Multimodal Analgesia Protocol after Head and Neck Surgery: Effect on Opioid Use and Pain Control

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No sponsorships or competing interests have been disclosed for this article.

Abstract
Objective. To assess the effect that implementation of a multimodal analgesic plan has on opioid requirements and pain control in head and neck (H&N) surgery patients.

Study Design. Prospective cohort.

Setting. Tertiary academic hospital.

Subjects and Methods. An institutional review board (IRB)–approved quality improvement initiative was undertaken to implement a multimodal analgesic protocol for all admitted H&N surgery patients starting November 2017. Postprotocol data from January to May 2018 were compared to preprotocol data from May to October 2017. Data were obtained from the electronic health records as well as through preoperative and postoperative surveys. Average pain scores and opioid use in morphine milligram equivalents (MMEs) before and after protocol implementation were compared.

Results. In total, 139 postprotocol patients were compared to 89 preprotocol patients. The adjusted MMEs in the first 24 hours after surgery decreased significantly from 93.7 mg to 58.6 mg (P = .026) with protocol implementation. When averaged over the length of stay (MME/hospital day), the change was no longer statistically significant (57.9 vs 46.8 mg, P = .211). The average pain score immediately after surgery and on day of discharge did not change with protocol implementation.

Conclusion. Implementation of a multimodal analgesic plan reduced opioid use immediately after surgery but not over the course of hospitalization without any change in reported pain scores. This study shows that multimodal opioid-sparing analgesia after H&N surgery is feasible. Future studies are needed further refine the optimal analgesic strategy for H&N patients and assess the long-term efficacy, safety, and cost of such regimens.

Keywords
multimodal analgesia protocol, opioid, pain control, head and neck surgery

Adequate pain control after surgery is important but can be difficult to achieve in some patients. Furthermore, the benefits of pain medications must be balanced against their potential adverse effects. In the United States, opioid medications are commonly used for postsurgical analgesia, but their use carries risk of adverse events, abuse, and dependence. Pain specialists and anesthesiologists advocate the use of multimodal pain regimens to reduce postsurgical opioid requirements. Multimodal analgesia (MMA) is the “use of a variety of analgesic medications and techniques that target different mechanisms of action in the peripheral and/or central nervous system for postoperative pain.”1 Previous systematic reviews found that the addition of other agents, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclo-oxygenase 2 (COX-2) inhibitors, decreased morphine use.2,3 A large-scale review of total hip replacement and knee arthroplasty patients found that use of additional analgesic modes was associated with fewer respiratory and gastrointestinal complications and a decrease in opioid prescription in a stepwise fashion.4 The authors recommended use of MMA in perioperative analgesic protocols but noted that the optimal regimen is unknown.

MMA studies, to date, have largely focused on general surgery and orthopedic procedures.1 However, the benefits of MMA have been extrapolated to head and neck (H&N)
procedures. A randomized controlled trial of mucosal H&N surgery patients found that perioperative gabapentin (300 mg twice daily) had no effect on opioid usage but some benefit in terms of pain score. Another recent retrospective, matched-control study showed that postoperative treatment with celecoxib decreased opioid use after H&N procedures involving free tissue reconstruction. To our knowledge, only 1 study has specifically looked at MMA in H&N patients. Oltman et al reported that at their institution, 64 of 222 (29%) patients undergoing outpatient H&N surgical procedures elected MMA for pain control. Of these patients, 39 avoided postoperative opioid medications completely. The objective of this study is to see if implementation of MMA after H&N surgery decreases inpatient opioid requirements.

Methods

Patient Selection

A prospective continuous quality improvement (CQI) initiative with institutional review board approval from the University of North Carolina—Chapel Hill was used to collect data between May 2017 and May 2018. All adult patients undergoing surgery with 1 of 6 H&N surgeons during this time period were included. H&N procedures included all soft tissue neck surgeries and surgeries involving the oral cavity, pharynx, and larynx. Free tissue transfer or local flap reconstruction after oncologic ablative procedures was also included. Surgeries that only involved tonsillectomy or endoscopic procedures such as direct laryngoscopy were excluded. Baseline data were collected from May 1, 2017, to October 31, 2017. An MMA protocol was implemented for all H&N surgery patients on November 1, 2017. We allowed for a 2-month adjustment period for house staff and nursing to become familiar with the protocol. Postimplementation data were collected from January 1, 2018, to May 31, 2018.

