Review Article

The analgesic efficacy and safety of non-steroidal anti-inflammatory agents (NSAIDs) in patients undergoing oral and maxillofacial surgery—a systematic review

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to alleviate postoperative pain in patients and stand as lower risk alternatives in comparison to opioids. The worldwide opioid epidemic has demonstrated how opioids can pose severe risks for patients including addiction and misuse. Thus, the objective of this review aims to evaluate the efficacies of NSAIDs and determine if NSAID-exclusive treatment stands as a suitable alternative to opioids, in treating pain after oral and maxillofacial surgery (OMFS).

Methods: A search of all relevant literature spanning databases including PubMed, The Cochrane Library, and https://www.clinicaltrials.gov/ was conducted for records outlining the use of NSAIDs and opioids in OMFS, dating up to 01/05/2023. The inclusion criteria specified for head-to-head randomized controlled trials (RCTs) comparing the efficacies of NSAIDs to opioids in patients undergoing OMFS. Non-RCT studies were excluded if they did not primarily compare the efficacies of a specific NSAID and opioid, used external drugs, or had no results released at the time of the search. Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias tool. A systematic review and meta-analysis were performed to analyze the data using the SPSS software.

Results: Six total studies were identified with 40–90 patients per study, comparing the use of one NSAID *vs.* one opioid in patients following OMFS. Three tramadol *vs.* ketorolac, one tramadol *vs.* celecoxib, one tramadol *vs.* lornoxicam, and one fentanyl *vs.* ketorolac study were found. Measurements of drug efficacy used included visual analogue scale (VAS) pain scores, adverse events (AEs), time to first rescue analgesic, and total rescue analgesic consumption. The meta-analysis showed no significant difference between the NSAID and opioid groups in VAS scores and rescue analgesic consumption. However, NSAID treatment yielded more favorable outcomes for AEs including dizziness, drowsiness, nausea, and vomiting following OMFS.

Conclusions: Despite there being no significant difference in VAS scores and rescue analgesic consumption, this study indicates that NSAID-based treatment can lead to more favorable outcomes regarding AEs. Thus, a transition to primarily NSAID-based therapies and opioid-sparing therapies can be considered in the future of oral and maxillofacial anesthesia.

Keywords: Postoperative pain; non-steroidal anti-inflammatory drugs (NSAIDs); opioids; oral and maxillofacial surgery (OMFS)

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used by perioperative patients to reduce pain and inflammation experienced after surgery (1). This common postoperative inflammation is often triggered by the biosynthesis of prostaglandins-lipid compounds synthesized by the cyclooxygenase (COX) enzyme and generated at infectious or tissue damaged sites (2). NSAIDs function to decrease inflammation through acting as competitive inhibitors that bind to one monomer of the COX dimer's active site, thereby inhibiting the synthesis of prostaglandins, and blocking any inflammatory response (2). The analgesic and anti-inflammatory effects of NSAIDs thus effectively induce temporary pain relief in patients, and stand as lower risk alternatives in comparison to opioid-based anesthetics (1).

As with any drug, NSAIDs do come with their own risks. The use of NSAIDs can impact various physiological systems within the body, presenting an increased risk of serious adverse events (AEs) such as gastrointestinal bleeding or cardiovascular disease (3). However, opioids pose more significant risks to patients, not only regarding their physical side effects (respiratory depression, nausea, drowsiness, dizziness, etc.), but additionally due to the tolerance that patients build over time, thereby leading to misuse, and eventual addiction (4). Currently, the United States stands amid an ongoing epidemic, where a rise in opioid-related drug overdose deaths has reached an alarming rate. The origins of this epidemic date back to the early 1990s, where pharmaceutical companies began initially prescribing opioid prescriptions for acute and chronic pain, under the impression that these analgesics posed minimal risks to patients (5). However, patients rapidly began to develop a tolerance towards opioids, and the dangerously addictive nature of the drug soon led to severe ramifications including misuse, overdose, and in more extreme cases, death. Consequently, in 2017, U.S. Department of Health and Human Services subsequently declared the opioid crisis to be a public health emergency (6). With the many risks that the ongoing opioid epidemic has given rise to, anesthesiologists have thus recently begun to transition towards prescribing NSAIDs more frequently as an effective alternative.

Various studies have assessed randomized controlled trials (RCTs) and ongoing clinical trials on the efficacies of opioid-free NSAID therapy, as a suitable alternative treatment (7). For example, a systematic review conducted by Bailey *et al.* [2013] has assessed the efficacies of opioid-free treatment with ibuprofen and/or paracetamol after wisdom teeth surgery. Results from the Bailey *et al.* review showed that ibuprofen could bring significant post-operative pain relief, indicating that NSAIDs can provide similar clinical benefits that opioids bring, while eliminating the added risks of addiction and misuse (7). Thus, this review will evaluate the efficacies of various NSAIDs compared to those of opioids, and examine the beneficial outcomes of transitioning to primarily NSAID-based therapies in the field of oral and maxillofacial surgery (OMFS). We present this article in accordance with the PRISMA reporting checklist (available at https://joma.amegroups.org/article/view/10.21037/joma-22-25/rc).

Highlight box

Key findings

- NSAID-exclusive treatment has shown to have a statistically significantly lower number of AEs in patients following OMFS.

What is known and what is new?

- Recent clinical trials have shown that various NSAIDs such as ibuprofen can induce significant post-operative pain relief in patients following surgery. This shows that NSAIDs can provide similar clinical benefits as opioids do, while eliminating added risks of overdependence and addiction. This manuscript examines the efficacies of various NSAIDs in postoperative pain control and affirms that NSAID-exclusive treatment can reduce AEs in patients following OMFS.

What is the implication, and what should change now?

- A shift to primarily NSAID-based and opioid-sparing therapies can be considered in the future of oral and maxillofacial anesthesia. Future research must be done in determining any statistically significant difference in the effects of NSAIDs *vs.* opioids in pain management through measurements of VAS scores and rescue analgesic consumption.

Methods

A systematic review was conducted for literature pertaining to the use of both NSAIDs and opioids in OMFS, to compare the efficacies of both drugs.

Literature search

A search of relevant literature spanned databases including PubMed, The Cochrane Library, and https://www.clinicaltrials.gov/ and included all relevant publications from origin dating up to 01/05/2023. The following

search strategy was utilized: ((((“anti inflammatory agents non steroidal”[Pharmacological Action] OR “anti inflammatory agents, non steroidal”[MeSH Terms] OR (“anti inflammatory”[All Fields] AND “agents”[All Fields] AND “non steroidal”[All Fields]) OR “non-steroidal anti-inflammatory agents”[All Fields] OR “nsaid”[All Fields] OR “nsaids”[All Fields] OR “nsaid s”[All Fields] OR ((“nonsteroid”[All Fields] OR “nonsteroidal”[All Fields] OR “nonsteroidals”[All Fields] OR “nonsteroids”[All Fields]) AND (“anti inflammatory agents”[Pharmacological Action] OR “anti inflammatory agents”[MeSH Terms] OR (“anti inflammatory”[All Fields] AND “agents”[All Fields]) OR “anti inflammatory agents”[All Fields] OR (“anti”[All Fields] AND “inflammatory”[All Fields] AND “drug”[All Fields]) OR “anti inflammatory drug”[All Fields]))) AND (“analgesics opioid”[Pharmacological Action] OR “analgesics, opioid”[MeSH Terms] OR (“analgesics”[All Fields] AND “opioid”[All Fields]) OR “opioid analgesics”[All Fields] OR “opioid”[All Fields] OR “opioids”[All Fields] OR “opioid s”[All Fields]) AND “OMFS”[All Fields]) OR ((“mouth”[MeSH Terms] OR “mouth”[All Fields] OR “oral”[All Fields]) AND “maxillofacial”[All Fields])) AND (“pain”[MeSH Terms] OR “pain”[All Fields])) AND (“clinicaltrial”[Filter] OR “randomizedcontrolledtrial”[Filter]). No formal protocol registration was performed.

