SYSTEMATIC REVIEW

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Systemic Nonsteroidal Anti-Inflammatories for Analgesia in Postoperative Critical Care Patients: A Systematic Review and Meta-Analysis of Randomized Control Trials

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OBJECTIVES: While opioids are part of usual care for analgesia in the ICU, there are concerns regarding excess use. This is a systematic review of nonsteroidal anti-inflammatory drugs (NSAIDs) use in postoperative critical care adult patients.

DATA SOURCES: We searched Medical Literature Analysis and Retrieval System Online, Excerpta Medica database, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, trial registries, Google Scholar, and relevant systematic reviews through March 2023.

STUDY SELECTION: Titles, abstracts, and full texts were reviewed independently and induplicate by two investigators to identify eligible studies. We included randomized control trials (RCTs) that compared NSAIDs alone or as an adjunct to opioids for systemic analgesia. The primary outcome was opioid utilization.

DATA EXTRACTION: In duplicate, investigators independently extracted study characteristics, patient demographics, intervention details, and outcomes of interest using predefined abstraction forms. Statistical analyses were conducted using Review Manager software Version 5.4. (The Cochrane Collaboration, Copenhagen, Denmark).

DATA SYNTHESIS: We included 15 RCTs ($n = 1,621$ patients) for admission to the ICU for postoperative management after elective procedures. Adjunctive NSAID therapy to opioids reduced 24-hour oral morphine equivalent consumption by 21.4 mg (95% CI, 11.8–31.0 mg reduction; high certainty) and probably reduced pain scores (measured by Visual Analog Scale) by 6.1 mm (95% CI, 12.2 decrease to 0.1 increase; moderate certainty). Adjunctive NSAID therapy probably had no impact on the duration of mechanical ventilation (1.6 hr reduction; 95% CI, 0.4 hr to 2.7 reduction; moderate certainty) and may have no impact on ICU length of stay (2.1 hr reduction; 95% CI, 6.1 hr reduction to 2.0 hr increase; low certainty). Variability in reporting adverse outcomes (e.g., gastrointestinal bleeding, acute kidney injury) precluded their meta-analysis.

CONCLUSIONS: In postoperative critical care adult patients, systemic NSAIDs reduced opioid use and probably reduced pain scores. However, the evidence is uncertain for the duration of mechanical ventilation or ICU length of stay. Further research is required to characterize the prevalence of NSAID-related adverse outcomes.

KEY WORDS: intensive care unit; ketorolac; meta-analysis; nonsteroidal anti-inflammatory drugs; opioid

Opioids are liberally administered in ICUs as part of analgesic and sedation regimens (1). However, prolonged opioid exposure can lead to patients developing tolerance, physical dependence, and withdrawal if abruptly discontinued (2). These effects may carry over even after discharge

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KEY POINTS

Question: Can adjunctive analgesic nonsteroidal anti-inflammatory drugs (NSAIDs) reduce opioid exposure in postoperative critical care adult patients?

Findings: In this systematic review and meta-analysis of 15 randomized control trials that included 1,621 postoperative critical care adult patients, adjunctive NSAID therapy to opioids reduced 24-hour oral morphine equivalent consumption by 21.4 mg (95% CI, 11.8–31.0 mg reduction; high certainty). In addition, NSAIDs modestly reduced pain with no impact on the duration of mechanical ventilation or ICU length of stay.

Meaning: Adjunctive NSAIDs reduce opioid use and probably reduce pain scores. Further research on adverse events with NSAIDs is required.

