SYSTEMATIC REVIEW AND META-ANALYSIS

A Systematic Review and Meta-analysis of Opioids vs Nonopioids in Acute Pancreatitis

Alfred D. Nelson,[1] Nahyr Sofía Lugo-Fagundo,[2] Soumya Jagannath Mahapatra,[3] Wisit Cheungpastiporn,[4] Charat Thongprayoon,[4] Karn Wijarnpreecha,[1] Gaurav Muktesh,[5] Rakesh Kochhar,[5] Pramod Garg,[3] Michael Wallace,[1] and Yan Bi[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, [2]Department of Internal Medicine, Mayo Clinic, Jacksonville, Florida, [3]Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India, [4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, and [5]Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

BACKGROUND AND AIMS: Although abdominal pain is one of the major criteria to diagnose acute pancreatitis (AP), there are no standardized guidelines to treat this troublesome symptom in the hospital setting. The aims of the study are to conduct a meta-analysis and to assess the efficacy of nonopioids vs opioids for pain management in AP. **METHODS:** We searched the medical literature through May 2021 to identify randomized controlled trials that examined the efficacy of opioids with nonopioids in AP pain management. Efficacy was reported as odds ratio (OR) with 95% confidence intervals (CIs) of each comparison tested. **RESULTS:** We identified 7 eligible randomized controlled trials, containing 389 patients. No significant difference in terms of pain intensity at day 1 (OR 0.82, 95% CI −2.55 to 4.19) was found between opioids and nonopioids. Nonopioids have a significantly high risk of supplementary analgesic use compared with opioids (OR 3.87, 95% CI 1.25–12.04). However, this significance is not seen when comparing nonsteroidal anti-inflammatory drugs and paracetamol with opioids (OR 1.67, 95% CI 0.73–3.82) after excluding trials with procaine. Opioids did not show a significant increase in the complications of pancreatitis, nausea and vomiting, sedation, and deaths when compared with nonopioids. **CONCLUSION:** We found nonopioids, especially nonsteroidal anti-inflammatory drugs and paracetamol, can provide adequate pain relief in patients with AP with no change in supplementary analgesic use and adverse events when compared with opioids. Further research is needed to optimize the use of nonopioids along or in combination with opioids for better pain control in patients with AP.

Keywords: Acute Pancreatitis; Opioids; Nonopioids; Paracetamol; NSAIDs

Introduction

Acute pancreatitis (AP) is characterized by the acute onset of local and systemic inflammatory response with varying clinical course depending on the severity.[1] It is the most common gastrointestinal cause leading to 250,000 hospitalizations and a significant cost burden in the United States.[2,3] The reported annual incidence of AP in the United States ranges up to 58 per 100,000 person-years.[3,4] Most patients will have mild AP, which is usually self-limiting with a mortality of around 3% which would rise to 20% in the presence of necrosis.[5]

Abdominal pain is one of the major criteria in diagnosing AP along with elevated levels of pancreatic enzymes (amylase or lipase >3 upper limit of normal) and radiological evidence (based on contrast-enhanced CT scan of the abdomen, MRI, or transabdominal ultrasound) although only 2 of 3 of the criteria are required for diagnosis based on the revised Atlanta consensus statement.[6] Gallstone and alcohol-associated pancreatitis are the most common causes of AP.[7]

Abdominal pain is the most common and sometimes the only presenting symptom in AP.[8] Fluid resuscitation helps with decreasing pain by preventing hypovolemia and hemoconcentration.[9] Despite this, most patients require analgesics for adequate control of pain. Pathogenesis of pain is complex with stimulation of presynaptic neurons by factors like proteases such as trypsin, leukotrienes, bradykinin, and arachidonic acid metabolites, which in turn release tachykinins, substance P, and calcitonin-gene-related peptide causing inflammation.[10]

Although step-up pain control has been suggested for cancer pain, there are no specific guidelines regarding AP pain control. In the United States, about 80% patients with

Abbreviations used in this paper: **AP, acute pancreatitis; CI, confidence interval; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; RCTs, randomized controlled trials; VAS, visual analog scale.**

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2021.09.006

AP used parenteral opioids as an initial treatment for pain control.[11] Among them, 9.6% end up with persistent opioid use up to 6 months after hospital discharge.[11] With opioid addiction being the most common problem in a long term along with a growing opioid epidemic in the United States, an effort to minimize its use of narcotics during hospitalization should be considered.

Previous Cochrane review had evaluated the effectiveness of opioids vs nonopioids as a subgroup analysis. However, the review included only 3 studies with low quality with moderate to high heterogeneity. Among these studies, only one study used anti-inflammatory medication (metamizole), and the other 2 used local anesthetics (procaine).[12] The most recent systemic review by Meng et al[13] included 8 studies in total with 3 comparing opioids vs nonopioids similar to the Cochrane review, 2 with 2 different opioids, and 3 with opioids or nonopioids with placebo. All previous studies had shown no analgesia is superior in terms of efficacy in controlling pain in AP. Since then, 4 studies that directly comparing opioids vs nonopioids in relieving pain in AP were published.[14–17] We, therefore, examined the efficacy of nonopioid vs opioid drugs for pain management of AP in a systematic review and meta-analysis.

Methods

Search Strategy and Study Selection

We conducted a comprehensive search of the multiple electronic databases till May 15, 2021, using Scopus (1960 to present), Web of Science (since inception), PubMed (1964 to present), EMBASE (1974 to present), and Cochrane database of systematic reviews (2005 to present). We also included clinicaltrials.gov (1964 to present) to search for trials that were not published with data to be potentially included as eligible studies. The search for the meta-analysis was conducted by an expert librarian with additional input from the authors. There were no language restrictions, and all foreign language articles were requested to get translated to English for review if needed. Studies on AP were identified using terms such as *acute pancreatitis*, *Pancreatitis*, and *Pancreatitis/complications* (both as medical subject headings and free-text terms), and *analgesic*, *anti-inflammatory agents*, *opioid analgesic*, *non-steroidal anti-inflammatory*, *drug therapy*, *drug treatment*, *anti-inflammatory* or *randomized control trial* (as free-text terms). These words were then combined with a specific set of operators 'AND/OR' to obtain multiple combinations along with filters for randomized clinical trials for identification of the abstracts based on the following: *Pancreatitis AND randomized control trial* (both as medical subject headings and free text) and *opioid analgesic OR non-steroidal anti-inflammatory OR analgesic* (as free-text terms) (Supplementary Section 1).