Selection criteria

A predetermined eligibility criteria for this literature search included (I) head-to-head RCTs concerning the efficacy of a NSAID to an opioid; (II) clinical trials assessing patient populations after undergoing OMFS. Exclusion criteria included (I) non-RCT studies (e.g., retrospective studies, single-arm trials, etc.); (II) studies that used external drugs other than NSAIDs and opioids in the experimental arm (anesthetics, steroids, paracetamol, etc.); (III) crossover studies that did not primarily compare the efficacies of a specific NSAID and opioid in the experimental arms; (IV) ongoing clinical trials that had no results released at the time of the literature search (V) systematic literature reviews, meta-analyses, etc.

Quality assessment

The risk of bias in this study was assessed through the Cochrane Collaboration’s Risk of Bias tool. Each study’s risk of bias was assessed based upon the protocol’s blinding, study design, and data/results. Different types of biases evaluated include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases (*Figure 1*).

Outcomes

The primary outcome of this study was assessments of numerical pain scores measured using the visual analogue scale (VAS). The secondary outcomes included (I) total rescue analgesic consumption for measuring efficacy, and (II) total number of AEs witnessed for measuring safety. All results that were compatible with each outcome in each study were sought and included in data extraction.

Statistical analysis

All analyses were executed using the IBM SPSS statistics 28.0 software. VAS scores and rescue analgesic consumption were analyzed separately in continuous meta-analyses, by measuring the unstandardized mean difference (unequal group variances), with a 95% confidence interval (CI) to assess overall efficacy of each drug. AEs were analyzed through a binary meta-analysis by measuring relative risk (RR), with a 95% CI to assess risk of adverse outcomes associated with each drug. Heterogeneity between each study was measured through τ^2, H^2, and I^2 calculations. A random-effects model was used. For the VAS scores and rescue analgesic consumption analyses, studies where the outcome was reported as a mean ± standard deviation (SD) were incorporated. For the AEs analysis, all studies that analyzed the AEs in question as outcomes, were incorporated into the analysis. Studies that did not measure certain outcomes of interest were not included in the respective analyses. Studies with data that were unable to be converted appropriately were also not included in the respective analyses.

Results

Literature search

A total of 1,616 records were identified amongst the aforementioned databases using the specified keywords. Among them, 151 duplicates were initially removed. The remaining 1,465 titles/abstracts were screened, and 1,438 articles were removed using the predetermined inclusion/exclusion criteria. Subsequently, 27 full-text articles were screened for final eligibility. Six identified studies that met the inclusion/exclusion criteria were included in the final

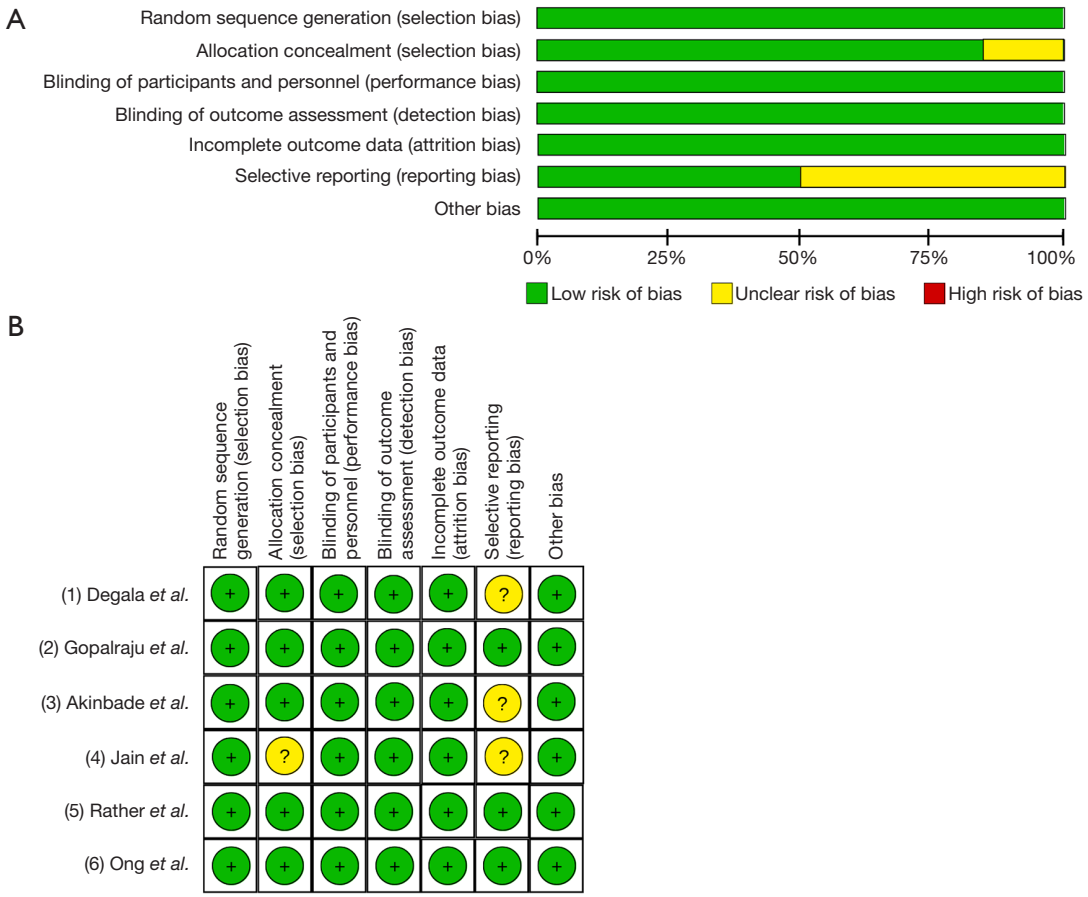

Figure 1 Risk of bias assessment. +, low risk of bias; ?, unknown risk of bias.

review (*Figure 2*).

Study characteristics

The selected studies from this literature search include 6 head-to-head RCTs utilizing one specifically selected NSAID and one specifically selected opioid for a head-to-head comparison (*Table 1*). The specific NSAID/opioid comparisons assessed include three tramadol *vs.* ketorolac studies, one tramadol *vs.* celecoxib study, one tramadol *vs.* lornoxicam study, and one fentanyl *vs.* ketorolac study. Sample sizes ranged from 40 to 90 patients, and each RCT used a study population of patients having undergone some type of oral-maxillofacial surgery (i.e., third molar extraction, reduction, and internal fixation, etc.). The efficacies of each NSAID and opioid in question were assessed by various means across all studies including (but not limited to) VAS pain scores, time to first rescue analgesic, total rescue analgesic consumption, total number of AEs, and overall global assessments.

