Review Article

Enhanced recovery after surgery: a narrative review on perioperative pain levels and opiate use following free flap reconstruction in patients with head and neck cancer

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Background and Objective: The purpose of this narrative review is to evaluate and discuss studies reporting on postoperative pain and opiate use in head and neck cancer (HNC) free flap patients whose treatments abided by the Enhanced Recovery After Surgery (ERAS) guidelines. ERAS is an evidence-based protocol designed to minimize postoperative morbidity and optimize treatment outcomes. Implementation of ERAS protocols have led to significant improvements in surgical outcomes for these patients, including shorter hospital stays, reduced morbidity, and fewer postoperative complications. The Multimodal Analgesia component of the ERAS pathway incorporates an opioid-sparing drug regimen to manage pain and minimize the influence of opioid-related complications and misuse. Literature dedicated to postoperative pain levels and opiate use in this patient population is scarce.

Methods: A PubMed search from the publication of HNC guidelines by the ERAS Society from March 1st, 2017, to November 1st, 2021. There were no limits set for publication language, country, or sample size. Our primary outcome measures were postoperative pain levels and opiate usage in HNC patients enrolled in an ERAS pathway who underwent microvascular free flap tissue transfer reconstruction.

Key Content and Findings: The search term variables included the key terms "head and neck surgery" and "head and neck cancer" and "perioperative outcomes" and "pain outcomes". Only primary studies with data on both perioperative pain and opiate-use in the context of an HNC ERAS pathway employed in free tissue transfer reconstruction surgery. Six studies met the inclusion criteria and were selected for analysis.

Conclusions: ERAS is an evidence-based care improvement pathway that optimizes surgical outcomes in head and neck oncologic surgery. Patients benefit from the multimodal anesthesia (MMA) clinical care pathway constituent. Notably, HNC patients experience reduced self-reported perioperative pain and reliance on postoperative narcotics for pain relief. Further research in this patient cohort is warranted to outline and implement specific pain management guidelines centered on HNC research.

Keywords: Perioperative pain control; postoperative pain; head and neck cancer (HNC); pain outcomes; perioperative outcomes

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Introduction

Rationale/background

Enhanced Recovery After Surgery (ERAS) protocol is a multifaceted, evidence-based protocol designed to minimize postoperative morbidity and complications while optimizing postoperative treatment outcomes (1). The structured treatment algorithm embraces a wholistic approach to patient pre-, intra-, and postoperative care to promote an efficient return of function (2). This is accomplished through systematically implemented measures, such as preadmission patient education, preoperative nutritional optimization, conservative blood transfusions, multimodal anesthesia (MMA), early postoperative mobilization and nutrition initiation among others (3,4). The earliest ERAS protocols guideline implementations were employed in colorectal surgery. Since the release of the head and neck cancer (HNC)-specific guidelines by Dort *et al.* in 2017 (3), several studies have explored the feasibility of indoctrinating ERAS guidelines at the institution level and their effects on clinical outcomes in HNC patients (5-9).

Microvascular free flap reconstruction surgeries for patients with head and neck malignancy are intricate, extensive, and costly procedures (10). Despite contemporary reconstructive technique, patients often experience significant pain and morbidity following oncologic resection, given the complex anatomy and sophisticated behavioral functions (11-13). Such procedures lend well to care pathways that preemptively aim to minimize the effects of patient comorbidities, malnutrition, fatigue, pain, and prolonged immobilization. Moreover, ERAS guidelines provide a structure that may aid in reducing variability in perioperative phases of care for HNC patients who underwent free flap reconstruction (14).

Implementation of ERAS protocols have been shown to reduce hospital length of stay (LOS), wound complications, and readmission rates without prolonging intensive care unit LOS, mortality, or increasing the need for reoperation in HNC patients receiving ablative and reconstructive procedures (9). Relatively few studies have explored post-operative pain and opiate-use in the context of the ERAS clinical pathway. While a few studies have reported reduced post-operative opioid consumption and lower overall perioperative pain levels in ERAS patient cohorts, sufficient data to generate HNC-specific treatment guidelines is scarce (3). This gap in the literature is reflected in the ERAS Society's appropriation of colorectal surgery clinical outcomes to guide HNC surgery recommendations (3).

Objective

Our narrative review will evaluate the effect of ERAS treatment protocols on reported outcomes of perioperative pain and opioid use for HNC patients who underwent microvascular free flap tissue transfer reconstruction. We present the following article in accordance with the Narrative Review reporting checklist (available at https://joma.amegroups.com/article/view/10.21037/joma-22-4/rc).