All eligible randomized controlled trials (RCTs) with adult patients (≥18 years) with a diagnosis of AP, based on specific criteria defined by the authors or Atlanta (1997) or modified Atlanta classification criteria (2013) for AP, were included. Studies recruiting patients with age <18 years old and pain management of chronic pancreatitis and studies for prevention of post–endoscopic retrograde cholangiopancreatography pancreatitis were ineligible for study inclusion. Only RCTs that examined the efficacy of opioids with nonopioids (nonsteroidal anti-inflammatory drugs [NSAIDs] or paracetamol or local anesthetics) were eligible for inclusion. All RCTs included with reported outcomes of interest in continuous variables and also dichotomous data were included. To maintain homogeneity between clinical trials, data were extracted at the end of the study for most of the endpoints even for studies conducted over a varying period. Visual analog scale (VAS) data were collected at the end of day 1. For studies with insufficient data in the original article or supplementary, we requested further information from the authors responsible for conducting the trial.

Two investigators (ADN and NSL) independently screened the abstracts identified based on the search criteria. Full-text articles were obtained for all potentially eligible abstracts. These were then evaluated as per the eligibility criteria by 2 investigators (ADN and NSL) independently, using predefined inclusion criteria (Supplementary Table 1). Disagreements were resolved by the senior author (YB). The agreement between the 2 investigators in the selection of full-text articles was assessed using the kappa statistic. This systematic review and meta-analysis was conducted follwoing PRISMA guidelines (Supplementary Table 2).

Outcome Assessment

We assessed the efficacy of opioid medications vs nonopioid medications in terms of pain intensity in response to therapy and the requirement of supplementary analgesia as primary endpoints.

The primary endpoints were as follows:

1. Intensity of pain measured by the VAS on day 1.
2. Number of participants requiring supplementary analgesic use.

The secondary endpoints of interest were also analyzed and mentioned in the following:

1. Number of participants with pancreatitis complications.
2. Number of participants with drug-related adverse events.
3. Number of deaths from any cause.

Data Extraction

Two investigators (ADN and NSL) independently extracted data for the necessary endpoints from the selected full-text articles using a Microsoft Excel spreadsheet as continuous variables and for dichotomous variables as well (Supplementary Section 2).

Quality Assessment and Risk of Bias

Two investigators (NSL and ADN) independently assessed the risk of bias at the study level. Disagreements were resolved by discussion or by involving the senior author (YB). The Cochrane risk of bias tool was used to assess the risk of bias, by documenting the method of the randomization process and treatment allocation concealment, by blinding of the study personnel, patients, and outcome assessment, and by determining any evidence of incomplete outcome data and evidence of selective reporting of outcomes.[18] For each of these components, the judgment is based on low, high, or unclear risk of bias, and the summary is presented in the form of a table.

Data Synthesis and Statistical Analysis

All data were extracted independently into a Microsoft Excel spreadsheet as a continuous variable in the form of mean, standard deviation, and the number of events for some endpoints (opioid vs nonopioid pain treatment for AP). Please see Supplementary Section 3 for more details.

Results

The search strategy identified 650 citations. Only 14 articles were reviewed for full text based on screening of the abstracts and titles with the aforementioned inclusion and exclusion criteria. After a thorough review, 7 articles were eligible for systematic review and meta-analysis which directly compared opioids vs non-opioids (local anesthetics, NSAIDs, and paracetamol) (Figure 1). Seven studies in total were excluded, and among them, 6 were compared either opioids vs opioids or opioids or nonopioids vs placebo, and one study was not completed. A total of 389 patients were randomized to either opioids or nonopioids. All medications were given intravenously except for morphine which was used subcutaneously in one study. Two RCTs compared local anesthetics (procaine) with buprenorphine and pentazocine.[19,20] Two RCTs compared paracetamol with hydromorphone and tramadol.[14,16] Two RCTs compared diclofenac with pentazocine and tramadol.[15,17] Other NSAIDs included were one RCT each with dexketoprofen and metamizole compared with tramadol and morphine, respectively.[16,21] Only one RCT compared 2 nonopioids (paracetamol and dextroketoprofen) with tramadol.[16] Table represents the baseline characteristics of the 7 RCTs. We have obtained data from the authors for endpoints that were not mentioned in the article. Agreement between 2 investigators for trial eligibility based on the selection of full text was excellent (kappa statistic = 0.85).

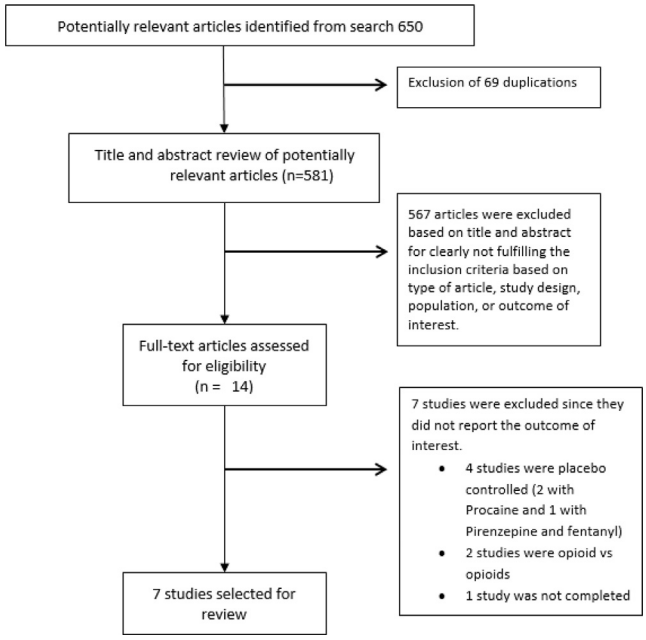

Figure 1. Flow diagram of included studies identified using a search strategy.

