



Opioid prescribing and consumption after head and neck free flap reconstruction: what is the evidence for multimodal analgesia?

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All opioids carry a risk of dependence, substance use disorder, and fatal overdose (1), and risk increases in proportion to the duration of opioid exposure (2). For patients with advanced head and neck cancer requiring ablative surgery and microvascular free tissue reconstruction, the risk of developing opioid use disorder is amplified by both the complexity of treatment and the prolonged recovery often required. Chronic opioid use is reported by 41–64% of head and neck cancer patients at 3 months after treatment (3,4). Although some patients receive opioid analgesia preoperatively for cancer-related pain, many patients undergoing head and neck cancer surgery have their initial exposure to opioids during or after surgery. In recent years, a growing number of investigators have investigated strategies to minimize persistent opioid use in this patient population, with an emphasis on opioid-sparing or reducing regimens.

Multimodal analgesia after free-flap reconstruction

Go *et al.* recently conducted a systematic review of multimodal analgesia in head and neck free flap reconstruction (5). They identified 10 studies including 1,253 patients (594 multimodal analgesia patients and 659 controls). These studies included 2 randomized controlled trials, 1 prospective matched cohort study, and 7 retrospective studies. The multimodal analgesia strategies were

heterogeneous, variously including gabapentin (73%), nonsteroidal anti-inflammatory drugs (NSAIDs; 45%), acetaminophen (44%), corticosteroids (25%) and ketamine (7%), as well as lower extremity nerve blocks (3%). Four studies used preoperative analgesia (acetaminophen and/or gabapentin and/or meloxicam/celecoxib and/or tramadol).

This synthesis of available studies highlights the potential benefits of multimodal analgesia in head and neck free flap reconstruction but also underscores the need for nuanced approaches. Multimodal analgesia significantly reduced perioperative opioid consumption in 8 of 10 studies, and one study found that multimodal analgesia reduced hospital length of stay from 10.6 to 7.8 days (6). Among the studies that did not achieve a reduction in postoperative opioid use, nonsteroidal anti-inflammatory drugs (NSAIDs) were not part of the standardized approach to analgesia. Townsend *et al.* investigated the effect of adding gabapentin 300 mg PO Q12 on postoperative days 0–3 and observed no effect on opioid consumption, consistent with the relatively weak analgesic efficacy of gabapentin described in another large systematic review and meta-analysis of postoperative pain (7). Schleiffarth *et al.*'s retrospective study used NSAIDs primarily for antiplatelet therapy (8), rendering it inconclusive.

The study by Schleiffarth *et al.* (8) was not designed as an investigation of multimodal analgesia, and its findings must be interpreted with particular attention to this context. One microvascular surgeon used ketorolac for antiplatelet

function, another used aspirin 325 mg as an antiplatelet agent, and a third did not use any antiplatelet agents; nowhere in the study is multimodal analgesia mentioned, so interpretations regarding analgesic outcomes related to NSAIDs are constrained. Also, the number of bone flaps was 40.5% in the ketorolac group versus 23% in the comparison group. When the authors controlled for bone flaps, aspirin use, and age, patients in the ketorolac group consumed 12 fewer morphine milligram equivalents per day, although the underpowered sub-analysis fell short of statistical significance ($P=0.07$). The challenges inherent in interpreting this study and the paucity of randomized studies in the literature emphasize the need for more prospective investigation on multimodal analgesia.

Gabapentin

Gabapentin has prompted more controversy than perhaps any other component of multimodal regimens. Gabapentin is FDA approved only for postherpetic neuralgia/seizures and not for postoperative pain; however, it has been extensively studied in the postoperative setting. Gabapentin is currently the most commonly employed analgesic agent in studies of multimodal analgesia after head and neck microvascular surgery (5). Gabapentin was administered as a single preoperative dose in four studies, and postoperatively in three studies (5). Verret *et al.* conducted a meta-analysis of 281 randomized controlled trials of gabapentin in the postoperative setting (24,682 patients) (7). Similar with Go *et al.*, these trials frequently examined gabapentin in the context of multimodal analgesia with 68% of trials examining the effectiveness of a single preoperative dose of gabapentin.

These analyses led to significant reappraisal of the role and risk-benefit tradeoffs of administering gabapentin. Gabapentin led to a statistically significant reduction in opioid consumption (-7.9 mg, CI: -8.8 to -7.0 mg) and postoperative nausea/vomiting (OR 0.77, CI: 0.72 to 0.82); however, the effect size for differences in acute pain were not clinically significant, nor was reduction in chronic post-surgical pain. These findings reflect the limited efficacy of gabapentin for postoperative pain. A Cochrane review of the efficacy of a single dose of gabapentin found that the number needed to treat (NNT) to reduce acute postoperative pain by 50% with gabapentin was 11 (95% CI: 6.4 to 35) (9). Gabapentin was associated with increased dizziness (OR 1.25, CI: 1.13 to 1.39) and visual disturbance (OR 1.89, CI: 1.53 to 2.33). Gabapentin also has risks of

sedation and addiction.