VAS analysis

The mean VAS scores from 4 studies (n=200) (9,10,12,13) were pooled into the data analysis: Gopalraju *et al.* [2013], Ong *et al.* [2004], Jain *et al.* [2017], and Rather *et al.* [2022]. Degala *et al.* [2018] (8) was excluded in the analysis, because the VAS scores were reported in ranges, and no mean/SD was reported, that could be used for the purposes of a meta-analysis. Akinbade *et al.* [2019] (11) was also excluded in this analysis, because the study reported VAS scores in terms of median and range, which could not be used in meta-analysis. For the 4 studies included in the analysis, the mean and SD data for VAS scores at 12-hour post-operatively in both opioid and NSAID groups were analyzed. The analysis demonstrated no significant difference (P=0.45) between the opioid and NSAID group with heterogeneity [mean difference (MD) =5.26; 95% CI: (–8.50, 19.01); I^2=95%] (*Figure 3*).

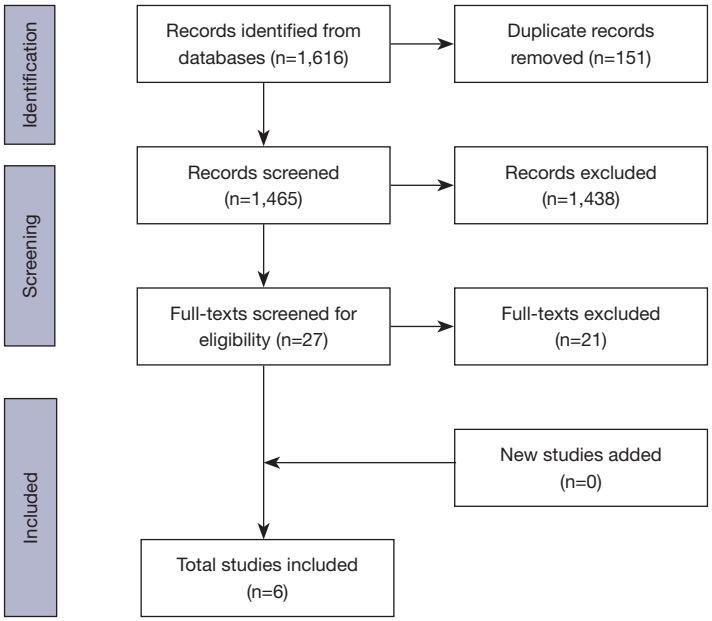

Figure 2 Flow diagram of included records.

Rescue analgesic analysis

The mean values for rescue analgesic consumption from 2 studies (n=120) (10,13) were pooled into another analysis: Ong *et al.* [2004] and Rather *et al.* [2022]. The remaining 4 studies were not included in this analysis because total rescue analgesic consumption was not measured for either group. For the 2 studies included in the analysis, the mean and SD data for total rescue analgesic tablets consumed within a 5-day recovery period, in both opioid and NSAID groups were analyzed. The analysis demonstrated no significant difference (P=0.62) between the opioid and NSAID group with heterogeneity [MD =−1.93; 95% CI: (−9.57, 5.70); I^2=98%] (*Figure 4*).

AEs analysis

Four AEs including dizziness, drowsiness/somnolence, nausea, and vomiting were included in the analysis for 4 of the selected studies (8,11-13). Akinbade *et al.* [2019] and Rather *et al.* [2022] were included in analysis for all 4 AEs, while Degala *et al.* [2018] and Jain *et al.* [2017] were only included in the analysis for nausea. The remaining studies were not included in this analysis because the AEs in question were not measured for either group. For the purposes of this analysis, the opioid group was considered the "treatment" group.

Dizziness

The meta-analysis for dizziness included Akinbade *et al.* [2019] and Rather *et al.* [2022] (n=150) (11,13), which indicated a significant difference in occurrence (P=0.03) between the opioid and NSAID groups, with no heterogeneity [RR =1.26; 95% CI: (0.15, 2.37); I^2=0%]. This analysis indicated that the NSAID group showed more favorable results pertaining to less AEs for dizziness (*Figure 5*).

Drowsiness/somnolence

The meta-analysis for drowsiness/somnolence included Akinbade *et al.* [2019] and Rather *et al.* [2022] (n=150) (11,13), which indicated a significant difference in occurrence (P=0.04) between the opioid and NSAID groups, with no heterogeneity [RR =2.11; 95% CI: (0.05, 4.18); I^2=0%]. This analysis indicated that the NSAID group showed more favorable results pertaining to less AEs for drowsiness/somnolence (*Figure 6*).

Nausea

The meta-analysis for nausea included Akinbade *et al.* [2019], Degala *et al.* [2018], Jain *et al.* [2017], and Rather *et al.* [2022] (n=236) (8,11-13), which indicated a significant difference in occurrence (P=0.01) between the opioid and

Table 1 Study characteristics

Study	Year	Size	Population	Opioid treatment	NSAID treatment	Endpoints	Conclusion
Degala *et al.* (8), tramadol *vs.* ketorolac	2018	46	Patients following maxillofacial surgery (i.e., open reduction internal fixation)	100 mg IV tramadol at time of closure, 8 h, and 16 h after	30 mg IV ketorolac at time of closure, 8 h, and 16 h after	(I) VAS pain scores (II) Adverse effects	Patients in the tramadol group experienced better pain control in comparison to those in the ketorolac group
Gopalraju *et al.* (9), tramadol *vs.* ketorolac	2013	40	Patients following mandibular third molar extraction	50 mg tramadol 10 min prior to surgery	30 mg ketorolac 10 min prior to surgery	(I) VAS pain scores (II) Time to rescue analgesic (III) Amount of rescue analgesic consumption (IV) 5-point global assessment	Patients in the ketorolac group experienced better control of postoperative pain and less adverse reactions, in comparison to those in the tramadol group
Ong *et al.* (10), tramadol *vs.* ketorolac	2004	60	Patients following mandibular third molar extraction	50 mg IV tramadol	30 mg IV ketorolac	(I) VAS pain scores (II) Time to rescue analgesic (III) Amount of rescue analgesic consumption (IV) Global assessment	Patients in the ketorolac group experienced better control of postoperative dental pain, in comparison to those in the tramadol group
Akinbade *et al.* (11), tramadol *vs.* celecoxib	2019	90	Patients following mandibular third molar extraction	100 mg tramadol every 8 h	400 mg celecoxib start, 200 mg celecoxib every 12 h after	(I) VAS pain scores (II) Adverse effects	Patients in the celecoxib group demonstrated better pain scores and less adverse effects, in comparison to those in the tramadol group
Jain *et al.* (12), tramadol *vs.* lornoxicam	2017	40	Patients following open reduction and internal fixation of mandibular fractures	50 mg IV tramadol at time of closure, 8 h, and 16 h after	8 mg IV lornoxicam at time of closure, 8 h, and 16 h after	(I) VAS pain scores (II) Adverse effects	Patients in the lornoxicam group demonstrated better pain control in comparison to those in the tramadol group
Rather *et al.* (13), fentanyl *vs.* ketorolac	2022	60	Patients diagnosed with dry socket 24–72 hours following teeth extraction	25 mcg/hour fentanyl patch	10 mg oral ketorolac tablet	(I) VAS pain scores (II) Safety/tolerability (III) Rescue medication consumption (IV) BPI questionnaire	Patients in the fentanyl group demonstrated better pain scores in comparison to those in the ketorolac group

NSAID, non-steroidal anti-inflammatory drug; IV, intravenous; VAS, visual analogue scale.