Quality Assessment

The risk of bias summary for all reported RCTs is presented in Figure 2A, and an overall assessment of risk of bias is presented in Figure 2B. The selection bias, performance bias, and detection bias were appropriate in 4 studies. All studies were at a low risk of attrition bias and reporting bias.

Publication Bias

There is no publication bias, no evidence of incomplete or selective reporting of outcomes among the included studies.

Primary Endpoints

Pain Intensity by the VAS at Day 1. Pain intensity was assessed in all 6 included studies, however, with different clinical endpoints. One study assessed the pain using the amount of morphine equivalents,[14] another study used VAS score change from baseline at 30 mins,[16] and the linear analog scale with only median and reduction of pain scores in day 1 and day 3 were reported by Jakobs et al.[19] Only 3 RCTs that assessed pain intensity using the VAS at day 1 reported as mean and standard deviation were used in the analysis. There is no difference in pain intensity between opioid use vs non-opioid use at day 1 using the VAS (odds ratio [OR] 0.82, 95% confidence interval [CI] −2.55 to 4.19) with high heterogeneity (98%) among the studies (Figure 3). The sensitivity analysis after removing the study by Peiro et al was mentioned in Figure A1 which showed no significance. The high heterogeneity is due to statistical significance in each of the studies as shown in the funnel plot (Figure A2).

Supplementary Analgesic Use. Six RCTs were included for assessing supplementary analgesic use which used different types of opioids as supplementary medications to relieve pain. The criteria and frequency to use of supplementary analgesic varied among trials. The odds of receiving supplementary analgesic while taking nonopioids were significant with a *P*-value of 0.02 (OR 3.87, 95% CI 1.25–12.04) (Figure 4A). The moderate heterogeneity of 64% is due to 2 studies both using procaine as shown in the funnel plot (Figure A3). The significance is due to procaine as shown in Figure 4B. The sensitivity analysis without these 2 procaine studies showed no significant difference in use of supplementary analgesic when NSAIDs and paracetamol were compared with opioids (OR 1.67, 95% CI 0.73–3.825) with no heterogeneity among studies (Figure 4C). There was also no significant difference when only NSAIDs were compared with opioids (OR 1.40, 95% CI 0.58–3.40) with no heterogeneity among studies (Figure 4D).

Table. Baseline Characteristics of the Included Studies

Study	Country and number of centers	Diagnostic criteria used for AP	Predominant etiology of pancreatitis	Study duration	Mean age of patients (mean in y)	Number of patients	Male/ Female	Number of patients assigned to an opioid vs nonopioid
Gulen 2016[16]	Turkey, 1 center	Acute abdominal pain + laboratory + CT diagnosis of AP	Gallstone and biliary (73.3%)	<1 h	53.5	90	53/37	30 in IV paracetamol 1 g, 30 in IV dexketoprofen 50 mg, and 30 in IV tramadol 1 mg/kg
Kumar 2019[17]	India, 1 center	Diagnosed as per the revised Atlanta classification	Gallstone and biliary (48.7%)	7 d	47.4	41	27/14	20 in IV diclofenac 1 mg/kg (up to 75 mg) over 5 min bid and 21 in IV tramadol 1 mg/kg over 5 min bid
Mahapatra 2019[15]	India, 1 center	Diagnosed as per the revised Atlanta classification	Idiopathic (40%)	7 d	41.3	50	24/26	26 in IV diclofenac 75 mg/8 h and 24 in IV pentazocine 30 mg/8 h
Peiro 2008[21]	Spain, 1 center	Upper abdominal pain + diagnosis of AP (>3 ULN of amylase or lipase)	Gallstone (50%)	2 d	54.7	16	8/8	8 in IV metamizole 2 g/8 h and 8 in SC morphine 10 mg/4 h
Dong 2019[14]	USA, 1 center	Diagnosed as per the revised Atlanta classification	Gallstone (60.9%)	7 d	53.1	46	21/25	24 in IV paracetamol 1 g q6h and 22 in IV hydromorphone was dosed at 0.2, 0.4, and 0.6 mg as needed for mild (1–3), moderate (4–6), or severe (7–10) pain scales, respectively.
Jakobs 2000[19]	Germany, 1 center	Clinical diagnosis: Upper abdominal pain some radiating to the back + elevated levels of serum amylase or serum lipase (>2 ULN) + and signs of AP on imaging	Alcohol (57.5%)	3 d	50	39	23/16	20 in IV procaine 2 g/d and 20 in IV buprenorphine (0.3 mg, initially + 2.4 mg/d)
Kahl 2004[20]	Germany, 1 center	Acute abdominal pain + diagnosis of AP (>3 ULN of amylase or lipase)	Alcohol (70.2%)	4 d	45	107	76/31	55 in IV procaine 2 g/d and 52 in IV pentazocine 30 mg/6 h