from the hospital. In the United States, 4.1% of patients admitted to the ICU postoperatively developed new persistent opioid use (3). Excess opioid prescription at discharge from hospital increases the risk of opioids available for inappropriate use. Additionally, concerns remain regarding the role of opioids in delirium, respiratory depression, and ileus (2, 4–7). Thus, a clear need for alternative adjunctive analgesics (using a multimodal approach) to reduce opioid use in the ICU for pain control is required (1).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the outpatient setting for its effective anti-inflammatory, anti-pyretic, and analgesic properties (8). These properties result from NSAIDs role in inhibiting cyclooxygenase (COX), which reduces prostaglandin synthesis to mitigate inflammation and pain. There are currently two distinct COX isoforms, COX-1, which has been implicated in the development of gastric injury and COX-2, which mediates NSAIDs anti-inflammatory and analgesic properties (9). This has resulted in the development of COX-2 selective inhibitors such as celecoxib in addition to traditional nonselective and COX-1 selective inhibitor NSAIDs such as ketorolac, ibuprofen, and naproxen. Prescription NSAIDs like ketorolac have been used extensively as a single dose in emergency medicine and for postoperative analgesia (10–13). However, concerns regarding NSAIDs (both nonselective and COX-2 selective) side-effect profile including renal dysfunction, gastrointestinal bleeding, and cardiac disease remain (14, 15). These adverse events are well documented in the literature, but their prevalence in the ICU setting remains unclear.

The Society of Critical Care Medicine guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) from 2018 included a weak recommendation against the use of NSAIDs in the critical care setting, citing only minor reduction in opioid use and risks of potential adverse outcomes such as kidney injury and gastrointestinal bleeding (1). Systematic reviews published since then have suggested that the opioid-sparing effect of NSAIDs may be understated while the prevalence of adverse outcomes remains uncertain (16). However, concerns remain surrounding the small number of studies analyzed, as well as the inconsistent inclusion of trials in pooled analysis across the PADIS guideline and recent reviews (1, 16, 17). Furthermore, there is evidence that lower dose NSAIDs (defined as lower than recommended dose on drug monograph) may be beneficial for specific patient populations (e.g., emergency department, post-surgical patients: orthopedic, spinal, cardiac, abdominal, obstetrical) (12, 13, 18–23). However, the evidence for opioid-sparing and analgesic effects of NSAIDS in critically ill populations remains uncertain.

To address this, we conducted a comprehensive and updated systematic review and meta-analysis of the available evidence on systemic NSAID use in the critically ill adult population.

METHODS

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and was registered with the International Prospective Register of Systematic Reviews (CRD42022332635) on May 26, 2022 (24). The completed PRISMA checklist is included in **Supplementary Table E1** (http://links.lww.com/CCX/B213).

Search Strategy

We developed the search strategy with the assistance of a medical librarian (J.Y.K.), and the strategy underwent

peer review before search translation (25). We conducted a systematic search in Ovid Medical Literature Analysis and Retrieval System Online, Ovid Excerpta Medica database, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Library (via Wiley) on May 29, 2022, and updated on March 30, 2023. In addition, we also searched trial registries (e.g., ClinicalTrials.gov), Google Scholar, and bibliographies from included studies as well as relevant systematic and narrative reviews. The search did not restrict results based on publication type or language. Search strategies for each database are listed in **Supplementary Table E2** (http://links.lww.com/CCX/B213).

Study Selection

Study selection was made independently and in duplicate by two investigators (C.M., K.B.T.) using Covidence systematic review software (Veritas Health Innovations, Melbourne, VIC, Australia). Titles and abstracts were screened for study design, population, and intervention. Any study that was identified as potentially eligible at this first stage was advanced to full-text review for assessment of eligibility. We resolved disagreements using a third party (V.I.L.) if needed. We recorded reasons for exclusion at the full-text review stage only.

We included randomized control trials (RCTs) that compared NSAIDs as adjunctive systemic analgesia to opioids alone in the adult critical care setting. Critical care patients included all medical, surgical, and trauma patients admitted to the ICU. The intervention group consisted of NSAIDs alone or as an adjunct to opioids. Opioid dosing could be either scheduled, through patient-controlled analgesia, or administered as needed. We excluded observational cohort studies, retrospective analyses, and nonpeer reviewed research. We also excluded studies that looked at preoperative or perioperative interventions or lacked opioid-only control/placebo groups.

