

Nonopioid perioperative analgesia in head and neck cancer surgery: A systematic review

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Abstract

Objective: Management of postoperative pain after head and neck cancer surgery is a complex issue, requiring a careful balance of analgesic properties and side effects. The objective of this review is to discuss the efficacy and safety of multimodal analgesia (MMA) for these patients.

Methods: Pubmed, Cochrane, Embase, Scopus, and clinicaltrials.gov were systematically searched for all comparative studies of patients receiving MMA (nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, anticonvulsants, local anesthetics, and corticosteroids) for head and neck cancer surgeries. The primary outcome was additional postoperative opioid usage, and secondary outcomes included subjective pain scores, complications, adverse effects, and 30-day outcomes.

Results: A total of five studies representing 592 patients (MMA, $n = 275$; non-MMA, $n = 317$) met inclusion criteria. The most commonly used agents were gabapentin, NSAIDs, and acetaminophen ($n = 221$), NSAIDs ($n = 221$), followed by corticosteroids ($n = 35$), dextromethorphan ($n = 40$), and local nerve block ($n = 19$). Four studies described a significant decrease in overall postoperative narcotic usage with two studies reporting a significant decrease in hospital time. Subjective pain scores widely varied with two studies reporting reduced pain at postoperative day 3. There were no differences in surgical outcomes, medical complications, adverse effects, or 30-day mortality and readmission rates.

Conclusion: MMA is an increasingly popular strategy that may reduce dependence on opioids for the treatment of postoperative pain. A variety of regimens and protocols are available for providers to utilize in the appropriate head and neck cancer patient.

KEYWORDS

analgesia, head and neck neoplasm, NSAID, opioids, pain management

Highlights

- Management of postoperative pain after head and neck cancer surgery is a complex issue, requiring a careful balance of analgesia and undesired side effects.

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- Five studies ($n = 592$ patients) reported on the use of nonsteroidal anti-inflammatory drugs, acetaminophen, anticonvulsants, local anesthetics, and corticosteroids.
- Four studies described a significant decrease in overall postoperative narcotic usage though subjective pain scores widely varied.
- Multimodal analgesia is a popular and effective strategy that may reduce dependence on opioids for the treatment of postoperative pain.

INTRODUCTION

Starting with the rise of prescription opioids in the 1990s, the opioid epidemic in the United States is now a public health emergency with significant health and financial burdens on individuals, their families, and society. From 1999 to 2019 alone, overdose deaths due to prescription opioids more than quadrupled.¹ Although prescribing rates have been declining in the past few years, misuse and abuse of these drugs still remain high, partially as a result of unfinished prescriptions for postsurgical pain.² In addition to the acute risks of opioids during the perioperative period, there may be lasting consequences due to over-prescription. One cross-sectional study reported rates of new persistent opioid use after minor and major surgeries ranged from 5.9% to 6.5% compared with 0.4% in the nonoperative cohort.³ As postoperative pain remains a nuanced, highly individualized issue, providers must balance the challenge of alleviating symptoms with the inherent risks of pain medications.

One increasingly popular strategy to reduce opioid consumption in the appropriate postoperative patient is multimodal analgesia (MMA). MMA is an approach that utilizes alternatives to opioids for postoperative relief, most commonly including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, anticonvulsants, local anesthetics, and corticosteroids. By targeting separate neurobiological pathways, these pharmacological agents seek to reduce the side effects of opioids while reducing complications associated with poor pain control. Implementation of MMA has been studied in a variety of fields including orthopedic surgery,^{4,5} neurosurgery,⁶ and general surgery.^{7,8} In otolaryngology, the use of MMA has been studied in patients undergoing endoscopic sinus surgery,⁹ rhinoplasty and septoplasty,¹⁰ otology,¹¹ and thyroidectomy and parathyroidectomy.¹² However, assessing the utility and impact of MMA in head and neck cancer patients, who typically require more extensive pain management, is not well reported.

Although opioid-sparing medications are becoming increasingly popular, there is no current consensus on the optimal approach, dosage, or administration in head and neck cancer patients. The purpose of this systematic review is to (1) discuss various MMA strategies for postoperative pain management after head and neck cancer surgery, (2) evaluate the efficacy and safety of the MMA approach by assessing additional postoperative narcotic consumption, subjective pain outcomes, complication rates, and 30-day outcomes.