NSAIDs

NSAIDs were the second most common category of analgesic employed in multimodal analgesia strategies for head and neck free flap reconstruction. Meta-analysis of randomized trials supports combination acetaminophen and NSAIDs as among the safest and most efficacious combination strategies for acute postoperative pain (9,10). For example, the combination of ibuprofen 400 mg and acetaminophen 1,000 mg has a number needed to treat to reduce acute postoperative pain by 50% of 1.5 (CI: 1.4 to 1.7), significantly better than combination oxycodone 10 mg and acetaminophen 650 mg (NNT 2.7; CI: 2.4 to 3.1) (9). Head and neck free flap reconstruction carries a high risk for postoperative bleeding, but also a high risk of anastomotic thrombosis, either of which can jeopardize flap survival. Whereas NSAIDs appear not to affect flap survival (11), the benefits of reducing opioid prescribing are pronounced (12-14).

While the favorable safety profile of NSAIDs in head and neck surgery and many other otolaryngology procedures is reassuring, surgeons should nonetheless have a nuanced understanding of medication-related bleeding risk. There are several categories of NSAIDs available. These NSAIDs include nonselective COX-1 and COX-2 inhibitors like ibuprofen; preferential COX-2 inhibitors like meloxicam; and selective COX-2 inhibitors like Celebrex. Selective COX-2 inhibitors do not increase risk of bleeding, whereas NSAIDs with strong COX-1 inhibition impair platelet function, with the potential to affect rates of bleeding, although such effects are not always detectable clinically (15).

Previous retrospective research not included in the systematic review has suggested that use of nonselective NSAIDs preoperatively or postoperatively is associated with increased risk for bleeding/hematoma in head and neck free flap reconstruction (16,17). Among the studies included in the systematic review by Go *et al.*, a variety of categories of NSAIDs were used including selective COX-2 inhibitors (celecoxib in four studies), partially selective COX2 inhibitors (meloxicam in one study), non-selective NSAIDs (ketorolac and ibuprofen in one study each) and aspirin (one study). None of the studies included in the review that used NSAIDs identified any increased risk of bleeding/hematoma or flap failure (5). However, the majority of data in the systematic review are based on selective COX-2 inhibitors.

The limited data and heterogeneous dosing regimens

preclude firm conclusion; however, a conservative interpretation of available evidence is that COX-2 inhibitors do not increase risk of bleeding, hematoma, or flap compromise in head and neck free flap reconstruction. More prospective data are needed to discern whether nonselective NSAIDs affect complications rates. Data from large meta-analyses in other surgical specialties point to a slightly increased risk of bleeding (OR 1.2) with non-selective NSAIDs; however, as bleeding is relatively infrequent, the absolute increased risk is small (18). Surgeons who are particularly concerned about the risk of bleeding may therefore prefer selective COX-2 inhibitors.

Standardizing multimodal analgesic practices

Perioperative pain management strategy in the head and neck population seems fraught with heterogeneity: patients differ in head and neck cancer site and stage, undergo many types of reconstructive procedures, and have a wide range of morbidities. To further complicate this picture, individuals with prior exposure to opioids add another layer of difficulty. The data support evidence-based, multimodal analgesia as the most promising strategy for improving pain management, but how can standardization be achieved?

An integrated approach to multimodal analgesia provides the surest path to best practices. It begins with engaging key stakeholders and collecting data on patient opioid consumption and patient-reported outcomes of pain management. Tracking clinician prescribing is equally critical. Knowledge of risk factors for either opioid use disorder or inadequate analgesia can further refine practice (12,19). Successful initiatives often apply a quality improvement lens, leveraging the data generated from routine practice across iterative improvement cycles (20). Ideally, there are also provisions that allow for high-risk patients to be connected to a specialist in pain management who can tailor therapy as necessary.

Ultimately, multimodal analgesia in head and neck cancer reconstruction is a highly collaborative endeavor that involves partnership across disciplines. Incorporating nurses, allied health professionals, and patients and families alongside surgeons and anesthesiologists improves care. Multidisciplinary approaches are particularly valuable in patients with tracheostomy or other complex needs (21,22). Furthermore, engaging learners is a key step in application of quality improvement initiatives (23,24) and affords the opportunity of cultivating future champions for effective opioid stewardship. Best practice in perioperative

management of head and neck surgery patients continues to rely heavily on consensus expertise (25). As the evidence base mature and cancer care evolves through advances surgery and chemoradiotherapy ongoing tailoring of approaches will be necessary.

Conclusions

The evidence base supports use of multimodal analgesic regimens after major head and neck surgery but also leaves us with more questions than answers. Multimodal analgesia can safely reduce perioperative opioid consumption without increasing pain or complications after head and neck free flap reconstruction. However, the heterogeneity both within and between studies highlights the need for a pathway for developing postoperative opioid prescribing best practices (20). Acetaminophen and NSAIDs-based regimens provide a reliable backbone for multimodal analgesia, with a less well-defined role for gabapentin and other adjuvant analgesics. Although gabapentin is modestly effective as an analgesic, the improvement in pain control is not necessarily clinically significant. Furthermore, gabapentin can be addictive and frequently causes dizziness, visual disturbances, and sedation. Limited evidence supports a role of corticosteroids, ketamine, and lower extremity nerve blocks. The optimal multimodal is as yet undetermined, and analgesic strategies will change as head and neck cancer care evolves.

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