The primary outcome was opioid utilization, which we standardized to oral morphine equivalent (OME) using published guidelines (26). We included the following secondary outcomes: differences in pain scores, duration of mechanical ventilation, ICU and hospital length of stay, delirium, and mortality (ICU and hospital). If multiple time points were reported for opioid utilization and pain scores, the time point with the most data available was subject to pooled analysis for our primary and secondary outcomes. We also included safety outcomes such as rates of adverse events (e.g., bleeding, renal dysfunction, constipation), and longer-term psychologic effects (e.g., chronic pain, post-traumatic stress disorder) defined by individual study authors.

Data Extraction

We completed data extraction independently and in duplicate by two investigators (C.-H.M., K.B.T.) using predefined abstraction forms. A third reviewer resolved any discrepancies (V.I.L.). We recorded study characteristics, patient demographics, intervention details, and outcomes of interest. We requested data from authors of studies with missing results, if applicable. We also extrapolated outcomes that were only presented graphically using a web plot digitizer (27).

Risk of Bias and Grading of Recommendations, Assessment, Development, and Evaluation Assessment

We assessed risk of bias using the modified Cochrane Collaboration risk of bias tool in the following domains: sequence generation, allocation concealment, participant/investigator blinding, selective reporting, outcome blinding, addressing incomplete data, and other biases (28). Each domain was assigned a low, probably low, probably high, or high risk of bias. We determined the overall risk of bias by taking the highest risk score in any individual domain. We assessed the overall certainty of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (29). We used the narrative summaries as endorsed by GRADE (moderate certainty is "probably," low certainty is "may," and very low certainty is "uncertain") to describe the effect size and certainty of evidence (30). Disagreements within the risk of bias and GRADE assessment were resolved by discussion and consensus.

Data Analysis

We conducted meta-analysis using Review Manager software Version 5.4. (The Cochrane Collaboration, Copenhagen, Denmark) using the DerSimonian and

Laird random-effects model to pool effect sizes for all outcomes of interest (31). We calculated the relative risk (RR) ratio for dichotomous outcomes and the mean difference for continuous outcomes, with corresponding 95% CIs. When necessary, we converted medians to mean and SD using methods suggested by the Cochrane Collaboration (32).

We assessed heterogeneity using the I^2 statistic, the chi-square test for homogeneity, and visual inspection of the forest plots. We considered directionality, the I^2 value, where greater than 50% may suggest substantial heterogeneity, and perceived heterogeneity in deciding when to downgrade the certainty of the evidence for inconsistency (33). Although we had planned to produce funnel plots and perform Egger's weighted regression plot analysis to assess for small study effects, none of the included outcomes had sufficient included trials (at least 10 studies) to allow for this analysis.

Subgroup Analyses

Several a priori subgroup analyses were considered (with hypothesized direct of effect) (34):

1) Ketorolac versus other NSAIDs (ketorolac use would result in greater opioid reduction compared with other NSAIDs);
2) Younger (age < 55) versus elderly (age ≥ 55) (NSAID-related adverse outcomes would be less in the younger patient population);
3) Higher Acute Physiology and Chronic Health Evaluation (APACHE) scores (≥ 25) versus lower APACHE scores (< 25) (NSAIDs would be more beneficial in patients with lower APACHE scores); and
4) High versus low risk of bias studies (high risk of biases would favor NSAID use).

At the request of peer reviewers, we also performed a post hoc subgroup analyses on high versus low intensity NSAID therapy to address the heterogeneous NSAID dosing schedules across included RCTs. Using standardized equianalgesic NSAID doses, RCTs with NSAID doses, which met or exceeded the daily maximum recommended dose on the drug monograph were categorized as high intensity (35).