METHODS

Search strategy

PubMed, Cochrane, EMBASE via OVID, Scopus, and clinicaltrials.org were systematically searched for all English studies reporting postoperative analgesia after head and neck cancer surgery. The search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, though study outcomes and measures were considered too heterogenous to conduct a meta-analysis.¹³ After an initial search, a manual search of all references of all articles was conducted to identify additional records. The final search was performed on November 15, 2020. Search details are outlined in Appendix A.

Study selection

After an initial search, all duplicates were removed, and titles and abstracts independently screened by two authors (B. C. G. and C. C. G.) for eligibility. Full-text articles were then identified and thoroughly assessed for eligibility. Any discrepancies were resolved by a third author (K. R.). Target studies included comparative groups of patients undergoing head and neck surgery receiving either MMA or standard opioid regimens (non-MMA). Any pharmacological method of pain management combining nonopioid treatment (i.e., gabapentin, NSAIDs, acetaminophen, corticosteroids, local nerve block etc.) with traditional opioid perioperative regimens was included in the MMA category. Inclusion criteria were adult patients undergoing head and neck cancer surgery without free flap reconstruction (i.e., radical neck dissection, transoral robotic surgery, thyroidectomy, oral cavity/oropharynx resections). Exclusion criteria included patients with chronic pain taking long-standing narcotic prescriptions.

Data extraction and quality assessment

Data were independently extracted using a standardized template by two authors (B. C. G. and C. C. G.), with a third author (K. R.) serving as a tiebreaker. Information gathered included study characteristics, patient demographics, perioperative analgesia regimen, objective and subjective

outcomes, and primary/secondary outcomes. Study characteristics included the year of publication, geographic location, study design, time period, inclusion/exclusion criteria, cohort size, and the total number of patients. The primary outcome was total postoperative narcotic usage. Secondary outcomes included length of stay, subjective pain scores, medical and surgical complications, adverse effects, and 30-day outcomes. The methodological quality of all included studies was assessed for risk of bias using the Cochrane Risk of Bias 2 (RoB 2) tool¹⁴ for randomized trials and methodological items for nonrandomized studies (MINORS) score¹⁵ for nonrandomized studies (Appendix A).

Statistical analysis

Due to the heterogeneity of the studies, a full meta-analysis was unable to be conducted. Patients were classified into either MMA or non-MMA groups based on study allocation and design. Study characteristics, patient demographics, and types of MMA were analyzed using standard descriptive statistics. Complications and adverse effects were aggregated and assessed using the χ^2 test. When appropriate, sample means were estimated using sample size, median, range, and interquartile range data as described by Luo et al.¹⁶ All analyses were conducted in RStudio (RStudio Inc.) with statistical significance defined as $P < 0.05$.

RESULTS

Study selection and characteristics

The search strategy yielded 4467 nonduplicate articles (Figure 1). After duplicate removal and screening by abstract and title, 66 full-

text articles were assessed with five studies (three randomized controlled trials [RCTs], two matched cohort studies) meeting inclusion criteria (Table 1).¹⁷⁻²¹ A total of 592 patients were included (275 patients in the MMA group; 317 in the non-MMA group). Using weighted averages, the overall population was 58.7 ± 9.2 years old and 65.8% male. Treatments in the MMA groups included gabapentin ($n = 221$), NSAIDs ($n = 221$), acetaminophen ($n = 221$), corticosteroids ($n = 35$), dextromethorphan ($n = 40$), and local nerve block ($n = 19$). A detailed overview of preoperative, perioperative, and postoperative pain regimens is described in Table 2.

Assessment of bias

Two nonrandomized studies^{19,20} were assessed using the MINORS score (Appendix A), receiving an average score of 16 ± 1.4 . Both studies had a clearly stated aim, inclusion of consecutive patients, appropriate endpoints, follow-up period, and loss to follow-up, and adequate control groups and statistical analyses. Neither study included an unbiased assessment of the study endpoint, sample size calculation, or baseline equivalence of groups. Du et al.¹⁹ reported a smaller proportion of females and more patients undergoing “major” procedures in the MMA group while Jandali et al.²⁰ reported higher preoperative narcotic usage in the control group. Three studies^{17,18,21} were assessed with the RoB 2 tool. All studies followed random sequence generation, allocation concealment, blinding of participants and assessors, and blinding of outcome assessment. Though conducted with a power analysis, Clayburgh et al.¹⁸ was not adequately powered to compare complication rates or swallowing outcomes between their two treatment groups.