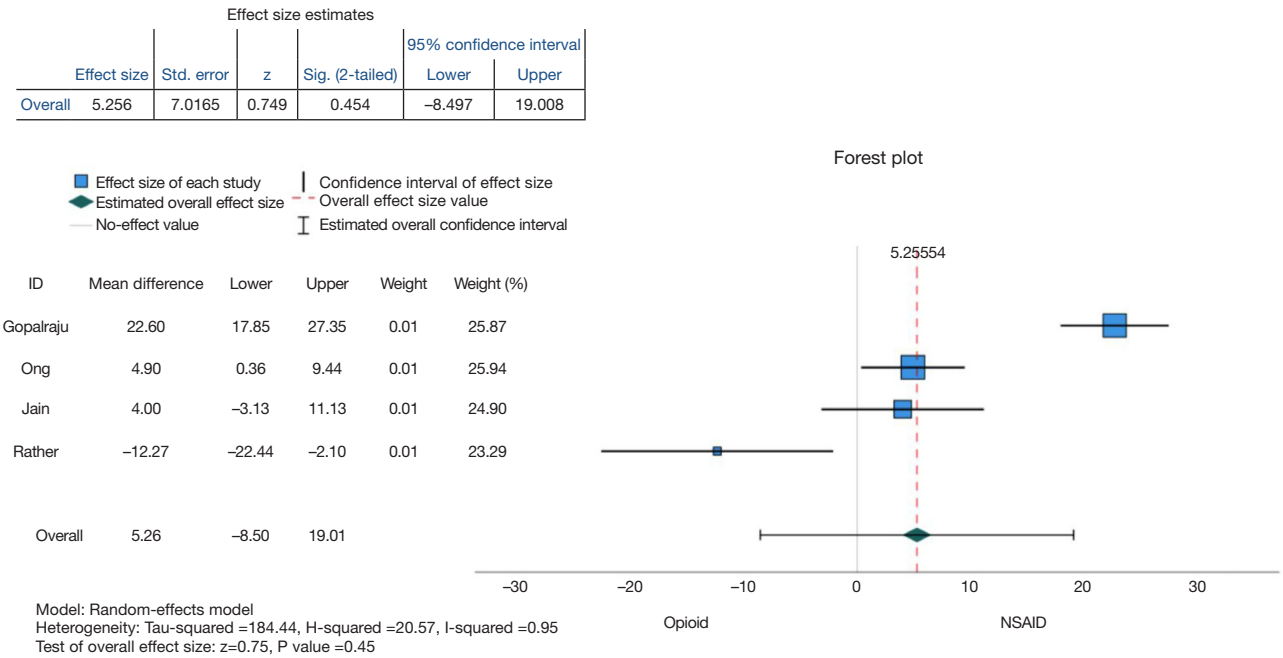

Figure 3 VAS pain scores meta-analysis. VAS, visual analogue scale; NSAID, non-steroidal anti-inflammatory drug.

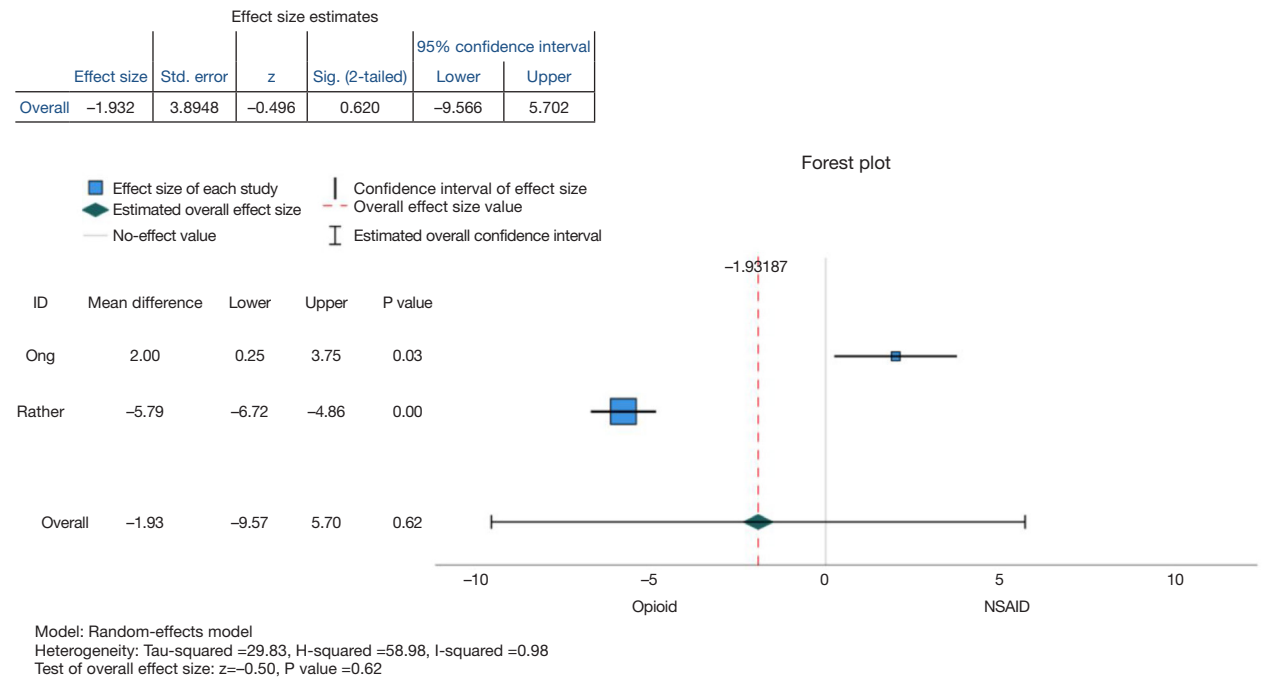

Figure 4 Rescue analgesic consumption meta-analyses. NSAID, non-steroidal anti-inflammatory drug.