MMA Protocol

The MMA plan was developed and agreed upon by all surgeons in the Division of Head and Neck Surgery. Given the diverse range of surgeries, we stratified procedures by extent of surgery and anticipated length of stay. Procedures such as thyroidectomy, parathyroidectomy, parotidectomy, lymph node excision, and neck mass excision, which can be done on an outpatient basis or with a short hospitalization (<3 days), were defined as “minor” H&N procedures. Procedures such as glossectomy, partial or total pharyngectomy, mandibulectomy, total laryngectomy, and modified or radical neck dissection were defined as “major” H&N procedures. This division also correlated with intermediate and high levels of anticipated postoperative pain.

The MMA protocol included acetaminophen (1000 mg intravenously [IV] or 650 mg per os [PO] every 4-6 hours as needed for mild pain, 4-g/24-hour limit) and ketorolac (15 mg IV every 6 hours for 48 hours) for all patients after surgery. In addition, for major H&N surgery patients, pregabalin (100 mg PO) was given preoperatively on day of surgery and continued at a dose of 50 mg PO twice daily for 10 days. As needed (PRN) opioid pain medication was ordered at the discretion of the provider. At our institution, this often consisted of oxycodone (5 mg PRN every 4-6 hours) and morphine (2-4 mg IV) for breakthrough pain. Major H&N surgery patients received a hydromorphone patient-controlled analgesia (PCA) pump for the first 24 to 48 hours postsurgery before transitioning to oxycodone. The protocol did not restrict the amount of pain medication patients could receive, and medications could be modified at the discretion of the clinical care team. Medications were held when contraindicated or if there were concern for side effects.

Data Collection

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools at the University of North Carolina. REDCap is a secure, web-based application designed to provide an interface for valid data entry, audit trails for tracking and data manipulation, and export and import procedures.

A preoperative survey queried patients’ prior chronic pain, baseline levels of pain, baseline opioid medication use, and anticipated level of postsurgical pain. Patients’ age, sex, race, smoking status, medical history, medication use at time of surgery, pathology from surgery, and surgical procedures were abstracted from the electronic medical record (EMR). Patients were designated as having chronic pain if they had an EMR-documented diagnosis of chronic pain or reported it on the preoperative survey. Surgical procedures were categorized as either “minor” or “major” as delineated above.

Outcomes

The primary outcome was inpatient opioid use as measured by morphine milligram equivalent (MME) in the first 24 hours after surgery and MME per day averaged throughout the hospitalization (MME/hospital day [HD]). Our secondary outcomes were average EMR documented pain scores in the first 24 hours after surgery and on day of discharge.

Statistical Analysis

Descriptive statistics were used for patient, disease, and treatment characteristics. Bivariate analysis for pain score was performed using the 2-sample $t$ test for categorical variables and Pearson's correlation for continuous variables. Bivariate analysis for MME and MME/HD was performed using the Wilcoxon rank-sum test for categorical variables and Spearman's correlation for continuous variables. Preprotocol and postprotocol opioid use and pain scores were analyzed with intention to treat based on date of surgery. Multivariate analysis assessing opioid usage and pain scores between the 2 groups was performed with adjustment for age, race, smoking status, history of chronic pain, preoperative narcotic use, anticipated postoperative pain, surgical pathology, and extent of surgery. Statistical analysis was performed using STATA version 15.1 (StataCorp LP, College Station, Texas).

Results

In total, 365 patients were initially captured in the database. Of these, 145 were excluded for the following reasons:
due to surgery cancellations, 37 due to the nature of the procedure, 47 because they occurred in the 2-month washout period, and 52 because they were admitted for less than 24 hours. The washout period of 2 months (November and December 2017) allowed for providers to become familiar with the protocol so that postinterventional results would better reflect active protocol use. A total of 220 patients were included for study analysis: 131 before protocol implementation and 89 after protocol implementation, and 184 patients completed a preoperative survey for an overall response rate of 85%. The preoperative survey response rate pre- and postprotocol was 84% and 92%, respectively.

The characteristics of study patients are shown in Table 1. The cohorts of patients before and after protocol implementation were similar in age, race, and smoking status. There was a smaller proportion of females (37% vs 45%) and more patients undergoing “major” H&N procedures (71% vs 61%) in the postprotocol group. There was no significant difference between the 2 groups in terms of mean length of hospitalization or complications requiring return to operating room. After protocol implementation, use of postoperative acetaminophen increased from 81% to 92%, and use of postoperative ketorolac increased from 10% to 67%. In patients undergoing major H&N procedures, 61% of patients received perioperative pregabalin postprotocol implementation compared to 13% preprotocol.

