenase	Ketorolac 15–30 mg IM or IV every 6 h No cyclooxygenase-2 inhibitor is available for IM or IV administration
Fentanyl	Selective mu-receptor agonist	Transdermal: 12–50 μg/h reapplied every 72 h
Buprenorphine	Partial mu-receptor agonist	Transdermal: 5–20 μg/h, reapplied every 7 d
Ketamine	NMDA receptor antagonist	IV infusion: 0.1–1.2 mg/kg/h

Abbreviations: CNS, central nervous system; IM, intramuscular; IV, intravenous; PR, per rectum.

in the prevention of pain in the acute setting, but also in chronic pain conditions as well.[9] There have been multiple studies evaluating the effectiveness of ketamine for analgesia in the perioperative setting. A 2015 review article evaluating 39 clinical trials found that low-dose ketamine infusions with a rate of less than 1.2 mg/kg/h decreased opioid consumption by as much as 40% and decreased pain scores.[28] In a review article from 2011 that evaluated 70 randomized, double-blind, and placebo-controlled studies and involved 4701 patients, it was found that ketamine had an opioid-sparing effect that was most profound in more painful surgeries and surgeries that involved the upper abdomen and thorax. Disappointingly, this study found no significant opioid-sparing effect for tonsillectomies or head and neck surgeries.[29] However, a 2014 meta-analysis by Cho and colleagues[30] that examined children undergoing tonsillectomy found that preoperative local or systemic administration of ketamine before tonsillectomy had a statistically significant decrease in postoperative pain, decreased postoperative analgesic requirements, and increased time to first analgesic requirement without adverse side effects, including nausea, vomiting, sedation, or psychomimetic manifestations. Ketamine not only has a role in pain management in the opioid-naïve patient, but is also an excellent choice for opioid-dependent patients for whom standard postoperative pain regimens are ineffective. A study conducted by Loftus and colleagues[31] observing 101 opioid-dependent patients undergoing spinal surgery found that patients who received a bolus of ketamine followed by a low-dose infusion of 0.1 μg/kg/min had a nearly 40% decrease in morphine consumption over a 48-hour period and also reported 26% lower pain scores 6-week after surgery. Although the use of ketamine in the perioperative setting may have limited effectiveness for ENT surgeries in the opioid-naïve adult, it has been shown to be beneficial in children receiving ENT surgeries, specifically tonsillectomies, by reducing opioid consumption and has been shown to have a role in reducing opioid requirements in opioid-tolerant adults.

SUMMARY

ENT surgeries provide unique challenges to ensuring adequate postoperative pain control owing to the location and nature of surgeries that may require patients to be

NPO for prolonged periods of time, and that make enteral medication administration difficult or impossible. The are many alternative routes of medication administration that bypass the GI tract and are effective in the perioperative setting, such as intravenous, transdermal, subcutaneous, and rectal administration. Opioids remain an effective analgesic in the perioperative setting, but a multimodal approach to analgesia is paramount for providing safe and effective pain control. For chronic pain, guidelines from the Centers for Disease Control and Prevention recommend that, if opioid therapy is initiated, the clinician should prescribe an immediate release opioid instead of extended release opioid.[32] **Table 2** summarizes the mechanism of action and common dosages of various nonopioid medications as well as several transdermal opioid formulations. Application of a combination of opioid delivery via intravenous boluses, PCA, or transdermal patches along with the addition of adjuncts such as acetaminophen, NSAIDs, and/or ketamine can lead to improved analgesia, decreased opioids consumption, and increased patient satisfaction after ENT surgery.

DISCLOSURE

The authors have nothing to disclose.

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