Methods

Inclusion criteria

Inclusion criteria were primary studies with data on both perioperative pain and opiate-use in the context of an HNC ERAS pathway employed in free tissue transfer reconstruction surgery. Studies that failed to report on the MMA component of ERAS, solely included locoregional and/or rotational flaps, reported on patients who underwent free flap reconstruction due to osteoradionecrosis or other non-malignant etiologies, or reported on postoperative pain and opiate use in patients who were not exposed to the ERAS pathway in its entirety were excluded. Conference abstracts, editorials, and commentaries were excluded.

Search methods

We conducted a PubMed search from the publication of Head and Neck guidelines by the ERAS society from March 1st, 2017, to November 1st, 2021. The search term variables included the key terms "head and neck surgery" and "head and neck cancer" and "perioperative outcomes" and "pain outcomes". Primary literature reference lists were also manually searched. There were no limits set for publication language, country, or sample size. Our preliminary search resulted in 30 studies using the combined search terms. A flow diagram of the selected studies is shown in *Figure 1*. A summary of the search methods is provided in *Table 1*.

Data collection

Two independent researchers (CXC and RU) performed the initial title screening and review of the selected abstracts. Seven studies met the inclusion criteria, but one article lacked a control group and thus, was removed from the list of selected studies after a group discussion. Data was manually extracted from the remaining six primary literature articles found in *Table 2* onto a standardized data

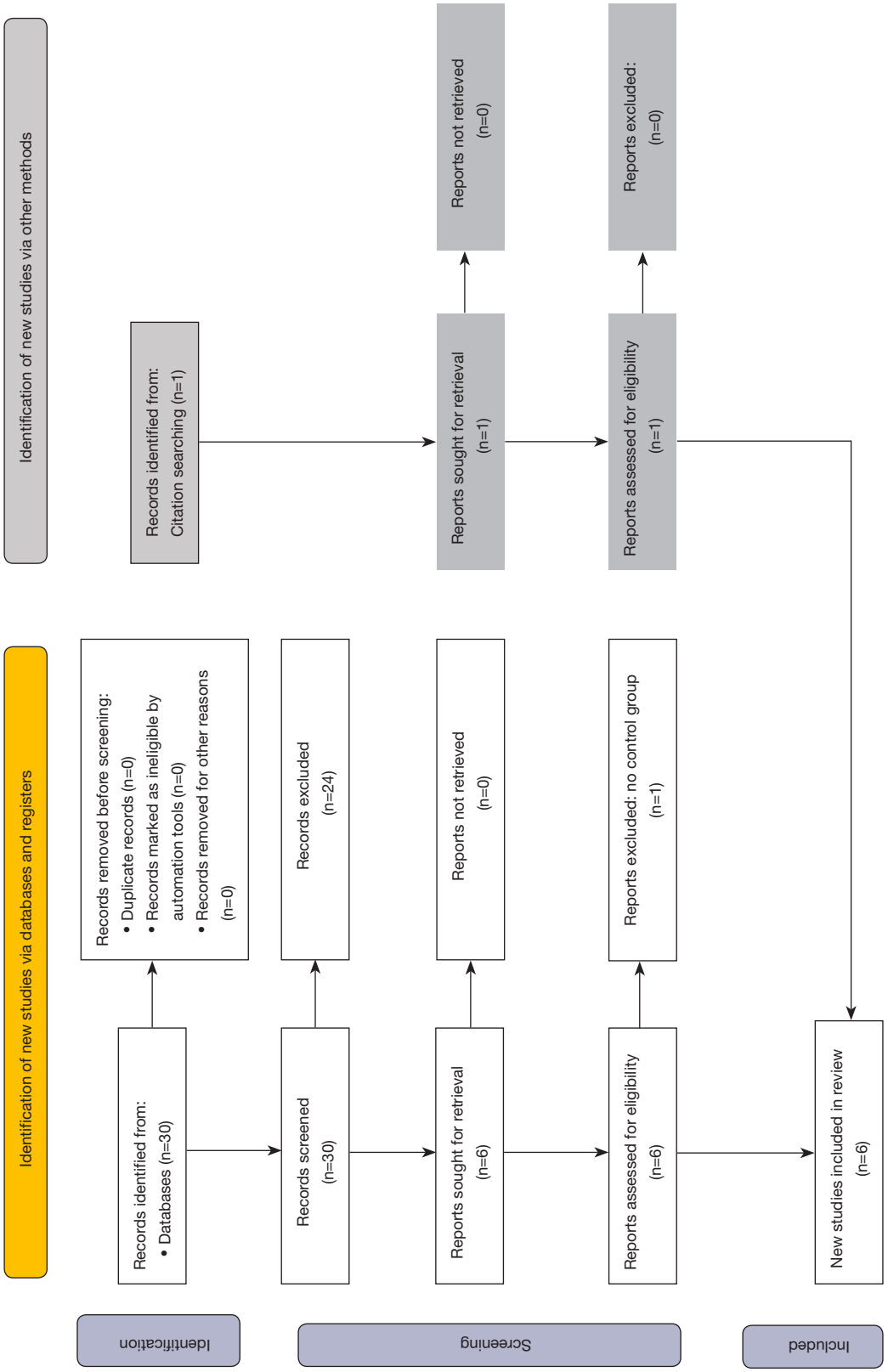

Figure 1 Selected items for narrative review evaluation and discussion flow chart.