Opioid use, as measured by MME in the first 24 hours after surgery and averaged over the course of the hospitalization (MME/HD), was examined. The distributions for both MME in the first 24 hours and MME/HD were both strongly positively skewed. The median opioid use in the first 24 hours was 48.0 mg (interquartile range [IQR], 22.5-90.0) with 16 patients not receiving any opioid medications postoperatively. Averaged over the hospital course, the median opioid use was 38.4 mg/d (IQR, 15.0-74.0). Bivariate analysis showed that age, race, smoking status, history of chronic pain, preoperative opioid use, anticipated postoperative pain scores, and extent of surgery were all significantly associated with opioid use in the first 24 hours after surgery (Table 2). Age, smoking status, preoperative history of chronic pain, opioid use, and anticipated postoperative pain were significantly associated with average MME/HD. Multivariate analysis with adjustments for significant covariates showed that patients after protocol implementation had a significant decrease in mean opioid use in the first 24 hours (93.7 vs 68.5 mg, \(P = .026\)) but not when averaged over the course of the hospitalization (57.9 vs 46.8 mg/d, \(P = .211\); Table 3).

In the first 24 hours after surgery, patient’s mean (SD) pain score was 3.8 (2.1). On the day of discharge, patient’s mean (SD) pain score was 2.7 (2.6). Bivariate analysis showed that the average pain score in the first 24 hours was
significantly associated with age and anticipated postoperative pain level (Table 4). In addition to these 2 factors, pain score on day of discharge was also significantly associated with preoperative opioid use. Aggregate patient-reported pain scores did not change after implementation of multimodal analgesia plan with multivariate analysis. The adjusted average 24-hour pain scores before and after protocol implementation were 3.9 and 3.8, respectively (P = .666;
The adjusted average discharge pain scores before and after protocol were 2.8 and 2.6, respectively ($P = .498$; Table 3).

**Discussion**

Our study, to our knowledge, is the first to study the effect of MMA in otolaryngology with an intention-to-treat study design. Different aspects of the MMA protocol were implemented with different degrees of success. Certain medications may have been omitted in error or due to contraindications or adverse reactions. We did not expect that perfect implementation of the protocol would be feasible. By comparing our outcomes pre- and postprotocol implementation, we wanted to assess both the feasibility of implementing the MMA plan and its effectiveness in actual clinical practice.

Our data showed a roughly one-third reduction in the amount of opioid pain medication used in the first 24 hours after implementation of the MMA protocol. Our findings are in line with previous studies that also show that nonopioid medications decrease morphine use. Adjustment for patient and surgical characteristics was made as the 2 cohorts differed in terms of sex, history of chronic pain, and extent of surgery. Given that these variables all significantly modify patients’ reported pain and tolerance of opioid medications, the adjusted values are more likely to reflect the actual effect of the regimen implementation. The decrease in opioid use in the first 24 hours was not associated with any change in reported pain scores. Interestingly, this reduction in opioid use did not carry throughout the hospital course. This may be due to a few reasons. First, ketorolac was limited to 48 hours in our protocol. Thus, we may not see a benefit from the protocol because patients had fewer nonopioid pain relief options later in their admission. Second, patients’ analgesia requirements are not evenly distributed throughout their postoperative course. Thus, differences in cumulative opioid use may be missed when averaged over the length of hospitalization.

While there was a significant reduction in the amount of opioids used in the first 24 hours, it is important to note that opioid consumption after protocol implementation remained high. Our postoperative opioid usage is higher than reported in other studies. This may be due to our inclusion of opioid medications given immediately in the postanesthesia care unit (PACU). Roughly a third of our patients reported chronic pain before surgery and had baseline opioid use. This may reflect the inclusion of surgical salvage patients who are more likely to have high baseline chronic opioid use related to their disease. Nevertheless, the Centers for Disease Control and Prevention (CDC) advises caution with opioid dosages of more than 50 MME/d and avoiding 90