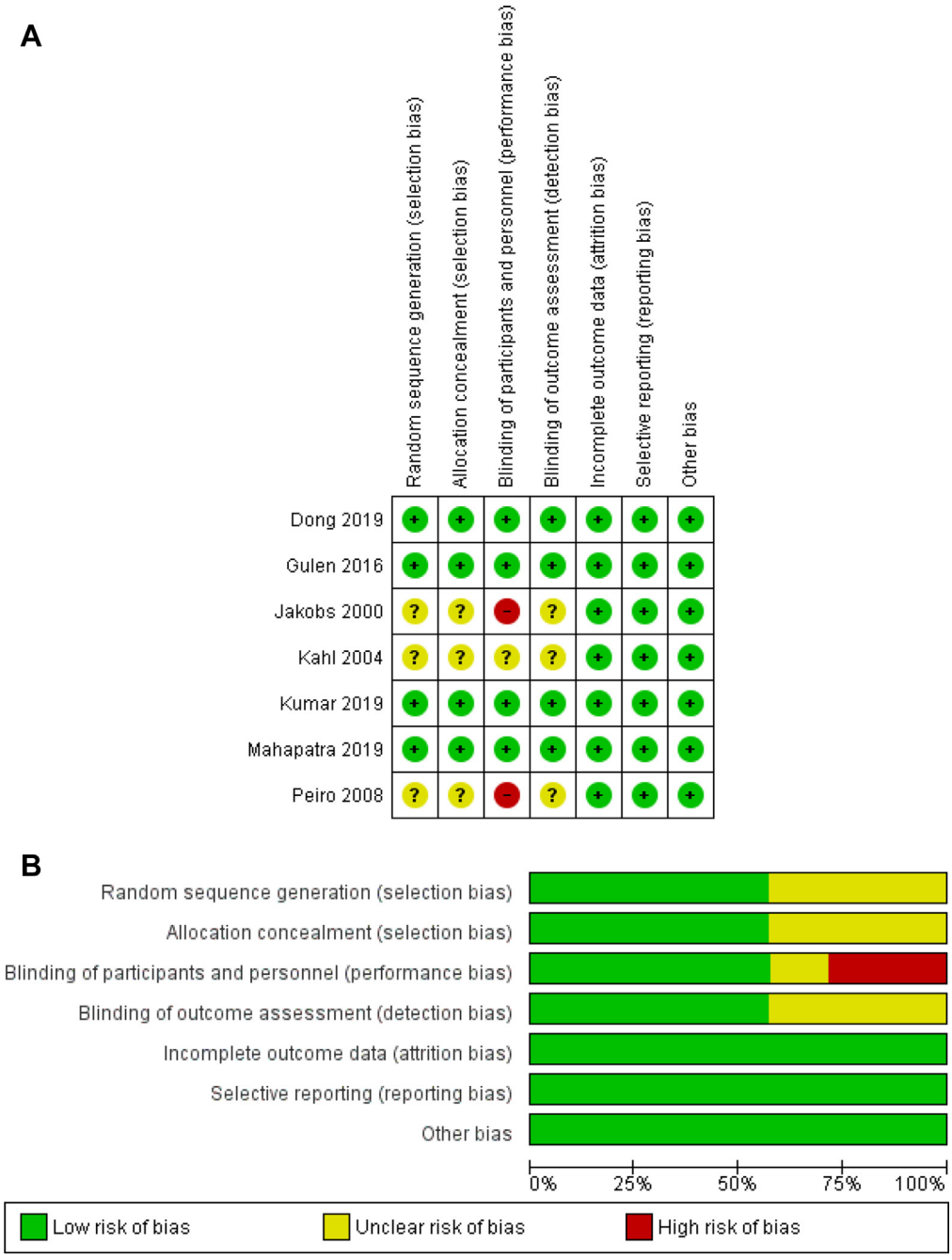

Figure 2. (A) Risk of bias summary of included studies. (B) Risk of bias graph of included studies.

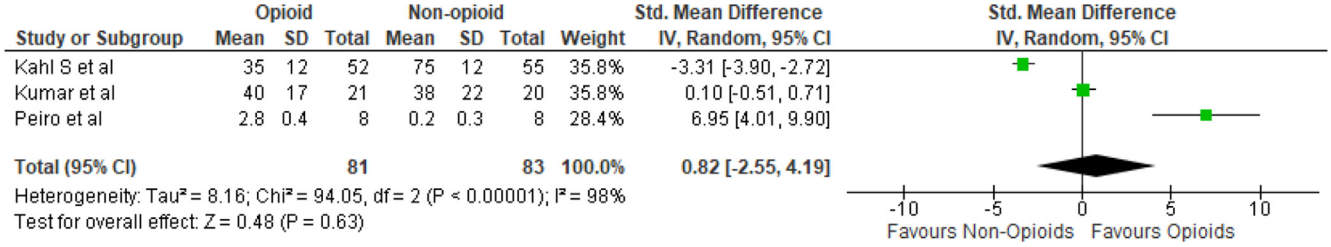

Figure 3. Comparison between opioids vs nonopioids of pain intensity by the VAS at day 1.