Table 1 Search strategy summary

Items	Specifications
Date of search	November 1, 2021
Databases and other sources searched	PubMed, primary literature references
Search terms used	Head and neck surgery, head and neck cancer, perioperative outcomes, and pain outcomes
Timeframe	March 1, 2017–November 1, 2021
Inclusion and exclusion criteria	Primary studies with data on both perioperative pain and opiate-use in the context of an HNC ERAS pathway employed in free tissue transfer reconstruction surgery. There were no language restrictions
Selection process	Two independent researchers performed the initial title screening and review of the selected abstracts. The final list of included studies was reached by a group discussion
Any additional considerations, if applicable	Included studies must have a control group

HNC, Head and Neck Cancer; ERAS, Enhanced Recovery After Surgery.

Table 2 Selected study characteristics

Study, year	Location	Study design	ERAS time range	Control time range	Total (N)	ERAS		Control	
						N	Age, years (SD)	N	Age, years (SD)
Clark 2020	United States	Retrospective cohort	July 2017–October 2019	July 2017–July 2018	198	132	64.7 (12.9)	66	60.7 (13.4)
Eggerstedt 2019	United States	Retrospective cohort	June 1, 2017–November 30, 2018	June 1, 2017–November 30, 2018	65	28	64.1 (12.3)	37	65.0 (11.0)
Hinther 2021	Canada	Retrospective cohort	December 2017–June 2019	January 2015–December 2015	138	97	61.9 (11.85)	41	61.2 (12.25)
Jandali 2020	United States	Retrospective cohort	July 2017–January 2019	January 2016–June 2017	185	92	64.6 (11.8)	93	63.7 (11.1)
Kiong 2021	United States	Case-matched analysis	June 2017–March 2019	March 2016–April 2017	400	200	62.4 (13.1)	200	62.4 (13.0)
Vu 2020	United States	Retrospective cohort	April 1, 2016–December 31, 2017	April 1, 2016–December 31, 2017	357	149	60.3 (13.7)	208	64.2 (13.6)

ERAS, Enhanced Recovery After Surgery; SD, standard deviation.

collection form.

General components of head and neck ERAS protocols

ERAS protocols may differ slightly between medical institutions while successfully addressing the best practice characteristics of the clinical pathway. In this review, the independent researchers included studies that clearly stated patients received treatment abiding HNC ERAS guidelines. A breakdown of core evidence-based recommendations was required. Of particular importance was the application of a perioperative opioid-sparing multimodal analgesia regimen. Other components of ERAS protocols included preoperative verbal or written patient education, nutrition optimization, goal-directed fluid management, routine postoperative ICU admission, frequent flap monitoring, and early mobilization. While a standard anesthetic protocol is strongly recommended, the low level of evidence available

to support this item was not sufficient to exclude a study from this review.

Outcome measures

Our primary outcome measures were postoperative pain levels and opiate usage in HNC patients enrolled in an ERAS pathway who underwent microvascular free flap tissue transfer reconstruction.

Discussion

There is mounting evidence that support improved clinical outcomes in surgical patients in the ERAS pathways (15-17). Recent literature further emphasizes the role of multidisciplinary approaches in optimizing surgical and functional outcomes for patients requiring composite ablation and free tissue transfer reconstruction (18). The studies included in our review report improved pain control and reduced opioid consumption when adopting MMA as part of their ERAS protocol. These findings support the previous literature that have shown ERAS protocols do not adversely affect the patient surgical experience and reduce the levels of perceived pain and fatigue (19).

Multimodal analgesia and postoperative pain

HNC patients report some of the most severe postoperative pain (20). Effective pain management is intimately associated with patient outcomes. Poor pain management leads to increased immobility, decreased functional outcomes. And indirectly to wound infection, poor wound healing, prolonged hospital stays, and poor quality of life (21). Suboptimal pain management may contribute to patient nonadherence to adjuvant oncologic therapies following surgery, which can worsen outcomes. Many studies report on inadequate pain management in HNC patients whose pain regimen heavily relied on opioid medications (22,23). Hence, an MMA regimen is necessary (8).