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<th>Table 4. Bivariate Analysis of Patient and Surgical Characteristics and Postoperative Pain Scores. a</th>
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*aSignificant $P$ values ($<.05$) are in bold.*
The side effects of opioid medications have been well documented. However, it is important to keep in mind that medications used in the MMA protocol also have potential adverse effects. The main concern in using NSAIDs after surgery, especially in the H&N region, is the risk of postoperative bleeding. We did not find any increase in hematoma or bleeding requiring reoperation after protocol implementation. A meta-analysis of 27 studies of randomized control trials did not find any increase in postoperative bleeding with ketorolac. Although other studies have also shown no significant difference in bleeding rates after H&N procedures or tonsillectomies with NSAIDs, there continues to be concern that NSAID administration may increase the severity of hemorrhage when it does occur or the ooziness of surgical wounds. Meticulous control of hemostasis and diligent monitoring of patients’ postoperative course are important to ensure that routine use of NSAIDs in postoperative care will not lead to deleterious outcomes. Gamma-aminobutyric acid (GABA) agonists, such as gabapentin and pregabalin, have been used in numerous surgical populations safely. Side effects include dizziness, drowsiness, nausea, extremity swelling, and constipation and appear to be dose dependent. GABA-agonists are considered to have low addictive potential, but there are some reports of individuals self-administering extremely high doses of these medications, often in conjunction with opioid medications. Finally, numerous studies have shown that polypharmacy itself can independently increase patients’ risk of adverse health outcomes, particularly in the elderly. Surgeries must be careful that by using multiple nonopioid medications to decrease use of opioids, we do not simply substitute one problem for another.

Other limitations of this study have not already been mentioned. First, our study is limited by the study design that resulted in different patient characteristics between the pre- and postprotocol groups. Multivariate analysis was used to account for these differences. However, statistical adjustments may not be sufficient to truly equalize the 2 groups, and thus our results ought to be interpreted with this in mind. Furthermore, the study results are limited to the inpatient course. While decreasing opioid use in the hospital is of value, it will be important to understand if MMA reduces postdischarge opioid use. Second, pain score and MME were measured in the first 24 hours after surgery because they were available for all patients. However, the immediate postoperative period may not be the optimal time to assess for changes resulting from multimodal analgesia. A previous study looking at pain assessments after H&N surgery found that median pain score was highest on postoperative day 6. Opioid usage, similarly, may vary throughout the hospital course. Another drawback is that the study design is the inability to parse out individual components of the multimodal analgesia plan. As such, the incremental benefit of adding each additional medication used remains unclear. Finally, this study included a wide range of surgical procedures spanning from relatively simple neck mass excisions to complex multicomponent ablative and reconstructive procedures. Given the difficulties in predicting the exact degree of pain associated with each surgical procedure, the division of surgical procedures into “minor” and “major” is somewhat arbitrary. The goal of grouping all H&N patients under a single MMA protocol was to show its feasibility and assess its general effects. However, the addition of nonopioid medications may be of substantial benefit in one subset and unnecessary in another.

Our findings suggest that MMA may be helpful in decreasing opioid use immediately after H&N surgery. However, there is a great deal regarding the optimal role of MMA that needs further investigation. Additional studies are needed to assess the safety and cost-effectiveness of MMA strategies. Future studies are also needed to assess whether such strategies are sufficient to decrease the long-term use of chronic opioid use.

Conclusion
A multimodal analgesia protocol was successfully initiated at our institution for use after H&N surgical procedures. Implementation of the protocol was associated with a decrease in opioid use immediately after surgery but did not alter patients’ pain scores. Patients’ experience of pain is largely influenced by their age and anticipation of pain. Although these variables also influence opioid doses, the quantity of opioid medications used after surgery is also associated with baseline opioid use and the extent of surgery. The experience at our institution suggests that multimodal analgesia protocols may be a valuable tool for postoperative pain control amid the current opioid epidemic. However, the optimal combination of these medications, their long-term effectiveness and safety, and the cost-effectiveness of these strategies compared to existing analgesia strategies merit further research and evaluation.

Author Contributions
Eugenie Du, conception, design, data acquisition, analysis, manuscript drafting and approval; Zainab Farzal, conception, design, data acquisition, analysis, manuscript drafting and approval; Elizabeth Stephenson, data acquisition, analysis, manuscript drafting, and approval; April Tanner, conception, design, manuscript drafting, and approval; Katherine Adams, conception, design, manuscript drafting, and approval; Douglas Farquhar, data analysis,
manuscript drafting, and approval; Mark Weisssler, conception, design, manuscript drafting, and approval; Samip Patel, conception, design, manuscript drafting, and approval; Jeffrey Blumberg, conception, design, manuscript drafting, and approval; Maryam Jowza, conception, design, manuscript drafting, and approval; Trevor Hackman, conception, design, manuscript drafting, and approval; Adam Zanation, conception, design, manuscript drafting, and approval.

Disclosures
Competing interests: None.
Sponsorships: None.
Funding source: None.

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