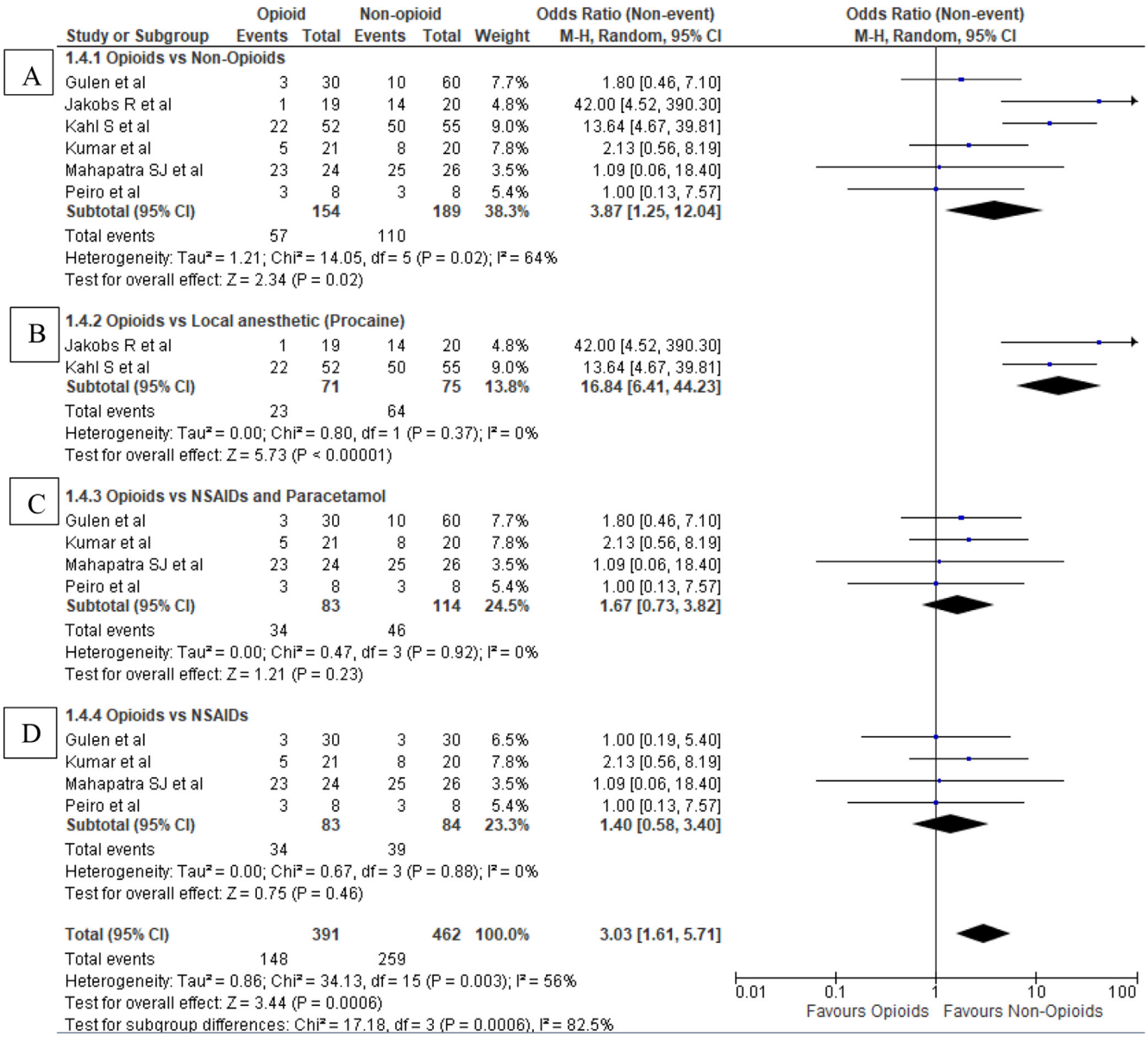

Figure 4. (A) Comparison between opioids vs nonopioids of supplementary analgesia use. (B) Sensitivity analysis of supplementary analgesic use with local anesthetics (procaine). (C) Sensitivity analysis of supplementary analgesic use with NSAIDs and paracetamol. (D) Sensitivity analysis of supplementary analgesic use with only NSAIDs.

Secondary Endpoints

Complications of Pancreatitis. The number of participants with complications of AP was presented in 6 RCTs showing no significant difference between opioid and nonopioid use (OR 1.44, 95% CI 0.79–2.63) with no heterogeneity among studies. No specific details about the type of complication from AP were mentioned in the studies except for Kumar et al (Figure A4).

Drug-related Adverse Event. Except for Kahl et al and Kumar et al, all the other 5 RCTs assessed number of participants with drug-related adverse effects at the end of the study period. Nonopioids had 15 participants with adverse events when compared with opioids which had 22 with no clinical significance with an OR of 2.19 (95% CI 0.71–6.75) with low heterogeneity (I^2 41%) (Figure 5). Among the adverse events, sedation is the more common with opioid use but was not significant with an OR of 4.19 (95% CI 0.80–21.96) when compared with opioids (Figure A5). In addition, the nausea and vomiting are less with nonopioids but no significant difference when compared with opioids with OR of 1.52 (95% 0.72–3.24) (Figure 6). There is no heterogeneity among studies if a specific adverse event was considered.

Number of Deaths From Any Cause. In all the included RCTs, 3 deaths were documented, one each for each RCT. Two deaths were reported in patients on

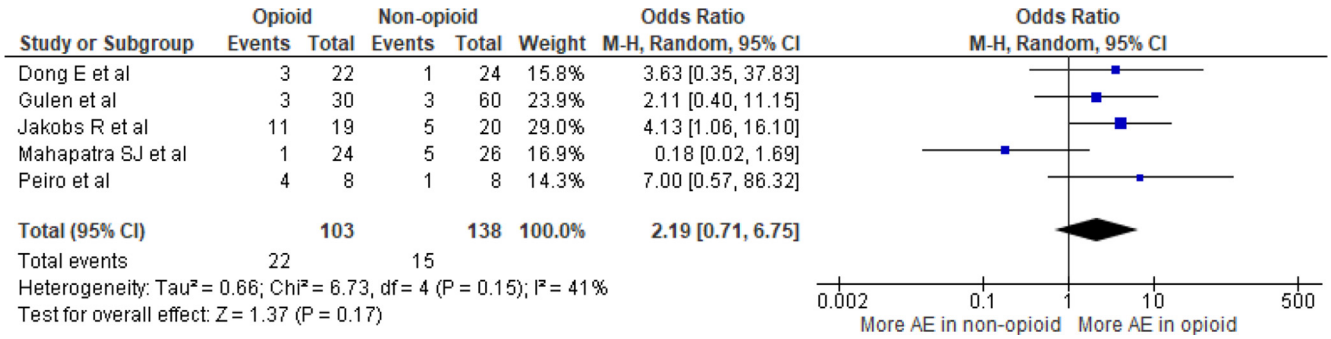

Figure 5. Comparison between opioids vs nonopioids: number of participants with drug-related adverse events (AE).

nonopioids and one with opioid use with no significance (OR 0.70, 95% CI 0.11–4.60) and with no heterogeneity (Figure A6).

Discussion

This systematic review is an update from the prior reviews by Meng et al and Cochrane review in 2013 to comprehensively evaluate opioids vs nonopioids for pain control in AP.[12,13] Seven independent RCTs comparing opioids vs nonopioids were included with 389 patients with AP. Among the studies, 2 RCTs compared procaine with buprenorphine and pentazocine, 2 compared paracetamol with hydromorphone and tramadol, 2 compared diclofenac with pentazocine and tramadol, one with dexketoprofen and tramadol, and one with metamizole and morphine.[14,17,19–21]

Among the studies included, there is no concern for publication bias, evidence of incomplete or selective reporting of outcomes. Only 3 studies were at low risk of bias among the 7 studies.