RESULTS

Search Results and Study Characteristics

We identified 3,029 citations, reviewed 73 full-text manuscripts, and included 15 RCTs in the meta-analysis (22, 36–49) (**Fig. 1**). **Supplementary Table E3** (http://links.lww.com/CCX/B213) provides further details on the demographics and baseline characteristics of included trials. The meta-analysis included 1,621 patients with an overall mean age of 58 ± 11.3 years, 23% of which were female. All studies had exclusion criteria that included either renal dysfunction, past gastrointestinal disease including bleeding history, or significant past cardiac disease. The indication for ICU admission in all trials was postoperative monitoring for elective surgeries. Cardiac surgeries accounted for 12 studies, 11 of which were post-coronary artery bypass grafts. Other studies included post-spinal fusion surgery (38), gastrectomy (39), major abdominal surgery (22), and hepatectomy (48). NSAIDs used in the trials included nonselective (diclofenac, ketoprofen, ketorolac, indomethacin) and COX-2 selective (parecoxib, valdecoxib, etodolac) inhibitors. Of note, Hynninen et al (42) compared three different NSAIDs with a placebo control group. Morphine was the most common opioid used in the trials (9/15 trials), but also included other opioids, such as fentanyl, tramadol, buprenorphine, codeine, oxycodone, and piritramide. Adjunctive acetaminophen was administered in three trials in addition to NSAIDs (42, 43, 47).

Risk of Bias Assessment

Six out of the 15 trials were deemed to have a low risk of bias (37–39, 42, 48, 49) (**Supplementary Table E4**, http://links.lww.com/CCX/B213). Five trials had inadequate sequence generation (22, 36, 40, 44, 47), three had inadequate allocation concealment (22, 40, 47), and three trials had concerns with blinding of participants/study personnel (40, 43, 46) (Supplementary Table E4, http://links.lww.com/CCX/B213). One trial had incomplete blinding of outcome assessment (47), another did not sufficiently address missing outcome data (41), and another had concerns with selective reporting (45).

Outcomes

Figure 2 summarizes the findings for each outcome, including the forest plot and GRADE certainty was summarized for each outcome in Figure 2 (opioid use, pain) and **Supplementary Figure E1** (http://links.lww.com/CCX/B213) (duration of mechanical ventilation,