MMA is an essential component of the HNC ERAS protocols with the goal of improved pain control. A carefully selected drug regimen is administered to synergistically achieve the components of an anesthetic state: amnesia, akinesia, and anti-nociception. Commonly used drugs include gabapentin, non-steroidal anti-inflammatory drugs, N-methyl-D-aspartate class of glutamate receptor antagonists, lidocaine, and regional anesthetic blocks (24). Historically, opiate-containing drugs composed the foundation of pain regimens following free flap reconstruction surgery (25). As a result, the prevalence of persistent postoperative opioid use can be as high as 52% in opioid-naïve patients and 82% in preoperative opioid users (26). Thus, MMA is a crucial approach to opioid-sparing pain management aiming to limit the potential for chronic opiate misuse and prevent opioid-related deaths (27,28). Moreover, HNC patients can be more susceptible opiate misuse. As found by Brummett *et al.*, preoperative tobacco, alcohol, and substance abuse were all associated with increased chronic opioid use after surgery (29). HNC patients tend to have high rates of alcohol and tobacco abuse and may be more prone to chronic opioid use after surgery (22).

All reviewed studies reported postoperative pain data scored using an eleven-point numeric scale. The numeric rating scale (NRS) uses a 0–10 scale to rate the intensity of pain with 10 being the most intense pain (30,31). The Defense and Veterans Pain and Rating Scale (DVPRS) expands upon a simple numeric scale by incorporating functional word descriptors, color coding and pictures of facial expressions to improve documentation between transitions in care (32). Since both scales operate similarly on a (0–10) numbering system, they were considered comparable by the research team. All studies included the use of gabapentin in their MMA regimen. Two used the combination of acetaminophen and gabapentin, and 2 studies utilized a regimen of tramadol, gabapentin, and celecoxib. An overview of the perioperative outcomes is shown in *Table 3*.

Vu *et al.* was the first to examine the association of a single dose of MMA prior to cancer resection and free flap reconstruction surgery with opioid administration during surgery and in the Post-Anesthesia Care Unit (PACU) (33) There was a modest effect size on patient's last pain score in the PACU for those under the MMA protocol (Cohen w =0.12; 95% CI: 0.06–0.24). Low effect sizes, less than 0.2, reflect a negligible difference between the mean pain scores for MMA and non-MMA cohorts in this study. Patients who received at least one MMA medication before surgery stayed in the PACU for a shorter duration (mean 22 minutes) when compared to the control group for a difference in the means of –0.36 (95% CI: –0.63 to –0.09) (33). The authors suggest that the benefits of their MMA protocol are immediate and can reduce opiate requirement even after one preoperative dose (33). The inability to detect a significant decrease in pain scores after a single dose of MMA is consistent with

Table 3 Perioperative patient outcomes overview

Study, year	Preop MMA	Pain reporting time frame	Pain scale	ERAS pain outcomes	Opiate reporting units	Opiate length of time from post-op	Opiate prescriptions at discharge recorded?	ERAS opiate outcomes
Vu *et al.*, 2020 (33)	Celecoxib 400 mg, gabapentin 300 mg, and/or tramadol hydrochloride 300 mg	PACU	Numeric (0–10)	Last Pain Score ↔	MEDD	Intraoperative, PACU, and combined	No	MEDDs given during surgery ↓*; MEDDs given in the PACU ↓*
Eggerstedt *et al.*, 2019 (34)	Acetaminophen 975 mg and gabapentin 900 mg	POD 1–3	Defense and Veterans Pain Rating Scale (0–10)	72 hours Postop↓*	MED	72 hours	Yes	Median MEDs given within 72 hours postop ↓*; median MEDs prescribed at discharge ↓*
Jandali *et al.*, 2020 (35)	Ketorolac 30 mg and acetaminophen 1,000 mg	POD 1–3	Defense and Veterans Pain Rating Scale (0–10)	72 hours Postop↓*	MED	72 hours	Yes	Mean MED consumed↓*; % discharged with opiates ↓*
Hinther *et al.*, 2021 (36)	NA	POD 1–14	Numeric (0–10)	POD 0–6 ↓*	OME	POD 1–14	No	Mean opiate consumption OME ↓*
Kiong *et al.*, 2021 (37)	Celecoxib 400 mg, tramadol 300 mg, and gabapentin 300 mg	POD 1, 3, DC	Numeric (0–10)	PACU time ↓*; PACU First Pain Score ↓*; POD1–Discharge Pain Score ↓	MME	72 hours	Yes	72 h PCA use ↓*; MME requirements ↓*; strong opioid*; prescription at discharge ↓*
Clark *et al.*, 2021 (38)	Celecoxib 200 mg, gabapentin 300 mg, acetaminophen 1,000 mg, aspirin 325 mg	POD 1–3	Numeric (0–10)	POD 0–3↓*	MME	120 hours	Yes	POD 0–5 opiate consumption MME ↓; total MME consumption ↓; MME consumption/POD ↓*

*, signifies statistical significance. MMA, multimodal anesthesia; ERAS, Enhanced Recovery After Surgery; PACU, post anesthesia care unit; POD, postoperative day; NA, non-applicable; DC, discharge; MEDD, morphine equivalent daily dose; Intraop, intraoperative; MED, morphine equivalent dose; OME, oral morphine equivalents; MME, morphine milligram equivalents; PCA, patient-controlled anesthesia.

findings by Du *et al.* reporting MMA did not alter the patients' post-operative pain scores (27).