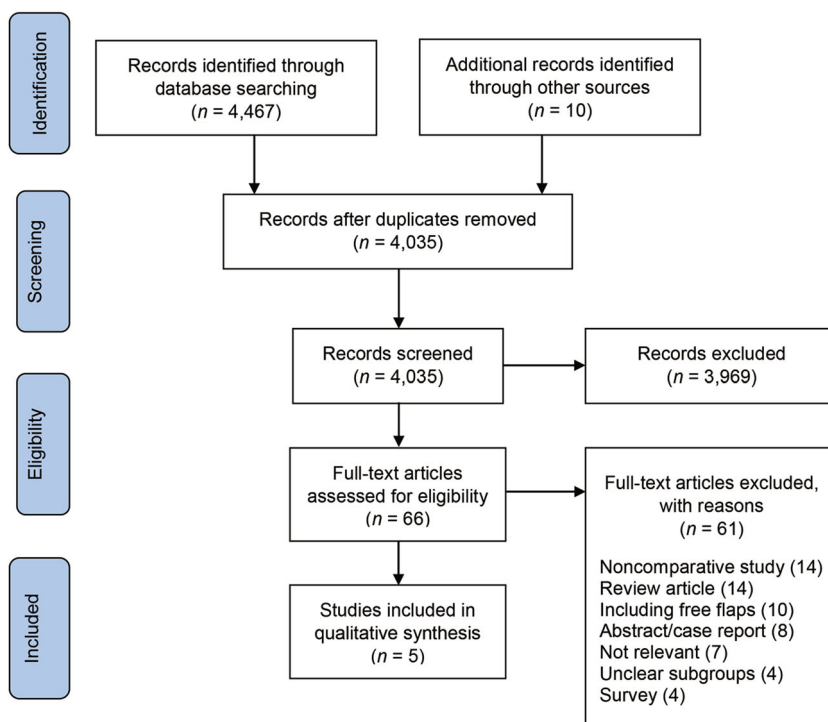


FIGURE 1 PRISMA flow diagram showing identification of included studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

TABLE 1 Overview of the included studies

Study, year	Location	Study design	MINORS	Type of operation	Type of MMA	MMA		Non-MMA	
						N total	Age (male %)	N	Age (male %)
Amiri, 2016	Iran	RCT	22	Radical neck dissection	Pregabalin, acetaminophen, naproxen, dextromethorphan	80	49.6 ± 14.0 (48)	40	49.8 ± 14.6 (55)
Clayburgh, 2017	USA	RCT	23	Transoral robotic surgery +/- neck dissection	Corticosteroid	68	55.6 ± 12.9 (94)	33	60.7 ± 7.6 (88)
Du, 2019	USA	Prospective matched cohort	17	Minor and major HNC surgery ^a	Acetaminophen, ketorolac, pregabalin	220	59.0 ± 1.6 (71)	131	57.8 ± 1.3 (42)
Jandali, 2020	USA	Retrospective matched cohort	15	Major HNC surgery ^b	Acetaminophen, gabapentin, celecoxib, ketorolac	185	64.6 ± 11.8 (70)	93	63.7 ± 11.1 (72)
Plantevin, 2007	France	RCT	22	Pharyngectomy, partial glossectomy	Mandibular nerve block	39	55.0 [40-70] (95) ^c	20	52.0 [37-76] (95) ^c

Abbreviations: HNC, head and neck cancer; MINORS, methodological items for nonrandomized studies; MMA, multimodal analgesia; RCT, randomized controlled trial.

^aMinor surgeries include thyroidectomy, parathyroidectomy, parotidectomy, lymph node excision, neck mass excision. Major surgeries include glossectomy, pharyngectomy, mandibulectomy, total laryngectomy, modified/radical neck dissection.