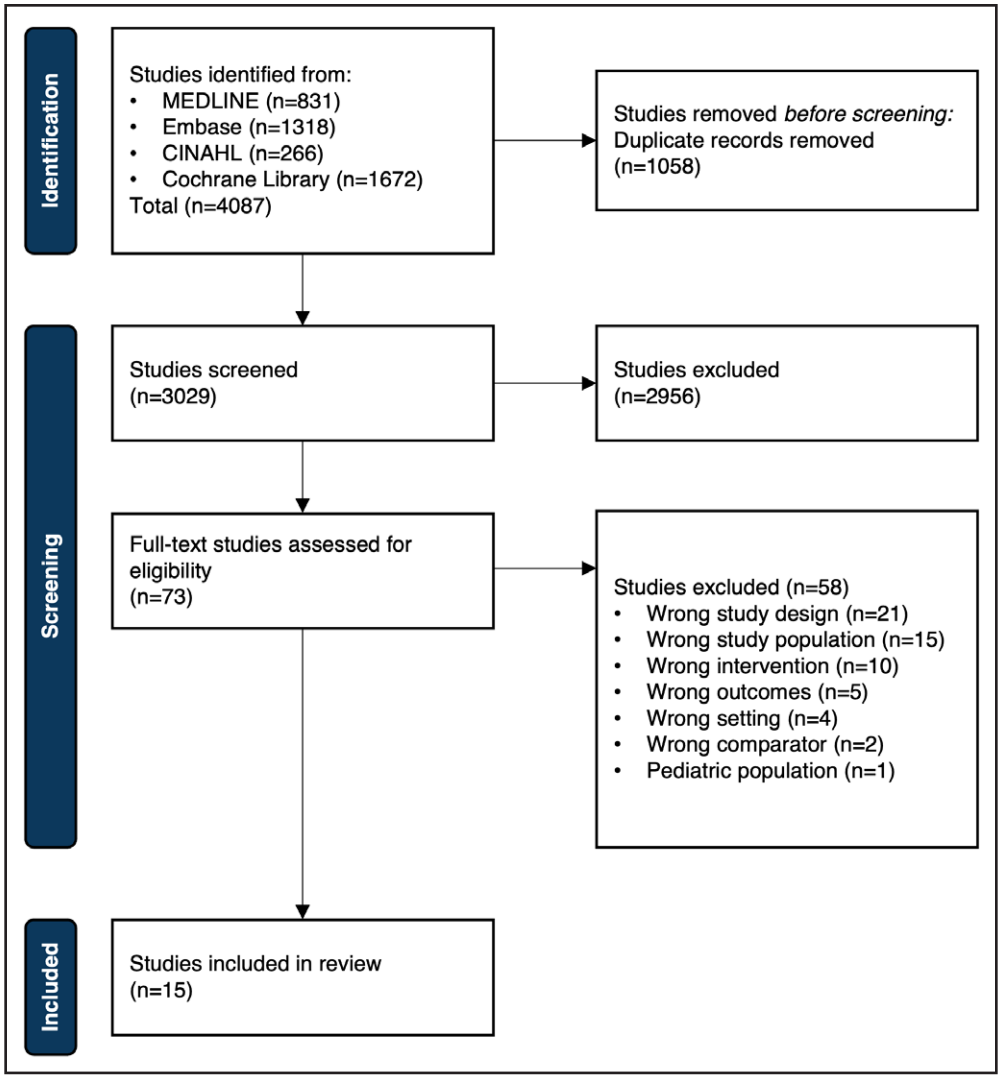

Figure 1. Flow chart of study selection. CINAHL = Cumulative Index to Nursing and Allied Health Literature, MEDLINE = Medical Literature Analysis and Retrieval System Online.

ICU length of stay, bleeding). We have also included the reasoning for rating down evidence in the GRADE analysis in **Supplementary Table E5** (http://links.lww.com/CCX/B213).

Addition of an NSAID as adjunctive analgesia reduced 24-hour OME utilization by 21.4 mg (95% CI, −11.8 to −31.0 mg reduction; high certainty). It also probably reduced pain measured by the Visual Analog Scale by 6.1 mm (95% CI, −12.2 to +0.1; moderate certainty) at 24 hours. There was probably no impact on mechanical ventilation with the NSAID group (−1.6 hr; 95% CI, −0.4 to −2.7; moderate certainty) and NSAIDs may not have an impact on ICU length of stay (−2.1 hr; 95% CI, −6.1 to +2.0 hr; low certainty). Hospital length of stay was not reported in any of the included trials.

Due to insufficient data, we were only able to complete a priori subgroup analysis on risk of bias of individual studies, which showed no evidence of effect modification by risk of bias (**Supplementary Fig. E2**, http://links.lww.com/CCX/B213). Our post hoc subgroup analyses indicate no evidence of effect modification by high intensity NSAID on reducing 24-hour opioid consumption (**Supplementary Fig. E3**, http://links.lww.com/CCX/B213).

Adverse Outcomes

For the outcome of bleeding, four trials (n = 265) examining blood loss after 24 hours showed that adjunctive use of NSAIDs probably did not impact blood loss (−32.7 mL; 95% CI, −23.0 to −42.3 mL; moderate certainty) compared with opioid analgesia alone (Supplementary Fig. E1, http://links.lww.com/CCX/B213). Pooled estimates also show that NSAIDs have an uncertain effect on nausea and vomiting (RR = 0.93 [95% CI, 0.68–1.28]; p = 0.66; very low certainty) (Supplementary Table E5, http://links.lww.com/CCX/B213). Furthermore, qualitative assessment of adverse outcomes that were not amenable to pooling did not suggest an increased risk of complications such as gastrointestinal bleeding (**Table 1**).

For the outcome of acute kidney injury (AKI) defined per individual study protocol, Oberhofer et al (22) and Rapanos et al (49) described no AKI events in either group. Of the remaining four papers that reported on AKI, two reported no difference in the occurrence of AKI (42, 47), and one did not report statistical significance of difference in oliguria prevalence (40). Khalil et al (44) showed a statistically significant increase in