However, Eggerstedt *et al.* found that patients who received repeated doses of MMA composed of celecoxib and gabapentin had lower postoperative pain scores (34). The MMA cohort reported a mean (SD) of 2.05 (1.41) and the control cohort reported 3.66 (1.99) during the first 72 hours after head and neck free flap reconstruction (P=0.001) (34). These results were later reproduced by Jandali *et al.* and Hinther *et al.* referenced in *Table 3* (35,36).

Kiong *et al.* showed that their ERAS group had a shorter PACU stay than their control (117±51 *vs.* 141±51 min, respectively; P<0.001), with a significantly lower first pain score in the PACU (2.5±3.2 *vs.* 3.5±3.4, respectively; P=0.003) (37). The mean pain score on POD1 (P=0.892), POD3 (P=0.236), and day of discharge (P=0.273) did not differ between the ERAS and control groups but showed an overall decreasing trend from POD1 to the day of discharge in both groups. Pain scores were not measured on POD2. Contrastingly, Clark *et al.* found a statistically significant decrease in mean peak pain scores in the immediate postoperative period (POD0: 4.6±3.6 *vs.* 6.5±3.5; P=0.004, POD1: 5.2±3.5 *vs.* 7.3±2.3; P=0.002, and POD2: 4.1±3.5 *vs.* 6.6±2.8; P=0.002 consistent with an overall lower trend for ERAS patients (38).

HNC patients undergoing free flap reconstruction offer an exceptionally difficult task in terms of postoperative pain management. Pain is the highest reported symptom for HNC patients compared to other cancer types (39). The pain associated with different head and neck anatomical sites is not uniform and the free flap donor site pain may introduce the greatest source of pain (40-42). Moreover, additional analgesic interventions in the form of local and regional blocks are often unavailable. The six studies included in this review support the findings of a large systematic review by Wick *et al.* asserting the safety and efficacy of MMA in the ERAS pathway. For optimal pain management, continuation of MMA throughout the perioperative period is essential (24). The results by Eggerstedt *et al.*, Jandali *et al.*, and Hinther *et al.* compared to those in Vu *et al.* highlight the importance of uninterrupted MMA (33-36). Despite their use of opioid-sparing analgesia, Jandali *et al.* and Kiong *et al.* reported a statistically significant reduction in hospital LOS (days) in their respective ERAS cohorts versus control cohorts (35,37). No study in this review detected a difference in ICU LOS between both cohorts. A theoretical concern for increased risk of postoperative bleeding exists for MMA protocols including nonsteroidal anti-inflammatory drugs (NSAIDs). A systematic review of 27 randomized clinical trials failed to detect a difference in postoperative bleeding between the patient cohort taking ketorolac tromethamine and the control group (24). Three of the six studies that reported on the rates of postoperative hematomas did not find a statistically significant difference between the ERAS and control groups.

Pain is a multifactorial and subjective experience that is difficult to measure. Determining statistical and clinically significant reduction in pain is not straightforward and one result cannot be inferred from the other (43). Literature in the field recommends two independent pain assessments spanning at least four days be used to generate a satisfactory assessment (30). Despite the presence of several assessment tools, obtaining pain data is usually done in the form of subjective patient reports. This is the case for all the studies in this review. Most of the studies found a statistically significant decrease in pain in the immediate postoperative period. Additionally, an overall decreasing trend in pain scores were seen with the ERAS group having lower mean scores throughout compared to control groups. Study design, rather than the number of patients in each cohort, may be the limiting factor in determining statistically significant reductions in pain scores (43). Instead, the frequency in obtaining pain scores, pain scale employed, and the metrics used to assess overall trends may need to be revised (43). Younger *et al.* advocates for the use of effect size, a specific metric (e.g., percent reduction of pain), and a cutoff that indicates a clinically meaningful change (43). Primary studies in the field of pain assessments attribute a 30% reduction of pain as clinically significant (44). When applied to the studies in this review, a 30% reduction corresponds with a two point drop on a 0 to 10 NRS (43,44).