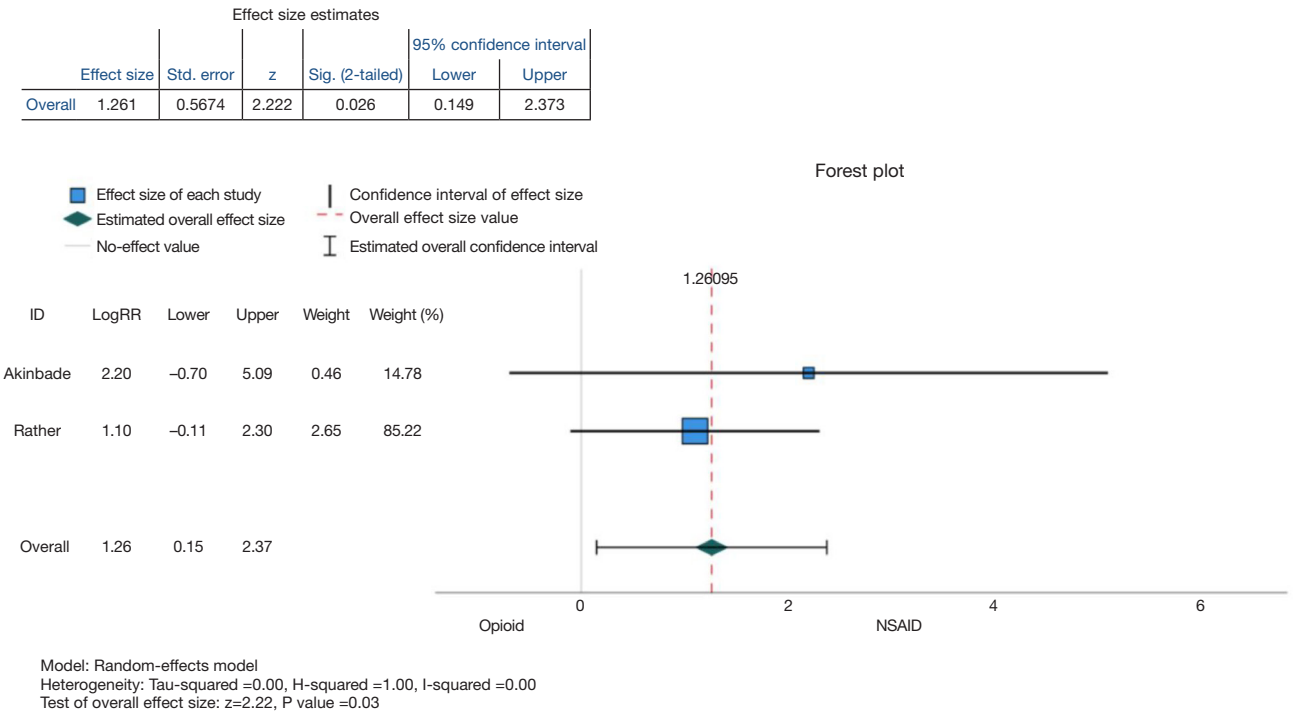

Figure 5 Adverse effects meta-analysis-dizziness. RR, relative risk; NSAID, non-steroidal anti-inflammatory drug.

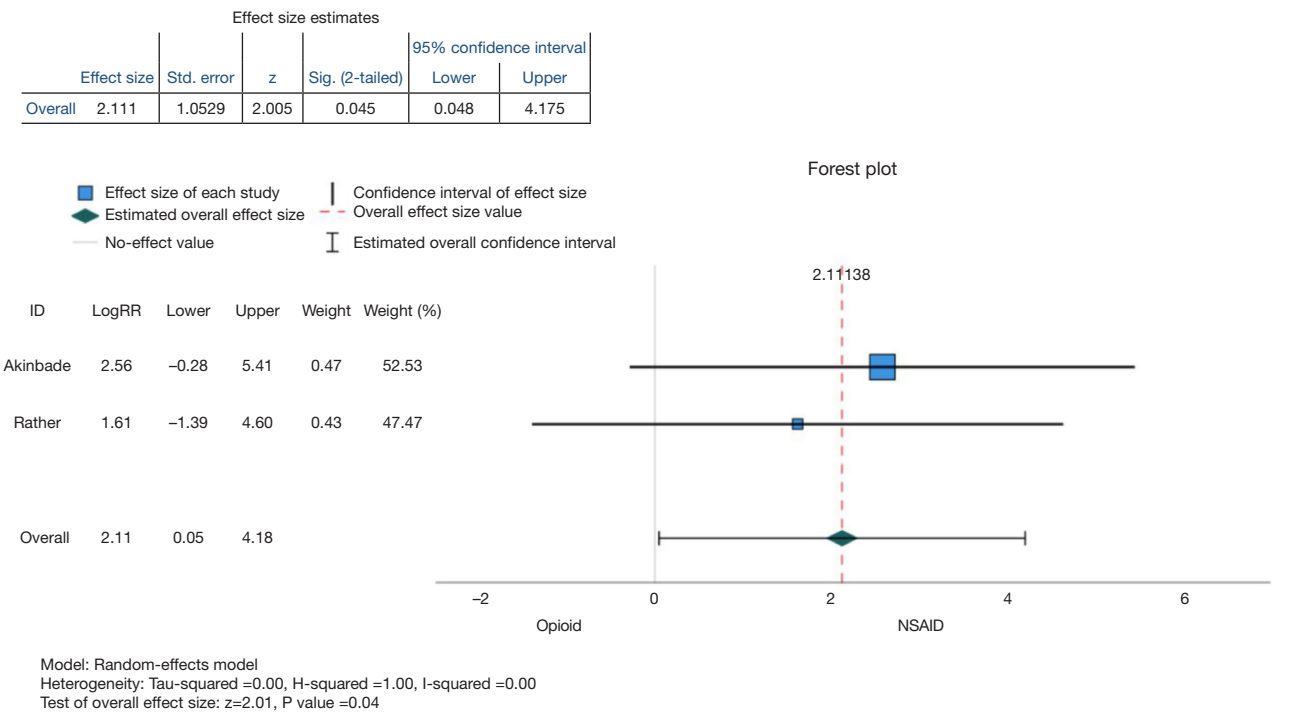

Figure 6 Adverse effects meta-analysis-drowsiness and somnolence. RR, relative risk; NSAID, non-steroidal anti-inflammatory drug.

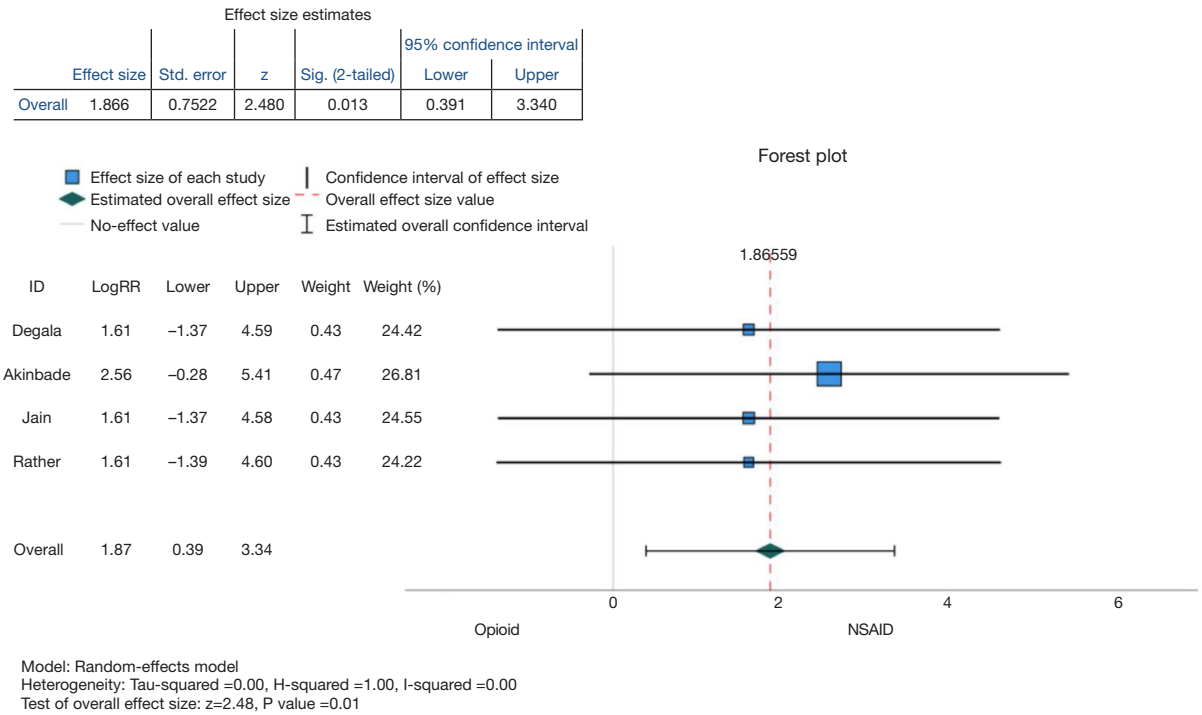

Figure 7 Adverse effects meta-analysis-nausea. RR, relative risk; NSAID, non-steroidal anti-inflammatory drug.