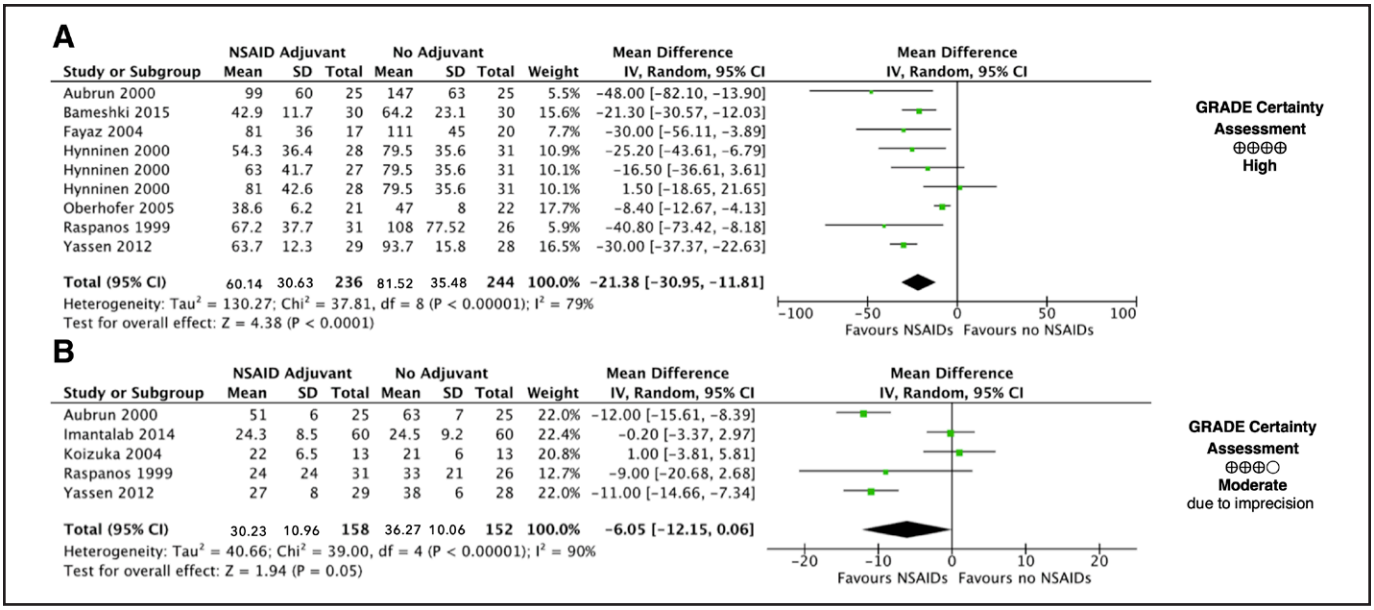

Figure 2. Pooled analysis of outcomes. Forest plot of opioid consumption in oral morphine equivalents (**A**) and pain scores in Visual Analog Scale (**B**). *df* = degrees of freedom, GRADE = Grading of Recommendations, Assessment, Development, and Evaluation, NSAIDs = nonsteroidal anti-inflammatory drugs.

TABLE 1.
Qualitative Description of Adverse Outcomes

Reported Adverse Events	Nonsteroidal Anti-Inflammatory Drug Adjuvant, *n* (%)	No Adjuvant, *n* (%)	Significance
Barilaro et al (40)	*n* = 15	*n* = 15	
ST segment elevation > 0.1 mm	1 (7)	1 (7)	NA
Contraction of diuresis	2 (13)	0	NA
Hynninen et al (42)	*n* = 83	*n* = 31	
≥ 20% increase in creatinine	5 (6)	1 (3)	Not significant
Khalil et al (44)	*n* = 21	*n* = 19	
Oliguria requiring diuretics	16 (76)	9 (47)	*p* = 0.04
Hypotension requiring inotrope support	7 (33)	8 (42)	NA
Ott et al (47)	*n* = 311	*n* = 151	
Myocardial infarct	5 (2)	1 (1)	*p* = 0.7
Gastrointestinal bleed	3 (1)	0	*p* = 0.6
Constipation	116 (37)	56 (37)	*p* > 1
Death	4 (1)	0	*p* = 0.3
Oliguria	15 (10)	45 (15)	*p* = 0.2

NA = not applicable (no significance was recorded), ST = the interval on an electrocardiogram between the end of the S wave and the beginning of the T wave.

oliguria treated with diuretics for patients allocated to the NSAID group compared with opioid-only group. However, none of the patients' AKI progressed to being treated with renal replacement therapy (44). Delirium was not assessed in any of the included trials.