^bOral cavity and oropharynx resection, laryngectomy, pharyngectomy.

^cMedian [range].

TABLE 2 Protocol details for the administration of multimodal analgesia

Study, year	MMA		Non-MMA		Rescue analgesia
	Preoperative	Intraoperative	Postoperative	Intraoperative	
Amiri, 2016	Pregabalin (PO 2.5 mg/kg), acetaminophen (PO 15 mg/kg), naproxen (PO 7 mg/kg), dextromethorphan (0.3 mg/kg)	-	Morphine	-	Morphine
Clayburgh, 2017	-	Dexamethasone (IV 10 mg)	Dexamethasone (PO 8 mg q8 from POD 0-4 or until discharge)	Dexamethasone (IV 10 mg)	Saline (PO q8 from POD 0-4 or until discharge)
Du, 2019	Pregabalin (PO 100 mg) (major H&N surgery)	-	Acetaminophen (IV/PO 1000 mg/650 mg), ketorolac (IV 15 mg q4-6), pregabalin (PO 50 mg q12)	-	-
Jandali, 2020	Acetaminophen (PO 975 mg), gabapentin (PO 900 mg)	Acetaminophen (IV 1000 mg), ketorolac (IV 30 mg)	Acetaminophen (PO 975 mg q8), gabapentin (PO 300 mg q8), celecoxib (PO 200 mg 12), ketorolac (IV 15 mg q6)	-	-
Plantevin, 2007	-	Ropivacaine (IV 10 ml)	Acetaminophen (IV 1000 mg q4), morphine (IV 0.15 mg/kg)	Saline (IV 3 ml)	Acetaminophen (IV 1000 mg q4), morphine (IV 0.15 mg/kg)
					Morphine (IV 3 mg q10 min) given if pain score > 4 For refractory pain: Nefopam (IV 20 mg) given if pain score >4 for 60 min after morphine administration Morphine-based PCA

Abbreviations: IV, intravenous; MMA, multimodal analgesia; PCA, patient-controlled analgesia; POD, postoperative day; PO, per os; PRN, pro re nata.

TABLE 3 Additional postoperative opiate usage

Study, year	Measure	MMA, mean (SD)	Non-MMA, mean (SD)	P-value
Amiri, 2016	Total morphine, mg	7.4	13.5	0.00
Clayburgh, 2017	Oxycodone equivalent from POD 1–3, mg	137.1 (115.2)	147.3 (90.4)	0.33
Du, 2019	MME at postop 24 h, mg	58.6 ^a	93.7 ^a	0.03
	MME/day, mg/day	46.8 ^a	57.9 ^a	0.21
Jandali, 2020	MME at POD 3, mg	17.5 (46.0)	82.7 (116.1)	<0.001
	Narcotics upon discharge (%)	20 (21.7)	84 (90.3)	<0.001
	Narcotic refills at POD 30 (%)	6 (6.5)	34 (36.6)	<0.001
	PCA usage (%)	6 (6.5)	17 (18.3)	0.028
Plantevin, 2007	Total morphine at postop 24 h, mg	26.7 (18)	48.5 (26.3)	<0.05

Abbreviations: CI, confidence interval; d, day; h, hours; IV, intravenous; MED, morphine equivalent dose; mg, milligrams; MMA, multimodal analgesia; MME, morphine milligram equivalent; PACU, postanesthesia care unit; PCA, patient-controlled analgesia; POD, postoperative day; SD, standard deviation; μ g, micrograms.

^aMedian, median (IQR).

Objective measures

Four of five studies^{17,19–21} ($n = 524$) described a significant decrease in overall postoperative narcotic usage (Table 3). Three studies^{19–21} used morphine milligram equivalents (MME) to assess additional narcotic usage, reporting lower MME at postoperative day (POD) 1,^{19,21} POD 3,²⁰ and at discharge.²⁰ Other functional metrics favoring the MMA group included performance status scale—normalcy of diet, time to bolus tube feeds, and time to ambulation.^{18,20} Hospital length of stay was assessed by three studies^{18–20}; Clayburgh et al.¹⁸ (MMA, 4 days vs. non-MMA, 5 days; $P < 0.001$) and Jandali et al.²⁰ (7.8 vs. 9.7 days; $P = 0.008$) reported a significant decrease in hospital time.