NSAID groups, with no heterogeneity [RR =1.87; 95% CI: (0.39, 3.34); I^2=0%]. This analysis indicated that the NSAID group showed more favorable results pertaining to less AEs for nausea (*Figure 7*).

Vomiting

The meta-analysis for vomiting included Akinbade *et al.* [2019] and Rather *et al.* [2022] (n=150) (11,13), which indicated a significant difference in occurrence (P<0.001) between the opioid and NSAID groups, and no heterogeneity [RR =1.64; 95% CI: (0.58, 2.71); I^2=0%]. This analysis indicated that the NSAID group showed more favorable results pertaining to less AEs for vomiting (*Figure 8*).

Discussion

Pain scores

In each of the 6 RCT studies (8-13), postoperative pain was evaluated in accordance with the VAS. Using the VAS, patients physically mark their perceived acute pain intensity along a 10 cm scale, where each end of the scale represents extreme limits of either no pain at all, or the most intense pain possible (14). The VAS serves as an essential measurement of experienced pain intensity, which can easily be attributed to the efficacy of NSAIDs and opioids in reducing postoperative pain. The 6 selected RCTs showed varying results for VAS scores when comparing each study's opioid group to the NSAID group (*Table 2*). In Degala *et al.* [2018], patients who were given preoperative 100 mg intravenous (IV) tramadol reported lower VAS scores in comparison to patients who were given 30 mg IV ketorolac, when measured 2, 4, 6, 12, and 24 h post-operatively (8). In Gopalraju *et al.* [2013], patients who were given 50 mg ketorolac preoperatively reported lower VAS scores, in comparison to patients given 30 mg tramadol preoperatively (9). In Ong *et al.* [2004], 50 mg ketorolac preoperatively reported lower VAS scores over the course of 12h, in comparison to those given 30 mg tramadol preoperatively (10). Akinbade *et al.* [2019] additionally indicated lower median VAS scores for patients given treatment with celecoxib in comparison to those who received tramadol, when measured at 0, 4, 8, 16, 24, and 48 h post-operatively (11). In Jain *et al.* [2017], patients who received 8 mg lornoxicam preoperatively reported lower mean VAS scores than those who received 50 mg tramadol,

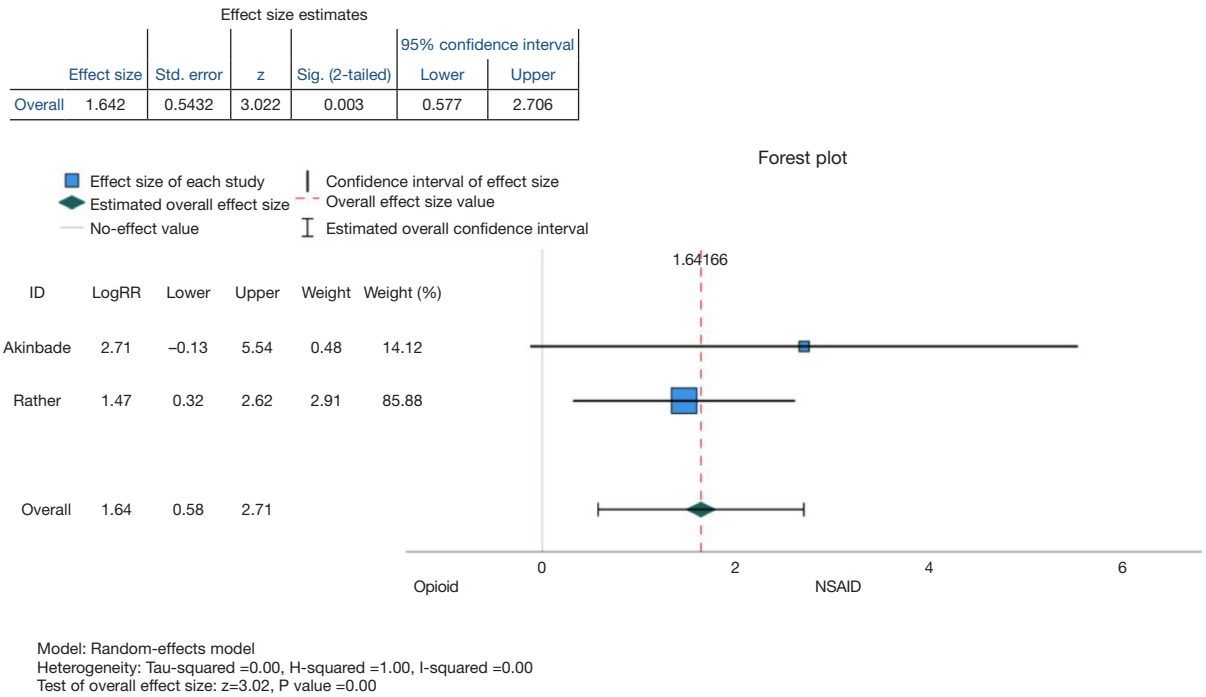

Figure 8 Adverse effects meta-analysis-vomiting. RR, relative risk; NSAID, non-steroidal anti-inflammatory drug.

when measured at 2, 4, 6, 12, and 24 h postoperatively (12). Lastly, in Rather *et al.* [2022], patients given a 25 mcg/h fentanyl patch reported lower mean VAS scores over the course of 6 days post-operatively, when compared to patients who consumed a 10 mg ketorolac tablet (13). Overall, 4 out of the 6 studies indicated that patients who received NSAIDs for pain treatment reported lower VAS scores in comparison to those who received opioids. As seen through the meta-analysis, no statistically significant difference was found between the pooled NSAID and opioid groups with regards to self-reported VAS scores. Thus, future research will be essential in establishing if NSAIDs can truly provide better pain control in terms of reduced VAS scores in comparison to opioids.