Early mobilization is a major tenant of the HNC ERAS guidelines (3). Twomey *et al.* reported fewer major complications and shorter hospital LOS in HNC ERAS cohort undergoing free flap reconstruction (45). In a systematic review, Khan *et al.* demonstrates that patient participation in ERAS treatment pathways lead to better pain outcomes (19). Moreover, studies in other surgical specialties assert that scheduled pain control protocols are integral to early mobilization (46). In this review, Clark *et al.* reports a shorter mean (SD) time to mobilization of 55.6 (43.9) hours for the ERAS cohort versus 93.4 (63.9) hours for the control (P=0.003) (38). Similarly, Hinther *et al.* and Jandali *et al.* detected a clinically significant reduction in time to mobilization in ERAS patients

postoperatively [1.7 (2.96) *vs.* 2.5 (2.12) days; P<0.001] and [1.4 (1.3) *vs.* 2.0 (1.6) days; P=0.006] respectively (35,36). Early mobilization may be the product of effective pain management through MMA.

As we will soon cover, many studies also reported reduced in-hospital opiate use among their ERAS patient cohorts postoperatively and at discharge in the form of fewer opiate prescriptions. Published work in other surgical specialties also have identified decreased opiate consumption suggestive of lower pain levels without achieving a statistically significant difference between ERAS and control groups (47).

Perioperative and chronic opiate use

Opioid medications are the cornerstone of pain regimens across multiple institutions. Narcotic analgesics can effectively address pain, but can have dangerous side-effects including respiratory depression, nausea and vomiting, impaired mobilization, and the risk of chronic dependence. It has been estimated that up to 80% of HNC patients experience pain and require treatment with prescription opioids (48). However, patient satisfaction with opioid-based pain management is low with 70–85% of patients reporting ineffective pain control (25). Moreover, the magnitude of the surgery may not necessarily correlate with chronic opiate consumption postoperatively (29). While the path to chronic opioid use is multifactorial, studies focusing on HNC have identified a few predisposing factors including preoperative opiate and tobacco use, race, adjuvant therapy, and advanced pathologic T-stage as risk factors (23,37).

Providing an overview on perioperative pain and opiate use presents a unique challenge due to the number of dosage conversion schemes. This aspect alone may account for the lack of formal evaluation of opiate use outcomes in systematic reviews on HNC ERAS clinical outcomes to date (9). The concept of equianalgesia can be quantitatively expressed as the dosage at which two opiate medications are considered to deliver comparable analgesic effects (49). Converting opiate drugs into a base metric helps healthcare providers compare the potency of multiple drugs and deliver adequate anesthesia (50). Equianalgesia is a useful concept in the prevention of unintentional overdose and minimizing the potential for prescription opiate misuse (51). Conversion calculators are not used to convert the dosage of one drug to another. Rather, equivalency factors allow providers to determine a dose of morphine that is equivalent to a dose of other various opioid-containing drugs to reflect their relative potencies (50). The resulting value from this conversion is referred to as the morphine milligram equivalents (MME). The calculation to determine MME often considers the drug quantity, time supply, and a specified conversion factor unique to each drug. MME reflect the total amount of opioids consumed by patients in a standardized manner that facilitates outcome comparisons in published literature. Morphine equivalent dosing (MED) then, is the summation of all medications containing opiates consumed by a patient in a 24-hour period. Another point of reference is the morphine equivalent daily dose (MEDD). The MEDD is used as an indicator of potential dose-related risk for adverse drug reactions, including overdose (52). MEDD is communicated in the form of a threshold value that indicates increased risk to the patient when a certain limit of opiate drugs is reached. Finally, oral morphine equivalents (OME) are analogous to MME in that it also a tool comprised of conversion factors collated and synthesized from previously published work to facilitate communication and comparison of opioid utilization study findings (53). Of note, MME, MED, MEDD, and OME may be used interchangeably depending on the literature at hand. Special attention to the definitions and calculations stipulated by the authors is paramount to interpreting the stated results. The opioid equivalency factors used in the articles included in this review is shown in *Table 4*.

Three studies detected reduced opiate consumption in ERAS patients over the immediate postoperative period (34,35,37). Eggerstedt *et al.* recorded MEDs given within 72 hours postop was 10.0 MME (IQR, 2.7–23.1) for MMA cohort *vs.* 89.6 (IQR, 60–104.5) for control cohort (P<0.001) (34). Jandali *et al.* found the mean MED administered within 72 hours following surgery to patients in the ERAS cohort (17.5±46.0 mg) was significantly lower when compared to the control group (82.7±116.1 mg; P<0.001) (35). During the same time frame, Kiong *et al.* found the ERAS group had decreased MME requirements (138.8±181.5 *vs.* 207.9±205.5; P<0.001) in addition to a significant reduction in postoperative PCA use (31.0% *vs.* 74.5%; P<0.001) (37). To facilitate comparison, the total MME values reported by Kiong *et al.* can be divided by 3 to estimate the mean MED consumed over 24 hours (37). These articles expanded on the immediate postoperative period to report on opiate use upon discharge. Eggerstedt *et al.* detected a median MED prescribed at discharge of 0 (IQR, 0–18.8) for MMA cohort *vs.* 300.0 (IQR, 262.5–412.5) for control cohort (P<0.001) (34).