Subjective measures

All five studies utilized an 11-point numerical scale (0 indicating “no pain” and 10 indicating “the worst pain imaginable”) to assess pain including the Visual Analog Scale (VAS) (two studies, $n = 107$),^{18,21} Defense & Veterans Pain Rating Scale (one study, $n = 185$),²⁰ Universal Pain Assessment Tool (one study, $n = 80$),¹⁷ and unspecified (one study, $n = 220$)¹⁹ (Table 4). There was a wide degree of heterogeneity with timing and method of assessing pain among the included studies. Of the four studies^{17–19,21} reporting average pain scores at POD 1, only Amiri et al.¹⁷ observed a significant decrease in pain in the MMA group (3.26 vs. 4.75; $P = 0.001$). However, two studies^{18,20} described a significant reduction in pain at POD 3 although a third study¹⁹ reported no difference at time of discharge. Other functional metrics such as EAT-10 and UM QOL did not differ at any timepoints.¹⁸

Complications and outcomes

Two of five studies^{18,20} ($n = 253$) reported medical and surgical complications, which were nonsignificant between the two groups (Table 5). The incidence of hematomas ranged from 3.0% to 6.5% for the MMA groups compared to 5.3%–5.7% for the non-MMA groups.^{18,20} While adverse effects like nausea/vomiting did not differ, Plantevin et al.²¹ reported that 31.6% of the MMA group undergoing mandibular nerve block experienced paresthesias. At 30 PODs, Jandali et al.²⁰ cited no difference in emergency department visits and readmissions rates.

DISCUSSION

Despite the recent advent of non-opioid medications for postoperative pain control, this review highlights the wide variability in application, efficacy, and utility of such regimens in head and neck cancer patients. MMA protocols differed in terms of choice of medication, mechanism of administration, dosage, frequency, and length of treatment. The majority of studies demonstrated a significant decrease in additional postoperative opiate usage after MMA, though endpoints for this metric greatly varied between studies. Subjective pain outcomes were less consistent, with three studies citing a significant reduction in pain scores at various postoperative timepoints. No differences in medical and surgical complications or 30-day outcomes were reported in any of the studies.

Five studies (three RCTs, two matched cohort studies) enrolling a total of 592 patients were included in this systematic review. Two studies^{19,20} were nonrandomized comparative studies with an average MINORS score of 16 ± 1.4 out of an ideal score of 24.

TABLE 4 Subjective outcomes

Study, year	Measure	Timepoint	MMA, mean (SD)	Non-MMA, mean (SD)	P-value
Amiri, 2016	UPAT	Overall	3.26 (1.98)	4.75 (1.70)	0.001
	UPAT Score Reduction	Postop 0–2, 2–4, 4–6, 12–24 h	–	–	NS
	UPAT Score Reduction	Postop 6–12 h	0.78 (1.20)	0.11 (1.35)	0.03
	UPAT Score Reduction	Postop 0–2, 0–4, 0–6, 0–24	–	–	NS
	UPAT Score Reduction	Postop 0–12 h	2.28 (1.52)	1.28 (1.80)	0.01
Clayburgh, 2017	VAS	Preop, POD 1–2, POD 7–21	–	–	NS
	VAS	POD 3	5.3 (2.0)	6.7 (1.9)	0.004
	VAS Score Reduction	Baseline-POD 1, Baseline-POD 2, Baseline-POD 7–21	–	–	NS
	VAS Score Reduction	Baseline-POD 3	4.1 (2.7)	6.0 (1.9)	0.001
Du, 2019	Pain Score	POD 1	3.7	3.6	0.787
	Pain Score	Discharge	2.7	2.7	0.952
Jandali, 2020	DVPRS	POD 3	2.6 (1.8)	3.6 (1.9)	<0.001
Plantevin, 2007	VAS	POD 1	–	–	NS
	VAS > 7 (%)	POD 1	3 (15.8)	10 (50.0)	<0.05

Abbreviations: CI, confidence interval; DVPRS, Defense & Veterans Pain Rating Scale; h, hours; MA, multimodal analgesia; MMA, multimodal analgesia; NS, not significant; PACU, postanesthesia care unit; POD, postoperative day; SD, standard deviation; UPAT, universal pain assessment tool; VAS, Visual Analog Scale.