Rescue analgesic needs

Within 3 of the studies (9,10,13), standard protocol allowed for rescue analgesics to be administered post-operatively, for enhanced management of pain (*Table 3*). Each study selected paracetamol—a non-opioid analgesic—to serve as the rescue drug. Measurements taken for each group included time elapsed prior to first rescue analgesic intake, and total rescue analgesic consumption. In Gopalraju *et al.* [2013], patients were given the option of taking 500 mg paracetamol as needed post-operatively (9). Looking at the median time to re-medication within the two groups, the ketorolac group appeared to show better control of post-operative pain when it came to rescue analgesic consumption, with a median time of 10 h, in comparison to the tramadol group with a median time of 7 h. In Ong *et al.* [2004], patients were advised to take 1,000 mg paracetamol as a rescue analgesic for postoperative pain (10). A total of 16.7% of the patients who received opioids did not consume any rescue analgesic within the 12 h observation period, while 36.7% of the patients who received NSAIDs did not consume any rescue analgesic (10). Overall, the ketorolac group reported both longer times before the first rescue analgesic consumption (9.5±3.0 h) and less tablets consumed total (4.4±3.1), in comparison to the tramadol group (7.6±2.7 h) and (6.4±3.8) respectively (10). According to the average times, ketorolac provided an additional 2h of pain relief in comparison to tramadol, and given the lower number of tablets consumed in the ketorolac group, this indicates that the NSAID may have better control of postoperative pain overall. Lastly, in Rather *et al.* [2022], a total average of 2.16±1.53 tablets of paracetamol medication were consumed amongst patients in the fentanyl group throughout a 6-day observational

Table 2 VAS outcomes

Study	VAS scale	Assessment times	Opioid group scores (VAS score: no. patients)	NSAID group scores (VAS score: no. patients)	Conclusion
Degala *et al.* (8), tramadol *vs.* ketorolac	100 mm	2, 4, 6, 12, and 24 h postoperatively	2 h: 0–10: 0 11–30: 11 31–60: 11 61–100: 1 4 h: 0–10: 5 11–30: 13 31–60: 5 61–100: 0 6 h: 0–10: 10 11–30: 10 31–60: 3 61–100: 0 12 h: 0–10: 11 11–30: 8 31–60: 3 61–100: 1 24 h: 0–10: 17 11–30: 6 31–60: 0 61–100: 0	2 h: 0–10: 0 11–30: 6 31–60: 17 61–100: 0 4 h: 0–10: 0 11–30: 12 31–60: 11 61–100: 0 6 h: 0–10: 1 11–30: 17 31–60: 5 61–100: 0 12 h: 0–10: 4 11–30: 18 31–60: 1 61–100: 0 24 h: 0–10: 5 11–30: 17 31–60: 1 61–100: 0	Patients in the tramadol group demonstrated lower mean VAS scores at each time point
Gopalraju *et al.* (9), tramadol *vs.* ketorolac	100 mm	Hourly for 12 h	Mean ± SD: 54.6±7.1	Mean ± SD: 32.9±8.18	Patients in the ketorolac group demonstrated lower mean VAS scores at over the course of 12 h
Ong *et al.* (10), tramadol *vs.* ketorolac	100 mm	Hourly for 12 h	Mean ± SD: 20.0±10.1	Mean ± SD: 15.1±7.7	Patients in the ketorolac group demonstrated lower mean VAS scores at over the course of 12 h
Akinbade *et al.* (11), tramadol *vs.* celecoxib	100 mm	0, 4, 8, 16, 24, and 48 h postoperatively	Median [range]: 0 h: 24.5 [0–98]; 4 h: 51.5 [5–100]; 8 h: 32.0 [0–98]; 16 h: 15.5 [0–78]; 24 h: 10.0 [0–79]; 48 h: 8.0 [0–80]	Median [range]: 0 h: 22.0 [0–100]; 4 h: 24.0 [0–97]; 8 h: 23.0 [0–83]; 16 h: 15.0 [0–98]; 24 h: 7.0 [0–98]; 48 h: 4.0 [0–89]	Patients in the celecoxib group demonstrated lower median VAS scores at each time point

Table 2 (*continued*)

Table 2 (*continued*)

Study	VAS scale	Assessment times	Opioid group scores (VAS score: no. patients)	NSAID group scores (VAS score: no. patients)	Conclusion
Jain *et al.* (12), tramadol *vs.* lornoxicam	10 cm	2, 4, 6, 12, and 24 h postoperatively	Mean ± SD: 2 h: 2.45±0.9; 4 h: 2.50±1.1; 6 h: 2.35±1.3; 12 h: 2.00±1.2; 24 h: 2.10±1.1	Mean ± SD: 2 h: 2.25±1.0; 4 h: 2.15±0.9; 6 h: 2.00±0.8; 12 h: 1.60±1.1; 24 h: 1.45±0.6	Patients in the lornoxicam group demonstrated lower mean VAS scores at each time point
Rather *et al.* (13), fentanyl *vs.* ketorolac	100 mm	Every AM and PM for 6 days	Mean ± SD: day 1 (AM): 70.36±14.95; day 1 (PM): 52.33±21.28; day 2 (AM): 29.86±24.09; day 2 (PM): 23.60±23.20; day 3 (AM): 15.26±16.27; day 3 (PM): 12.06±15.80; day 4 (AM): 12.10±18.24; day 4 (PM): 11.10±14.64; day 5 (AM): 8.33±9.48; day 5 (PM): 6.33±7.22; day 6 (AM): 4.90±6.00; day 6 (PM): 4.86±7.66	Mean ± SD: day 1 (AM): 74.86±15.77; day 1 (PM): 64.60±18.84; day 2 (AM): 61.13±19.79; day 2 (PM): 56.56±19.85; day 3 (AM): 57.50±22.26; day 3 (PM): 53.86±23.37; day 4 (AM): 52.43±21.33; day 4 (PM): 45.90±22.25; day 5 (AM): 42.66±23.14; day 5 (PM): 35.46±21.63; day 6 (AM): 29.63±18.85; day 6 (PM): 27.46±21.35	Patients in the fentanyl group demonstrated lower mean VAS scores at each time point

VAS, visual analogue scale; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; AM, morning; PM, evening.

Table 3 Rescue analgesic outcomes

Study	Medication	Opioid group time to re-medication (h)	NSAID group time to re-medication (h)	Opioid group total analgesic consumption (no. tablets)	NSAID group total analgesic consumption (no. tablets)
Gopalraju *et al.* (9), tramadol *vs.* ketorolac	Paracetamol 500 mg	Median [range]: 7 [5–15]	Median [range]: 10 [8–14]	N/A	N/A
Ong *et al.* (10), tramadol *vs.* ketorolac	Paracetamol: 1,000 mg	Mean ± SD (range): 7.6±2.7 (6.7–8.7)	Mean ± SD (range): 9.5±3.0 (8.4–10.6)	Mean ± SD (range): 6.4±3.8 (5.0–7.8)	Mean ± SD (range): 4.4±3.1 (3.2–5.6)
Rather *et al.* (13), fentanyl *vs.* ketorolac	Paracetamol: 650 mg	N/A	N/A	Mean ± SD: day 1: 1.26±0.78; day 2: 0.40±0.67; day 3: 0.20±0.40; day 4: 0.23±0.62; day 5: 0.06±0.25; day 6: 0.00	Mean ± SD: day 1: 1.93±0.90; day 2: 1.76±0.77; day 3: 1.86±1.19; day 4: 1.46±1.07; day 5: 0.93±1.08; day 6: 0.53±0.89

NSAID, non-steroidal anti-inflammatory drug; N/A, not available; SD, standard deviation.

period (13). This number was significantly lower in comparison to the 8.50±3.98 average tablets consumed in the ketorolac group (13). Overall, results from all studies indicated a mixed need for rescue analgesic for patients given treatment with opioids, in comparison to those who were given NSAIDs. The use of ketorolac appeared to provide better pain control (both in terms of time elapsed prior to the first intake and total amount consumed), when compared head-to-head with IV tramadol in the first two studies. However, when ketorolac was compared with a fentanyl patch in the third study, the fentanyl patch seemed to provide better pain control postoperatively. As seen through the meta-analysis, no statistically significant difference was found between the pooled NSAID and opioid groups with regards to rescue analgesic consumption. Thus, future research must be conducted, comparing other NSAIDs to other opioids, in order to affirm whether or not NSAIDs can truly provide better pain control in regards to