Table 4 Opioid equivalency factors reporting scheme

Drug name	Dosage	Chorath *et al.*, MME	Bavisha *et al.*, MME	Jandali *et al.*, MED	Eggerstedt *et al.*, MED	Vu *et al.*, MEDD	Hinther *et al.*, OME
Codeine	1 mg	0.1	0.1	0.15	0.15	–	0.1
Fentanyl (buccal/sublingual)	1 mcg	0.1	0.1	0.125	0.125	–	0.1
Fentanyl (patch)	1 mcg/h	2.4	2.4	2.4	2.4	–	2.4
Hydrocodone	1 mg	1	1.2	1	1	1	1.2
Hydromorphone	1 mg	4	5	4	4	4	5
Methadone	1 mg	4	4.7	3	3	–	4.7
Morphine	1 mg	1	1	1	1	1	1
Oxycodone	1 mg	1.5	1.5	1.5	1.5	1.5	1.5
Oxymorphone	1 mg	3	3	3	3	3	3
Tapentadol	1 mg	0.4	0.4	–	–	–	0.4
Tramadol	1 mg	0.1	0.2	0.1	0.1	–	0.2

MME, morphine milligram equivalents; MED, morphine equivalent dose; MEDD, morphine equivalent daily dose; OME, oral morphine equivalents.

While the remaining three studies discovered similar trends, their study design captured postoperative opioid use across an extended timeframe. Clark *et al.* found that ERAS patients consumed significantly less opioid-based analgesic drugs POD0–5 compared to the non-ERAS cohort (38). The reduction in mean MME consumption was significant in the total and individual post-op day measurements (POD0 adjusted P=0.010, POD1–5 adjusted P=0.000). Interestingly, there was a significant decrease in opioid consumption during hospitalization regardless of history of prior opioid use without compromising pain management. Hinther *et al.* also expands on previous results demonstrating the association between MMA and reduced opiate consumption observed an association between MMA and low pain scores along the entire postoperative course from POD0–14 (36). Mean daily opioid consumption was 29.7 mg (SD 5.0) in the MMA group versus 43.3 mg (SD 18.8) in the control group (P=0.04 Wilcoxon). Interestingly, daily OME consumption is slightly lower in the control group for the first four postoperative days. After postoperative day four, OME consumption is much higher in the control group. The overall trend for opioid consumption increases over the duration of hospital stay, particularly in the control group. Vu *et al.* quantified opiate use in MEDD across two settings; during surgery and in the PACU (33). In the combined settings, patients in the treatment group were 79% less likely to receive more than 66 MEDD of opioid compared with patients in the control group (OR, 0.21; 95% CI: 0.12–0.36). The authors attributed a moderate treatment effect on the amount of opioid given during surgery or during surgery and in the PACU attributed to pre-op analgesia. The authors looked at the percentage of patients who achieved clinically meaningful reduction in MEDD across the two settings and then combined. Overall, 92 of 141 patients (65.2%) in the treatment group and 54 of 181 patients (29.8%) in the control group achieved a clinically meaningful reduction in MEDD, for a difference between the groups of 35.4% (95% CI: 24.6–45.0%). The treatment group achieved a higher percentage of clinically meaningful reduction in MEDDs during surgery, in the PACU and in the combined setting.

Kiong *et al.* noted fewer patients in the ERAS group received a strong opioid analgesic discharge prescription (64.5% *vs.* 81.5%; P<0.001) (37). Opioid analgesics were defined as strong or weak in this study based on the World Health Organization's analgesic ladder and the United States Drug Enforcement Administration (37). Jandali *et al.* revealed that the percentage of patients discharged with narcotics was significantly lower in the ERAS group when compared to control (21.7% vs 90.3%; P<0.001) (35). This proportion was the lowest reported percentage in all the studies reviewed. The benefits for

the ERAS were enduring. In fact, Jandali *et al.* reported fewer patients required a discharge narcotic prescription refill within 30 days postoperatively (6.5% *vs.* 36.6%; P<0.001) (35).