TABLE 5 Complications, adverse effects, and 30-day outcomes

Measure	No. of studies (N)	Study	MMA (%)	Non-MMA (%)	P value
<i>Surgical outcomes</i>					
Hematoma	2 (253)	Clayburgh (2017)	3.0	5.7	NS
		Jandali (2020)	6.5	5.3	0.74
<i>Medical complications</i>					
Infectious	1 (68)	Clayburgh (2017)	9.1	0	NS
Abscess	1 (68)	Clayburgh (2017)	0	2.9	NS
<i>Adverse effects</i>					
Nausea/Vomiting	1 (39)	Plantevin (2007)	4.8	4.8	NS
Paresthesia	1 (39)	Plantevin (2007)	31.6	0	NR
<i>30-day outcomes</i>					
ED visits	1 (185)	Jandali (2020)	15.2	6.5	0.92
Readmissions	1 (185)	Jandali (2020)	17.4	20.4	0.73

Abbreviations: CI, confidence interval; ED, emergency department; MMA, multimodal analgesia; NR, not reported; NS, not significant; OR, odds ratio.

Missing criteria included lack of prospective data collection in one study,²⁰ unbiased assessments of study endpoints in both, study size calculation in both, contemporary groups in both, and baseline equivalence in both. As Jandali et al.²⁰ studied the effects of a newly implemented ERAS protocol in one group, additional implementations

(i.e., standardization of consults, ambulation and diet goals, wound care, etc.) besides the addition of MMA medications may have profound impacts on the outcomes of interest. Although Du et al.¹⁹ utilized multivariate analysis to account for the differences in baseline characteristics between groups, the two groups may not have been

truly equalized. Three studies^{17,18,21} were randomized, double-blind, placebo-controlled trials with low risk for selection, performance, and detection bias. However, other potential biases may have occurred: Amiri et al.¹⁷ selected drug intervention based on personal experience rather than an established protocol, Clayburgh et al.¹⁸ was not adequately powered to assess complication rates, and Plantevin et al.²¹ could not evaluate successful mandibular nerve block to maintain patient blinding. Finally, the term “head and neck cancer surgery” may refer to both “minor” and “major” surgeries. Even among the same procedures, results may be dependent on patient comorbidities, tumor characteristics, surgeon preference, and institutional guidelines. However, as there is no current consensus on the optimal administration of postoperative MMA, the overall quality of this body of literature is fair, with inclusion of appropriate patient populations and outcomes.

The goal of this systematic review was to assess the efficacy and safety of MMA regimens in head and neck cancer patients. Although all five studies addressed the efficacy of an MMA protocol, safety data were less well reported. When assessing for overall completeness, all five studies reported additional postoperative opiate usage using a variety of metrics including MME,^{19,20} total morphine,^{17,21} and oxycodone equivalents¹⁸ at multiple timepoints. When looking at subjective outcomes, all five studies utilized an 11-point scale to report pain levels, though at different timepoints including preoperative,¹⁸ POD 1,^{18,19,21} POD 2,¹⁸ POD 3,^{18,20} at discharge,^{18,19} and overall.¹⁷ Score reduction in pain was assessed in two studies.^{17,18} Safety data were more sparsely reported: medical and surgical complications were addressed by two studies^{18,20} while adverse effects and 30-day outcomes were each addressed by one study.^{20,21} Additional studies on this topic should seek to include both objective and subjective metrics at consistent timepoints, with thorough reporting of complications and safety data.

In spite of the wide variability in the administration of MMA for head and neck cancer patients, this review highlights the promising utility of nonopioid medications for pain control in the appropriate patient. Although opioids have been long touted as the gold standard for managing postoperative pain in cancer patients, opioid-related overuse and abuse have become a public health epidemic in the United States with substantial economic and social consequences. In particular, patients with head and neck cancer diagnoses were found to have significantly higher odds of being prescribed an opioid when compared to those with lung or colon cancer.²² In a study assessing patients undergoing surgery for oral cavity tumors, chronic opioid use was associated with decreased disease-free survival.²³ National trends in opioid prescribing patterns also highly vary, ranging from 0 to more than 60 doses for the most common otolaryngologic procedures.²⁴ Though opioid analgesics may still play an important role in the recovery process, the majority of individual articles report encouraging results, demonstrating decreased postoperative opiate usage with improved quality of life metrics including time to feeding, ambulation, and discharge. Although a meta-analysis was not able to be conducted due to data heterogeneity, this review presents

multiple strategies that may be additionally personalized depending on patient and provider preference.