Table 4 Adverse effects

Study	Opioid group		NSAID group	
	Size	No. patients (%)	Size	No. patients (%)
Degala *et al.* (8), tramadol *vs.* ketorolac	23	Nausea/vomiting: 2 (8.7)	23	Nausea/vomiting: 0 (0.0)
		Sweating/nausea: 0 (0.0)		Sweating/nausea: 1 (4.3)
		Abnormal vitals: 0 (0.0)		Abnormal vitals: 0 (0.0)
Akinbade *et al.* (11), tramadol *vs.* celecoxib	45	Drowsiness: 6 (13.3)	45	Drowsiness: 0 (0.0)
		Vomiting: 7 (15.6)		Vomiting: 0 (0.0)
		Nausea: 5 (11.1)		Nausea: 0 (0.0)
		Dizziness: 4 (8.9)		Dizziness: 0 (0.0)
		Others: 3 (6.7)		Others: 0 (0.0)
Jain *et al.* (12), tramadol *vs.* lornoxicam	20	Nausea/vomiting: 2 (10.0)	20	Nausea/vomiting: 0 (0.0)
		Gastric acidity: 0 (0.0)		Gastric acidity: 1 (5.0)
		Abnormal vitals: 0 (0.0)		Abnormal vitals: 0 (0.0)
Rather *et al.* (13), fentanyl *vs.* ketorolac	30	Nausea: 14 (46.0)	30	Nausea: 9 (30.0)
		Vomiting: 13 (43.3)		Vomiting: 3 (10.0)
		Somnolence: 2 (6.6)		Somnolence: 0 (0.0)
		Dizziness: 9 (30.0)		Dizziness: 3 (10.0)
		Headache: 11 (36.6)		Headache: 16 (53.3)
		Application site reaction: 0 (0.0)		Application site reaction: 0 (0.0)
		Constipation: 11 (36.6)		Constipation: 3 (10.0)
		Epigastric pain: 3 (10.0)		Epigastric pain: 11 (36.6)

NSAID, non-steroidal anti-inflammatory drug.

less rescue analgesic needs.

AEs

Four out of the 6 studies monitored vitals and various AEs to assess the safety and tolerability of the drugs in question (*Table 4*) (8,11-13). In Degala *et al.* [2018], vitals and AEs were monitored between the tramadol and ketorolac group (8). Vitals were found to remain normal, while two reportings of nausea/vomiting were found in the tramadol group, and one event of sweating and nausea was reported from the ketorolac group (8). In Akinbade *et al.* [2019], AEs including drowsiness, nausea, vomiting, and dizziness were measured between the celecoxib and tramadol groups (11). Within the tramadol group, 25 (55.56%) out of the total 42 patients experienced AEs of some sort, whereas none of the 45 patients in the celecoxib group reported no AEs of any kind (11). In Jain *et al.* [2017], vital signs and side effects such as nausea/vomiting and gastric acidity were evaluated between the group who received 8 mg lornoxicam and those who received 50 mg tramadol (12). Data indicated that 2 out of the 20 patients in the tramadol group experienced nausea/vomiting, while 1 out of the 20 patients in the lornoxicam group experienced gastric acidity (12). Both statistics, however, were not significant, and could potentially be attributed to normal side effects of anesthesia and pre-surgical fasting (12). Additionally, all patients had vitals within normal limits (12). Lastly, in Rather *et al.* [2022], several AEs including nausea/vomiting, somnolence, dizziness, headache, application site reaction, constipation, and epigastric pain were monitored between the fentanyl and ketorolac group (13). Overall, (with the two exceptions of headache and epigastric pain), a greater number of patients in the fentanyl group seemed to experience more

AEs in comparison to those in the ketorolac group (13). This study also measured antiemetic consumption amongst the opioid and NSAID group. While no antiemetics were consumed within the ketorolac group, the fentanyl group averaged a total of 0.56±1.30 tablets of antiemetic medication over the course of the 6-day observational period (13). The consumption of antiemetic medication within the fentanyl group aligns with the indication that the use of fentanyl for pain relief may present a greater likelihood of observed AEs associated with nausea and vomiting. In the end, although some studies showed insignificant differences in side effects between the opioid and NSAID group, it should be noted that patients receiving opioids appear to be experiencing more AEs, particularly when looking at the tramadol *vs.* celecoxib trial and the fentanyl *vs.* ketorolac trial. As seen through the meta-analysis, the NSAID groups within the pooled studies all exhibited significantly more favorable outcomes for AEs in comparison to the opioid groups. Thus, there is an evident benefit to using NSAID treatment over opioid treatment, with regards to mitigating the occurrence of such AEs.

Limitations

This study is primarily limited in the sense that only head-to-head trials that compared the efficacies of one specific NSAID and one specific opioid were included. The goal of this review was to evaluate the efficacies of NSAIDs independently, in comparison to other types of opioid treatments; thus, studies that compared the efficacies of combinatorial therapies (i.e., NSAIDs and opioids combined) or treatments involving other types of anesthetics were excluded. Moreover, primary and secondary outcomes for VAS scores, rescue analgesic consumption, and AEs were oftentimes not reported in a consistent means across all 6 studies assessed. For example, not every study reported their VAS outcomes as a mean ± SD; some reported them as a median, and others reported them in ranges. While reporting VAS scores as a median or range may have been a more comprehensive statistic given the nature of the results for certain studies, this made it difficult to incorporate all 6 studies together within a quantitative meta-analysis. Consequently, only 4 studies were included in the analysis for the primary outcome of VAS pain scores. This same limitation was seen in the analysis for rescue analgesic consumption and AEs, where certain studies in the review did not measure these given outcomes in a way that could be incorporated into the analysis. Particularly for the outcome of AEs, only a limited number (4) of AEs were analyzed. Thus, future head-to-head trials have the potential to assess more AEs to a greater degree when comparing the efficacy and safety of both drugs. Finally, the sample sizes for each RCT were also relatively small, with the largest sample size only consisting of 90 patients. Thus, further studies generalizing research to a larger population would be increasingly beneficial in confirming the results found from these studies.

Conclusions

In conclusion, this review demonstrates that NSAIDs have the potential to serve as a safe and suitable therapy in treating postoperative pain with OMFS, when considering assessments of pain control and AEs. While no significant difference in VAS scores and rescue analgesic consumption was indicated in the meta-analysis, 4 out of the 6 studies still exhibited lower VAS scores in the NSAID group, when compared to the opioid group. Additionally, the NSAID groups exhibited significantly better outcomes in terms of AEs. This finding is important when assessing the safety and tolerability of opioids, when considering the consequences of the ongoing global epidemic. If opioids pose patients at a greater risk for AEs in addition to addiction, it may be worthwhile to consider transitioning from primarily opioid-based therapies to opioid-free or opioid-sparing anesthesia. In the end, the studies assessed in this review focused primarily on the independent efficacies of NSAIDs and opioids in OMFS. However, future research looking into an assessment of combinatorial therapies with NSAIDs and opioids used in conjunction with one another, can also be useful in understanding the potential benefits of opioid-sparing therapies.

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