All studies reported on the quantity of opiates consumed in the postoperative period. Opiate use was quantified at a range of 24 hours to 14 days postoperatively. There was no predominant unit for opiate measurement across all six studies; the units used were OME, MED, MEDD, and MME. Reduction in postoperative opiate use was seen in all ERAS cohorts when compared to non-ERAS cohorts. Preoperative opiate use is a known contributor to chronic opiate use (23). No study included in this review explores the reasons for preoperative opiate use in their patient cohorts. One study identified predisposing characteristics for increased risk of persistent opiate use which include preoperative opiate analgesic use, prior radiotherapy, African American race, and ICU admission (37). While previous work established the ability of MMA to reduce opiate use in HNC patients specifically, the benefits were in patients exposed to a single element of ERAS opposed to the complete protocol (5,27).

The measurements of opiate-based analgesic medications for HNC ERAS patients predominantly occur in the broad time ranges of immediate postoperative period (72 hours) and the acute setting spanning anywhere between discharge and one month after surgery in the existing literature. Chronic opioid use, defined as the consumption of narcotics over ninety days, is yet to be studied in HNC ERAS patients (23). Hinther *et al.* retrospectively quantified the opiate use in 212 patients with primary HNC undergoing free flap reconstruction at 3 and 12 months to reveal 136 (64%) and 116 (55%) of patients, respectively, continued to require opiate medications (36). These patients were not subject to the ERAS protocol in its entirety, but instead were only exposed to the MMA component. Institutions with well-established ERAS programs and good protocol adherence rates may now be capable of studying its enduring effects on pain and opiate use. For instance, Kiong *et al.* has improved upon the conventional cohorts matched over a period spanning a few months to present results on 400 patients case matched over a period of two years (37).

Common limitations of the studies in this review include the non-blinded retrospective observation of small patient cohorts. The implementation of ERAS programs at the institution level will inevitably vary given the department resources, patient education and health literacy, protocol adherence, and personnel training, and hospital unit availability. Depending on regional practicing patterns, studies may rely on opioid dispensing patterns as a surrogate for opiate use. This is an additional layer of intricacy that underscores the need for careful study planning. In California, studies seeking to prospectively quantify chronic opiate use will require patient consent and collaboration with the Controlled Substance Utilization and Review Evaluation System (CURES). A crucial limitation when quantifying opiate use in the postoperative period is the lack of cohort matching. For example, Jandali *et al.* noted a significantly greater number of patients in the control group were utilizing narcotics preoperatively (35). This could be a confounder and be associated with increased discharge narcotic prescriptions in the control group when compared to the ERAS cohort. Conducting a formal analysis of perioperative opiate use is challenging. Even across the six articles in this review there were four different reporting schemes: MME, OME, MED, and MEDD. Moreover, authors may use these terms interchangeably, albeit incorrectly at times. The adoption of a reliable set of equivalency factors would greatly facilitate evaluation of the effects of ERAS on opiate use. In theory, mean total MME over 72 hours can be divided by three to approximate the mean MED over three days. Studies quantifying opiate use in OME and MEDD are difficult to incorporate into a formal evaluation. Specifically, the literature recommendations for OME equivalency ratios vary among two drugs, hydrocodone, and methadone, compared to the MME ratios set forth by the Centers for Disease Control (CDC) (54). As previously stated, MEDD also uses a set of equivalency factors to compare the potencies of different opiate drugs. MEDD has a specific role of setting a threshold value discouraging further opiate prescription. As these threshold values may vary between different states and organizations, MME would a more reliable method of quantifying use for data comparison. In the future, this will result in a formal appraisal and eventually evidenced-based HNC-specific data to create guidelines for this particular population. Further study will aid in identifying and appropriately triaging patients with predisposing factors for chronic opiate use, safely administering an MMA, and monitoring pain management to judiciously introduce opiate medications when indicated.

Conclusions

The ERAS care pathway provides evidenced-based recommendations that guide patient care through the

perioperative experience. The literature evaluated emphasize the significant role of multimodal analgesia within the ERAS treatment algorithm on reduced reported perioperative pain and opioid use. Further study of ERAS pathways employed in the care of HNC patients undergoing microvascular free flap reconstruction is ultimately warranted to generate guideline recommendations based on HNC-specific data. The study of perioperative pain and opioid use can effectively be compared to other studies when outcomes are measured using numeric (0–10) scales and the MME conversion scheme for pain and opioid use respectively. Our review of the current literature supports the use of MMA in postoperative HNC patients after cancer resection and free tissue reconstruction surgery. MMA usage has been shown to both decrease postoperative self-reported pain scores and reduce the amount of opiates consumed both in the hospital and after discharge. Further studies are necessary to optimize specific MMA regimen that can be implemented in our HNC patients. Standardized evaluation of pain and opioid use outcomes in future research may facilitate formal evaluation to support HNC ERAS guidelines.

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Footnote

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