This systematic review and meta-analysis of pain management in AP showed that nonopioids had equal efficacy in relieving pain based on the VAS at day 1 when compared with opioids. Patients with AP treated with nonopioids tend to have less overall adverse effects but with more frequent requirement of supplementary analgesic use. Opioids did not significantly increase the complications of pancreatitis, nausea, vomiting, sedation, and deaths when compared with nonopioids. The need for supplementary analgesia was significantly higher in nonopiod use; however, when a sensitivity analysis was performed with NSAIDs and paracetamol, only NSAIDS showed no significant difference (Figures 4C and D). The moderate to high heterogeneity noted with the VAS at day 1 and supplementary analgesic use endpoints are likely due to varying methods of assessment of the VAS and difference in criteria and frequency of supplementary analgesic use.

Severe pain is a hallmark for AP, and most patients require hospitalization for pain control. Insufficient pain management can lead to physical and psychological distress to patients, family members, and the care team. Although the current consensus recommendations suggest the use of parenteral analgesics to control pain during an episode of AP, it does not specify the type of analgesics to be used.[22] Common pharmacological treatment for acute pain includes NSAIDs, acetaminophen, and opioids although steroids and muscle relaxants can be used for a certain type of pain.[23] Opioids function through a complex interaction with 3 types of opioid receptors: mu receptor, delta receptor, and the Kappa receptor in the central nervous system.[24] Opioids also reduced calcium influx, decreasing neurotransmitter release at the presynaptic level, and enhance potassium iron efflux, leading to postsynaptic hyperpolarization of the dorsal horn pain signal neurons.[25] Overall, opioids decrease nociceptive transmission and alleviate pain. NSAIDs manifest analgesic effects by inhibiting the cyclooxygenase (COX) enzymes, blocking the synthesis of prostaglandins, and reducing inflammation and pain.[26] Non-selective NSAIDs (eg, ibuprofen, diclofenac, naproxen) inhibit both COX-1 and COX-2 enzymes while selective COX-2 (eg, nimesulide,

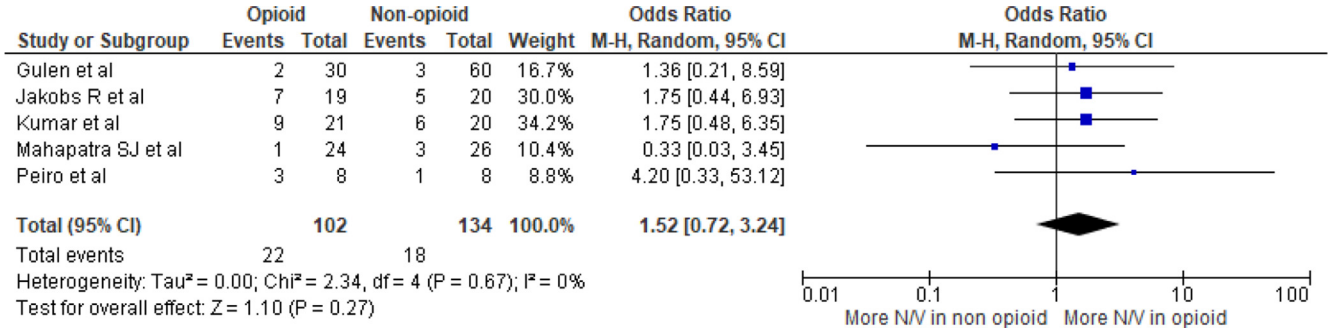

Figure 6. Comparison between opioids vs nonopioids: number of participants with nausea and vomiting.

celecoxib) inhibitors predominately the COX-2 enzymes. Acetaminophen (N-acetyl para-aminophenol or paracetamol) is one of the most widely used analgesics although its exact mechanism remains unclear. It may reduce the activity of COX in the central nervous system without binding to the active site of either the COX-1 or COX-2 enzyme, different from NSAIDS.

In our meta-analysis, 2 studies compared procaine with opioids.[19,20] Local anesthetics like procaine were initially recommended around the 2000s in German and Chinese guidelines for the management of pain control.[27,28] However, it was proven to be ineffective later.[27] In addition, a longer time of onset, shorter duration of action, and increase in the number of adverse events such as nausea and vomiting make it less preferable to use.[19] In our study, patients who used procaine for pain control tend to request more supplementary analgesic use (Figure 3B). In this meta-analysis, 2 RCTs compared paracetamol with hydromorphone and tramadol, but it had only one endpoint in common.[14,16] Opioid-related adverse events were more when compared with paracetamol use.[14,16] Four RCTs compared NSAIDs with opioids; among them, 2 compared diclofenac with pentazocine and tramadol, one with dexketoprofen and tramadol, and one with metamizole and morphine.[15,17,21] Metamizole is not available in the United States because of possible association with agranulocytosis.[29] Rectal NSAIDs had shown efficacy in preventing post–endoscopic retrograde cholangiopancreatography pancreatitis.[30] Ibuprofen and diclofenac alone can be utilized in decreasing complications of AP.[30] Animal studies with diclofenac showed promising results with decreased pancreatic injury and decreased kidney, lung, and liver injury by reducing apoptosis and necrosis.[31,32] It was reported that 2 had acute kidney injury with diclofenac by Mahapatra et al,[15] but both these events could not be attributed to diclofenac. Four events of acute lung injury with diclofenac are seen which are less but significant when compared with 9 with tramadol.[17] Because the production of prostaglandins is responsible for gastric epithelial protection and hemostasis, blocking COX-1 also reduced gastric protection, leading to an increased risk for gastrointestinal complications (eg, gastric ulcer, perforation, gastrointestinal bleeding).[33]