Among the assortment of nonopioid options, providers may be most reluctant to use NSAIDs due to perceptions of decreased potency compared with opioids and adverse effects. After surgery, patients may perceive that opioids are the single best option of pain control. However, a recent Cochrane review on single-dose oral analgesics demonstrated that ibuprofen combined with acetaminophen was more likely to reduce acute postoperative pain compared to standard oxycodone 15 mg.²⁵ Adverse effects including an unacceptable risk of bleeding associated with nonselective NSAIDs may further dissuade physicians. In reality, the incidence of bleeding complications may actually be quite limited. In a systematic review assessing perioperative use of NSAIDs, gastrointestinal bleeding was reported in four total cases out of all patients enrolled in 32 total clinical trials.²⁶ No surgery-related bleeding complications were observed. A review of over 350 studies with 35,000 patients further demonstrated no statistically significant difference in adverse events between most NSAIDs and placebo, except for aspirin 1000 mg and diflunisal 1000 mg.²⁷ In the head and neck population, a recent systematic review also reported no increased risk of bleeding among free flap reconstructive patients receiving MMA.²⁸ The evidence in this current review is in line with the prior literature, with no significant difference in the incidence of hematomas.

Multiple evidence-based guidelines have suggested that opioid-sparing, NSAID-based multimodal regimens should be first-line after surgery.²⁹⁻³¹ Overall, the risks associated with MMA medications should be balanced with the benefits of avoiding the adverse effects and addiction potential with opioids. MMA regimens may not be appropriate for all patients undergoing head and neck cancer surgery. Several primary studies excluded patients with severe renal, hepatic, or heart disease,²¹ extensive cancer burden,¹⁸ and chronic substance use.^{17,18} Patients with advanced chronic kidney disease, renal insufficiency may benefit from avoiding NSAIDs in their treatment regimen; a short course and low dose may lower the possibility of NSAID toxicity while maintaining an appropriate level of analgesia. Corticosteroids should be used with care in patients with a history of diabetes mellitus or elevated glucose.

There are several limitations to this study. First, all systematic reviews are inherently susceptible to potential biases during the review process. However, this review was conducted with strict accordance to PRISMA guidelines with a clear statement of the objectives, inclusion/exclusion criteria, flow chart of study selection. Risks of biases associated with publication, data collection, and quality assessment were mitigated with adherence to search strategy, critical appraisal, careful selection of included primary studies, systematic evaluation, and independent data collection. Second, as the primary and secondary outcome measures were too heterogeneous to warrant a meta-analysis, careful interpretation of the results is warranted. However, the goal of this systematic review was to highlight a variety of MMA interventions that have been studied and compared with placebo groups. Future investigations should include

RCTs with larger, multi-institutional cohorts treated with a standardized MMA protocol.

CONCLUSION

Nonopioid analgesia in head and neck cancer patients may reduce additional postoperative narcotic usage without increasing complication rates and adverse effects. Although this review reports a number of MMA strategies, additional larger trials with standardized regimens are required to further assess subjective pain outcomes.

AUTHOR CONTRIBUTIONS

Beatrice C. Go, Camille C. Go: *Study conception and design, acquisition, analysis and interpretation of data, drafting and revising work, final approval, agreement to be accountable for work.* Kevin Chorath, Alvaro Moreira: *Acquisition, analysis and interpretation of data, critical revisal of work, final approval, agreement to be accountable for work.* Karthik Rajasekaran: *Study conception and design, analysis and interpretation of data, drafting and revising work, final approval, agreement to be accountable for work.*

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CONFLICTS OF INTEREST

The authors declare conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Karthik Rajasekaran, upon reasonable request.