DISCUSSION

This systematic review and meta-analysis demonstrated that adjunctive NSAID analgesia in the postoperative critical care setting, compared with opioids alone, reduced 24-hour opioid utilization (high certainty evidence) and probably reduced pain scores at 24 hours (moderate certainty evidence). Adjunctive NSAIDs probably did not impact duration of mechanical ventilation (moderate certainty evidence) and may not have impacted ICU length of stay (low certainty evidence). For adverse outcomes, NSAIDs probably have no effect on blood loss 24 hours postoperatively (moderate certainty evidence) and have an uncertain effect on nausea or vomiting (very low certainty evidence). Other adverse outcomes were inconsistently reported, which prevented a pooled analysis, specifically AKI and gastrointestinal bleeding, two of the most well-known complications of NSAID use. However, a qualitative assessment of the studies suggested minimal differences in renal, gastrointestinal bleeding, and cardiac dysfunction between the two groups.

The current PADIS 2018 guidelines included a weak recommendation against using COX-1 selective NSAIDs as an adjunct to opioid therapy with no recommendations for COX-2 selective inhibitors due to lack of evidence (1). The PADIS guideline was informed by a pooled analysis of two trials by Hynninen et al (42) and Oberhofer et al (22), which showed that adjunctive NSAID analgesia reduced 24-hour opioid use by 1.61 mg morphine equivalent (4.8 mg OME) with a nonsignificant reduction in pain scores at 24 hours (1). The PADIS guideline concluded that the potential risk of harm superseded the small opioid-sparing effect of NSAIDs. Since then, a meta-analysis of four trials by Wheeler et al (16), including the study by Hynninen et al (42), showed that NSAIDs reduced 24-hour opioid use by 11.1 mg OME, more than double what was initially described in the PADIS guideline. Our pooled analysis for opioid reduction involved seven RCTs and demonstrated that the addition of NSAIDs reduced total opioid use by 21.4 mg OME in 24 hours.

Our findings challenge the notion that NSAIDs may have only a small beneficial impact on reducing opioid use, although the clinical significance of the reduction remains unclear. Furthermore, opioid dependence as an outcome was not studied in this review. Gaps in evidence remain regarding clinically significant opioid reduction in critically ill patients, as they typically have higher opioid requirements and higher baseline pain secondary to pain from critical illness, invasive ventilation, and monitoring. In the ICU setting, where continuous infusions (0–2 mg/hr) of IV hydromorphone are commonly used, daily hydromorphone exposure can be up to 48 mg (50). However, there is evidence to indicate that any opioid dose over 20 mg OME per day can increase the risk of future overdoses (51, 52). Furthermore, reducing opioid use from greater than or equal to 50 mg OME daily to less than 20 mg can decrease the risk of overdose by half. Our systematic review suggests that the role of NSAIDs in the arsenal of multimodal analgesia may be considered to achieve a clinically significant reduction in opioid use and possibly pain scores.

The perceived adverse events specific to NSAID use, including AKI, gastrointestinal bleeds, and cardiovascular events, remain a significant barrier to their widespread use in the ICU. Although these risks have been extensively investigated, their prevalence in the ICU has not been well documented since, historically, NSAIDs have been avoided in critically ill patients (53). Standard ICU clinical practices, which include close monitoring of creatinine, early fluid resuscitation, and stress ulcer prophylaxis, can reduce adverse outcomes from NSAIDs (54, 55). Studies in hospitalized patients with preserved kidney function have found that short-term NSAID use was not associated with an increased risk of AKI (56–58). Even in cases of NSAID-induced AKI, cessation of the drug usually led to a favorable prognosis and was not associated with progression to long-term dialysis (59, 60). In gastrointestinal bleeds, the coadministration of PPIs significantly reduces the risk of ulcers and is recommended across various treatment guidelines, although this has not been validated in critical care patients (61, 62). Last, more recent evidence has indicated that adverse cardiac events are less than previously thought (11, 53, 63–65). In a RCT assessing adverse outcomes of NSAID use in postoperative cardiac surgery patients on the ward, a 7-day course of ibuprofen for systemic