Five different opioids were used in 7 included RTCs, 2 trials with tramadol and pentazocine, one each with morphine, hydromorphone, and buprenorphine. Pentazocine is a k-receptor agonist and partial μ-receptor antagonist which is advantageous with fewer gastrointestinal adverse effects than other opioids.[15] In addition, pentazocine may modulate nuclear factor-kB and decrease inflammation from AP.[34] Previous animal models showed increased intestinal permeability by bacterial translocation and resulting in the prevention of pancreatic regeneration.[35] Tramadol is a weak μ receptor agonist and has atypical inhibition of serotonin and norepinephrine reuptake concomitantly, and the N-methyl-D-aspartate receptor antagonist at higher concentrations could offer better pain control with less addition along with a better safety profile.[36] In addition, the synergistic effect of opioids along with opioids used for supplementary analgesic use acts in the central pain pathway, leading to better pain control than nonopioids.[37] However, to consider the drawbacks of using opioids that are the longer duration of hospital stay, chronic use leading to addiction, and mortality should be reminded before discharge.[11,38] When opioids such as buprenorphine or fentanyl and pethidine were compared with pethidine, there is no difference in the pain improvement and also the number of adverse events reported.[39,40]

Some of the limitations worth mentioning are as follows: (1) small sample size: the largest trial had 107 patients in total, whereas the smallest trial has only 16 patients included. It is uncommon as it is notoriously difficult to recruit patients with AP for trials. (2) Heterogenous studies: the included studies used different narcotics, different NSAIDs, different administration routes, and different reported clinical outcomes. Lack of information about one of the major primary endpoints (pain intensity by the VAS at day 1) in multiple studies limits the possibility of evaluating accurately and comprehensively the effects of opioids vs nonopioids for treatment of pain in AP. For example, Dong et al measured the pain scores by morphine equivalents rather than the VAS at day 1. Importantly, there was moderate to high evidence of heterogeneity in our primary endpoints of interest. Most of the data were obtained at the end of the study which varied among studies because of variation in the length of the study period, and the long-term complications of these medications were unknown. (3) The indication of supplementary analgesic use varied among studies. Some studies did not have the amount of supplementary analgesics reported. Simple binary representation of yes or no supplementary analgesic use without the actual dosage may not be a sensitive way to assess pain control. (4) Severity of AP was not reported in multiple studies.

To provide better pain control and prevent addiction, opioid-sparing or reduction should be considered in treating AP. A step up method to control cancer pain has been suggested by World Health Organization: step I is to use nonopioids; step II is to use nonopioids in combination with low-potency opioid; step III is high-potency opioid, and step IV is interventional.[41] This could be applied to acute pain due to AP. Future research on AP pain control should consider regimens avoiding or lowering opioids: (1) intravenous NSAIDs or acetaminophen and (2) combining 2 or more drugs with different mechanisms of action to synergistically reach a sufficient analgesic effect. The combination will allow lower doses and, therefore, reduce side effects. However, not all drug combinations are equal, and different combinations of analgesic agents should be evaluated experimentally or clinically to gain insight into their potential clinical use. Studies may consider use of NSAIDs with

longer half-life. Novel combination like diclofenac plus B vitamins has been shown more effective in reducing pain than diclofenac alone.[42] Dexketoprofen and dicyclomine are more effective than diclofenac and dicyclomine for the treatment of acute renal colic.[43] (3) Further research on pain management in patients with AP should also focus on the designing of clinical trials with a larger sample size and a standardized method of pain assessment. As it is notorious to recruit patients with AP for trials in 1 center, effort should be made to form a consortium in recruiting AP for future studies.

Conclusion

In conclusion, this meta-analysis suggests that non-opioids, especially NSAIDs and paracetamol, can be used for adequate relief of pain in patients with AP with no increase in requirement of supplementary analgesic but with an overall decrease in adverse effects when compared with opioid use. Use of opioids showed an increase in the overall adverse effects but no difference in the complications of pancreatitis or nausea and vomiting and sedation. The results of the meta-analysis should be interpreted with caution because of the diverse nature of medications, both the opioids and nonopioids used in clinical studies, efficacy outcomes, small sample sizes, and unclear bias in 3 studies lowering the quality of studies.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2021.09.006.

References

1. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994;330:1198–1210.
2. Brindise E, Elkhatib I, Kuruvilla A, et al. Temporal trends in incidence and outcomes of acute pancreatitis in hospitalized patients in the United States from 2002 to 2013. Pancreas 2019;48:169–175.
3. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology 2019;156:254–272.e11.
4. Xiao AY, Tan ML, Wu LM, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol 2016;1:45–55.
5. Singh VK, Bollen TL, Wu BU, et al. An assessment of the severity of interstitial pancreatitis. Clin Gastroenterol Hepatol 2011;9:1098–1103.
6. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–111.
7. Roberts SE, Morrison-Rees S, John A, et al. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology 2017;17:155–165.
8. Banks PA, Conwell DL, Toskes PP. The management of acute and chronic pancreatitis. Gastroenterol Hepatol (N Y) 2010;6(2 Suppl 3):1–16.
9. Wu BU, Conwell DL, Singh VK, et al. Early hemoconcentration is associated with pancreatic necrosis only among transferred patients. Pancreas 2010;39:572–576.
10. Liddle RA, Nathan JD. Neurogenic inflammation and pancreatitis. Pancreatology 2004;4:551–559, discussion 9-60.
11. Wu BU, Butler RK, Chen W. Factors associated with opioid use in patients hospitalized for acute pancreatitis. JAMA Netw Open 2019;2:e191827.
12. Basurto Ona X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. Cochrane Database Syst Rev 2013;CD009179.
13. Meng W, Yuan J, Zhang C, et al. Parenteral analgesics for pain relief in acute pancreatitis: a systematic review. Pancreatology 2013;13:201–206.
14. Dong E, Chang JI, Verma D, et al. Enhanced recovery in mild acute pancreatitis: a randomized controlled trial. Pancreas 2019;48:176–181.
15. Mahapatra SJ, Jain S, Bopanna S, et al. Pentazocine, a kappa-opioid agonist, is better than diclofenac for analgesia in acute pancreatitis: a randomized controlled trial. Am J Gastroenterol 2019;114:813–821.
16. Gülen B, Dur A, Serinken M, et al. Pain treatment in patients with acute pancreatitis: a randomized controlled trial. Turk J Gastroenterol 2016;27:192–196.
17. Kumar NS, Muktesh G, Samra T, et al. Comparison of efficacy of diclofenac and tramadol in relieving pain in patients of acute pancreatitis: a randomized parallel group double blind active controlled pilot study. Eur J Pain 2020;24:639–648.
18. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
19. Jakobs R, Adamek MU, von Bubnoff AC, et al. Buprenorphine or procaine for pain relief in acute pancreatitis. A prospective randomized study. Scand J Gastroenterol 2000;35:1319–1323.
20. Kahl S, Zimmermann S, Pross M, et al. Procaine hydrochloride fails to relieve pain in patients with acute pancreatitis. Digestion 2004;69:5–9.
21. Peiró AM, Martínez J, Martínez E, et al. Efficacy and tolerance of metamizole versus morphine for acute pancreatitis pain. Pancreatology 2008;8:25–29.
22. Vivian E, Cler L, Conwell D, et al. Acute pancreatitis task force on quality: development of quality indicators for acute pancreatitis management. Am J Gastroenterol 2019;114:1322–1342.
23. Blondell RD, Azadfard M, Wisniewski AM. Pharmacologic therapy for acute pain. Am Fam Physician 2013;87:766–772.
24. Dietis N, Rowbotham DJ, Lambert DG. Opioid receptor subtypes: fact or artifact? Br J Anaesth 2011;107:8–18.
25. Trescot AM, Datta S, Lee M, et al. Opioid pharmacology. Pain Physician 2008;11(2 Suppl):S133–S153.