ETHICS STATEMENT

This protocol was a Non-Human Subject Research project conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines

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APPENDIX A

See Tables A1 and A2, Figure A1

TABLE A1 Search strategies

Search strategy	
Pubmed	("Head and Neck Neoplasms"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck"[Mesh] OR "head and neck" OR "head" OR "neck" OR "head neck surgery") AND ("Analgesia"[Mesh] OR "Pain Management"[Mesh] OR "Chronic Pain"[Mesh] OR "analgesia" OR "pain management" OR "chronic pain" OR "pain control" OR "surgical pain")
Cochrane	<ol style="list-style-type: none"> 1) MeSH descriptor: [Head and Neck Neoplasms] explode all trees 2) MeSH descriptor: [Squamous Cell Carcinoma of Head and Neck] explode all trees 3) "head and neck" OR "head" OR "neck" OR "head neck surgery" 4) Surger* OR surgic* OR operation* OR operative* 5) #1 OR #2 OR #3 OR #4 6) MeSH descriptor: [Pain Management] explode all trees 7) MeSH descriptor: [Chronic Pain] explode all trees 8) MeSH descriptor: [Analgesia] explode all trees 9) "analgesia" OR "pain management" OR "pain control" OR "surgical pain" 10) #6 OR #7 OR #8 OR #9 11) #5 AND #10
Embase	("head and neck disease"/exp OR "head and neck tumor"/exp OR "head and neck cancer"/exp OR "head and neck surgery"/exp OR "head and neck infection"/exp OR "head and neck" OR "head" OR "neck") AND ("analgesia"/exp OR "analgesia" OR "pain management"/exp OR "pain management" OR "chronic pain"/exp OR "chronic pain" OR "pain control"/exp OR "pain control" OR "surgical pain")
Scopus	ALL (surger* OR surgic* OR operation* OR operative) AND ALL ("head and neck" OR "head" OR "neck" OR "head neck surgery") AND ALL ("analgesia" OR "pain management" OR "chronic pain" OR "pain control" OR "surgical pain")
Clinicaltrials.gov	Head and neck surgery

TABLE A2 MINORS criteria scoring

Study, year	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study aim	Loss to follow up <5%	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Du, 2019	2	2	2	2	0	2	2	0	2	0	1	2	17
Jandali, 2020	2	2	0	2	0	2	2	0	2	0	1	2	15

Abbreviation: MINORS, methodological items for nonrandomized studies.

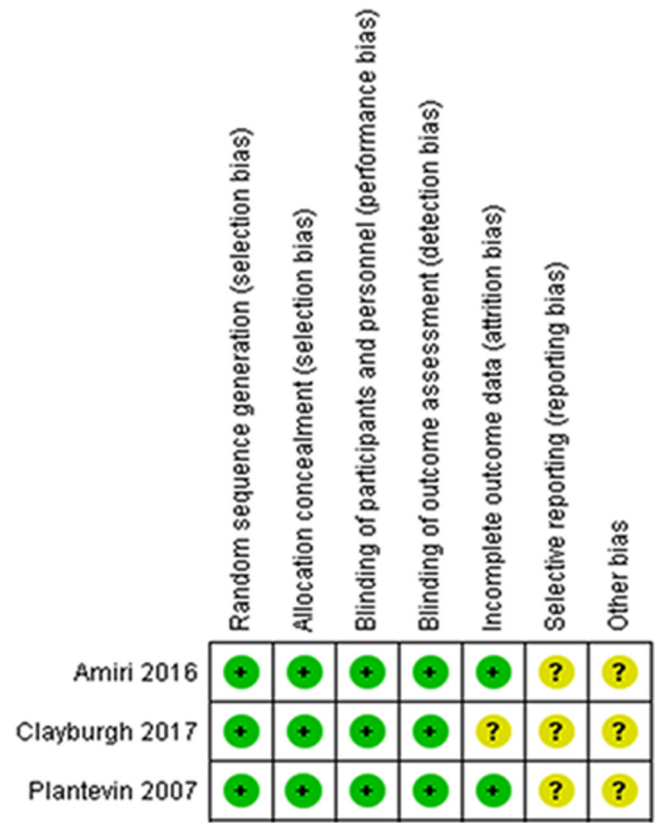


FIGURE A1 Risk of bias summary for all randomized controlled trials