analgesia compared with oxycodone suggests no significant difference in rates of myocardial infarction or gastrointestinal bleeding (66). An increased rate of AKIs was noted in the ibuprofen group, although there was no progression to dialysis (66). In summary, the adverse effects of NSAIDs in the critical care setting remains unclear. Recent guidelines have suggested that IV ketorolac can be used as an adjunctive analgesic in the ICU for up to 5 days (67). This recommendation was based on level C quality evidence where expert opinion supported the recommendation but acknowledged a paucity of specific evidence.

Our review has several strengths. First, this is the most comprehensive meta-analysis on NSAID use in the ICU to date. The adverse outcome of NSAID use (bleeding) was subjected to a pooled analysis for the first time. Further strengths are its inclusion of strictly RCTs, adherence to our preregistered protocol, and inclusion of studies published in a non-English language.

Our review also has several limitations. The inclusion of only postoperative ICU patients with results limited to the first 24 hours, in small sample size RCTs, reduces the generalizability of our findings (to the broader nonsurgical ICU patient population) and may underestimate the true prevalence of adverse outcomes, particularly when NSAID exposure is prolonged. Patients with preexisting renal insufficiency, gastrointestinal disease, bleed history, or significant cardiac disease were also excluded, which too restricts the generalizability of our findings. In addition, the majority of included RCTs were published greater than 10 years ago when nonopioid analgesic regimens, including enhanced recovery after surgery protocols, were infrequently used (39). The lack of available RCTs that assessed the opioid sparing effects of NSAIDs in the context of a multimodal analgesic regimen may lead to a potential overestimation of the opioid sparing effects of NSAIDs. Our findings are also based on some low-quality trials with high risks of bias, which is reflected in our GRADE analysis (Supplementary Table E5, http://links.lww.com/CCX/B213). However, most studies had low risk of bias, and our subgroup analyses did not show any effect modification. This limitation was also present in previous systematic reviews, emphasizing the need for further, methodologically rigorous research investigating NSAIDs in ICU patients.

While the opioid crisis rages, there remains a demand for adjunctive analgesics to reduce opioid consumption in the ICU setting, where other researchers are also looking at alternatives such as ketamine, gabapentin, lidocaine, and tramadol (1, 16, 68–71). Opioid utilization may be further reduced when we consider the well-documented synergistic analgesic effects of NSAID in addition to acetaminophen, a commonly used adjunctive analgesic in the critical care setting (1, 72, 73). While our meta-analysis indicates that NSAIDs reduce 24-hour opioid consumption, further research is required to characterize the adverse outcomes in a diverse cohort of ICU patients exposed to NSAIDs for a longer duration. The effect of longer duration exposure to NSAIDs on clinically important ICU outcomes such as duration of mechanical ventilation and/or ICU length of stay also requires further research. As suggested by our post hoc subgroup analysis on high versus low intensity NSAID doses, lower dosage NSAIDs can also be considered to reduce the prevalence of adverse outcomes while maintaining its opioid-sparing analgesic effect (74). Ketorolac, available in IV formulations, has been shown in low doses to be as effective in pain relief compared with higher doses (12, 13, 18–21, 23, 48). In conclusion, further research involving a diverse ICU population, with longer-term follow-up monitoring and varied doses and durations of NSAIDs, is necessary to provide much-needed evidence on the suitability of NSAIDs within a multimodal analgesic regimen in the ICU setting.

CONCLUSIONS

This systematic review and meta-analysis found that in postoperative critical care adult patients undergoing elective procedures, adjunctive systemic NSAIDs to an opioid analgesic regimen reduce 24-hour opioid utilization (high certainty evidence) and probably reduce pain scores at 24 hours (moderate certainty evidence). More robust data on adverse events with prolonged NSAID exposure is required.

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