26. Limbird LE, Hardman JG, Goodman Gilman A. Goodman & Gilman's the pharmacological basis of therapeutics. New York, NY: McGraw-Hill Professional Publishing, 2011:959–1000.
27. Rünzi M, Layer P, Büchler MW, et al. Therapie der akuten Pankreatitis. Gemeinsame Leitlinien [The therapy of acute pancreatitis. General guidelines. Working Group of the Society for Scientific-Medical Specialties]. Z Gastroenterol 2000;38:571–581.
28. Xiao Chunming YZ, Fang X, Wang C. Treatment effect of procaine in severe acute pancreatitis. Chin J Bases Clin General Surg 2002;427–428.
29. Torres LM, Collado F, Almarcha JM, et al. Tratamiento del dolor postoperatorio con sistema de PCA intravenoso. Comparación entre morfina, metamizol y buprenorfina [Treatment of postoperative pain with intravenous PCA system. Comparison with morphine, metamizole, and buprenorphine]. Rev Esp Anestesiol Reanim 1993;40:181–184.
30. Hou YC, Hu Q, Huang J, et al. Efficacy and safety of rectal nonsteroidal anti-inflammatory drugs for prophylaxis against post-ERCP pancreatitis: a systematic review and meta-analysis. Sci Rep 2017;7:46650.
31. Ozer Cakir O, Esen H, Toker A, et al. Effects of diclofenac sodium and octreotide on treatment of caerulein-induced acute pancreatitis in mice. Int J Clin Exp Med 2015;8:17551–17564.
32. Ozer Cakir O, Findik S. Diclofenac sodium treatment ameliorates extrapancreatic organ injuries in a murine model of acute pancreatitis induced by caerulein. Gastroenterol Res Pract 2018;2018:9829208.
33. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther 2013;15 Suppl 3(Suppl 3):S3.
34. Lin J, Wang H, Li J, et al. κ-Opioid receptor stimulation modulates TLR4/NF-κB signaling in the rat heart subjected to ischemia-reperfusion. Cytokine 2013;61:842–848.
35. Barlass U, Dutta R, Cheema H, et al. Morphine worsens the severity and prevents pancreatic regeneration in mouse models of acute pancreatitis. Gut 2018;67:600–602.
36. Vadivelu N, Chang D, Helander EM, et al. Ketorolac, oxymorphone, tapentadol, and tramadol: a comprehensive review. Anesthesiol Clin 2017;35:e1–e20.
37. Levine JD, Gordon NC. Synergism between the analgesic actions of morphine and pentazocine. Pain 1988;33:369–372.
38. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015;372:241–248.
39. Blamey SL, Finlay IG, Carter DC, et al. Analgesia in acute pancreatitis: comparison of buprenorphine and pethidine. Br Med J (Clin Res Ed) 1984;288:1494–1495.
40. Stevens M, Esler R, Asher G. Transdermal fentanyl for the management of acute pancreatitis pain. Appl Nurs Res 2002;15:102–110.
41. Cascella M, Muzio MR, Viscardi D, et al. Features and role of minimally invasive palliative procedures for pain management in malignant pelvic diseases: a review. Am J Hosp Palliat Care 2017;34:524–531.
42. Ponce-Monter HA, Ortiz MI, Garza-Hernández AF, et al. Effect of diclofenac with B vitamins on the treatment of acute pain originated by lower-limb fracture and surgery. Pain Res Treat 2012;2012:104782.
43. Porwal A, Mahajan AD, Oswal DS, et al. Efficacy and tolerability of fixed-dose combination of dexketoprofen and dicyclomine injection in acute renal colic. Pain Res Treat 2012;2012:295926.

Received August 16, 2021. Accepted September 16, 2021.

Correspondence:
Address correspondence to: Yan Bi, MD, PhD, Assistant Professor of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, Florida 32224. e-mail: bi.yan@mayo.edu; fax: 904-953-6225.

Acknowledgments:
The authors thank Ms Diana Almader-Douglas for her help with the literature search.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
The authors report no funding.

Authors' Contributions:
Alfred D. Nelson and Yan Bi conceived and drafted the study. Alfred D. Nelson and Nahyr Sofía Lugo-Fagundo screened abstracts, collected all data, and assessed quality of the RCTs. Wisit Cheungpastiporn, Charat Thongprayoon, and Karn Wijarnpreecha analyzed data, and Alfred D. Nelson and Karn Wijarnpreecha interpreted the data. Alfred D. Nelson and Yan Bi drafted the manuscript. All authors commented on drafts of the article. All authors have approved the final draft of the manuscript.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
The authors declare that all supporting data are available within the article and its online supplementary files.

Writing assistance:
None.