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Contents

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SYSTEMATIC REVIEWS

Pain management in acute musculoskeletal injury: Effect of opioid *vs* nonopioid medications

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Abstract

BACKGROUND

The use of opioids for pain is linked to an increased risk of developing opioid use disorder, and has resulted in the emergence of the opioid crisis over the last few years.

AIM

The systematic review question is "How does the use of opioid medications in pain management, compared with non-opioid medications, affect pain intensity over the short, intermediate, and long-term in adults with acute traumatic pain?".

METHODS

The protocol was prospectively registered on the International Prospective Register of Systematic Reviews: CRD42021279639. Medline and Google Scholar were electronically searched for controlled peer-reviewed studies published in full, with the PICO framework: P: Adult patients with traumatic injuries, I: Opioid medications, C: Non-opioid medi-cations, O: A minimum clinically important

difference (MCID) in pain.

RESULTS

After full-text screening, we included 14 studies in the qualitative synthesis. Of these 14 studies, 12 were randomized clinical trials (RCTs) and 2 were pseudo-RCTs with a total of 2347 patients enrolled. There was heterogeneity in both medication utilized and outcome in these studies; only two studies were homogeneous regarding the type of study conducted, the opioid used, its comparator, and the outcome explored. The MCID was evaluated in 8 studies, while in 6 studies, any measured pain reduction was considered as an outcome. In 11 cases, the setting of care was the Emergency Department; in 2 cases, care occurred out-of-hospital; and in one case, the setting was not well-specified. The included studies were found to have a low-moderate risk of bias.

CONCLUSION

Non-opioids can be considered an alternative to opioids for short-term pain management of acute musculoskeletal injury. Intravenous ketamine may cause more adverse events than other routes of administration.

Key Words: Acute musculoskeletal injury; Acute traumatic pain; Non-opioid analgesia; Non-opioid pain control; Opioid-sparing analgesia; Opioid crisis; Opioid disorder; Systematic review

Core Tip: Opioid use is linked to an increased risk of developing opioid use disorder. This systematic review question is "How does the use of opioid medications in pain management, compared with non-opioid medications, affect pain intensity over the short, intermediate, and long-term in adults with acute traumatic pain?". The search was performed using Medline and Google Scholar. We included 14 studies in the final synthesis [12 were randomized clinical trials (RCTs) and 2 were pseudo-RCTs]. Most retrieved studies on the use of non-opioids concluded that non-opioid drugs are non-inferior to opioids for the control of acute pain in acute musculoskeletal injury.

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INTRODUCTION

In the late 90s, the pharmaceutical industry assured the medical community that opioids prescribed for pain relief would not result in addiction. In turn, medical doctors increased their rates of opioid prescription, with the well-intentioned belief that they were effectively treating pain with little risk of harm. Increased awareness of the addictive quality of these medications has led to a reduction in the prescription of opiates in recent years. However, paradoxically, although the prescription rate has been reduced, deaths from overdoses associated with opioids continue to increase[1]. Opioid overdose deaths in the United States have increased significantly over the past decade. In California, opioid overdose death rates increased by more than threefold between 2018 and 2021[2]. By 2021, unintentional opioid toxicity caused 1 out of every 22 deaths in the United States[3]. The Centers for Disease Control and Prevention (CDC) released its most recent Clinical Practice Guideline for Prescribing Opioids for Pain in 2022 that addresses the prescription of opioids for acute pain in many common minor traumatic orthopedic conditions such as sprains and strains[4]. However, the CDC guideline does not provide non-opioid recommendations for more catastrophic traumatic conditions such as fractures necessitating surgery or hospitalization.

The question being addressed in this systematic review is "How does the use of opioid medications in pain management, compared with non-opioid medications, affect pain intensity over the short, intermediate, and long-term in adults with acute traumatic pain?". The results can be applied by orthopedic practices and other specialties (*e.g.* emergency physicians and anaesthesiologists) to adequately and appropriately utilize non-opioid medications for the management of acute pain following musculoskeletal injury.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the updated guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[5].

The protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO): CRD42021279639 on November 18, 2021 after searching the main electronic registers (the Cochrane

database of systematic reviews, the JBI database of systematic reviews, and implementation reports and PROSPERO) to exclude existing systematic reviews on the same subject.

Study search

The participants, intervention, comparison, outcomes, study design method was utilized to conduct the search strategy (Table 1). The databases utilized were Medline through PubMed and Google Scholar *via* Publish or Perish software[6].

Table 1 Participants, intervention, comparison, outcomes, study design method for selecting clinical studies for the systematic reviews

Participants	Intervention	Comparison	Outcomes	Study design
Adult patients with catastrophic orthopedic trauma	Opioid medications	Non-opioid medications	A minimum clinically important difference in pain	Randomized controlled trials and observational studies

The search strategy used Boolean operators to combine selected keywords in detail (Supplementary Table 1). A first comprehensive search was performed, which began at the inception of the search strategy and ceased in December 2021. The search was re-run, updating the data collection definitively until May 15, 2024.

Study selection

After searching, we eliminated duplicate studies utilizing Endnote VX9 (Clarivate Analytics, Philadelphia, PA, United States), a citation management software. Randomized clinical trials (RCTs) and non-RCTs with a control group, were considered eligible studies. Two authors (Barletta and Visconti) evaluated the eligible studies independently through initial screening based on the title and abstract, without any restrictions. The authors (Barletta and Visconti) conducted full-text screening of the selected articles to ensure their suitability for final inclusion. Any disagreements about study eligibility or data extraction was resolved by a third author (McCaffery). Two independent reviewers (Barletta and Visconti) reviewed the entire text of the selected citations and documented the reason for excluding full-text studies that did not meet the inclusion criteria; McCaffery performed a final check as well. Each step of the search is represented in the PRISMA flow diagram (Figure 1).

Definition and outcome

For this study, catastrophic orthopedic trauma was defined as any trauma that necessitated surgery or hospitalization. We excluded trauma that necessitated access to and evaluation in the emergency department (ED) but did not require surgery or hospitalization, such as whiplash or sprained ankle. The primary outcome was a minimum clinically important difference (MCID) in pain intensity. The secondary outcome was a reduction in pain as defined by the authors of the primary studies. Patients with a trauma-related pain diagnosis were evaluated for all outcomes.

Data extraction and quality assessment

The Cochrane data collection form for intervention reviews in RCT and non-RCT studies was used by two authors (McCaffery and Nasto) to extract data independently from the included studies. The quality of the methodology and risk of bias were evaluated by the authors (McCaffery and Nasto) using the Cochrane Collaboration Revised Assessment Tool [7].

RESULTS

Overall, 58958 papers were retrieved: 13471 on Medline and 45487 on Google Scholar, and 13269 duplicates were identified and excluded. The flowchart (Figure 1) shows that 45689 titles were identified as potentially relevant and screened. After screening the title and abstract, we excluded 45652 papers. We excluded 23 papers from the full-text evaluation of the remaining 37 papers because of 4 main reasons (Figure 1). Fourteen studies (12 were RCT and 2 were pseudo-RCT) were included in the qualitative synthesis (Table 2) after full-text screening. The MCID in pain intensity was evaluated in 8 studies, while in 6 studies, any measured pain reduction was considered as an outcome. In 11 cases, the setting of care was the ED; in 2 cases, care occurred out-of-hospital; and in one case, the setting was not well-specified (Table 2). The included studies were found to have a low-moderate risk of bias (Supplementary Table 2).

The first published study on the topic, written by Soave *et al*[8], dates back more than 40 years. In this double-blind, randomized, parallel-group study, the analgesic activity of indoprofen and pentazocine was evaluated in 60 patients with severe pain due to fractures. Twenty patients received indoprofen 400 mg intravenous (IV), 20 patients received pentazocine 30 mg IV, and 20 patients received placebo. The intensity of pain was assessed prior to medication administration and at 0.5 hour, 1 hour, 2 hours, 4 hours, and 6 hours following administration. The evaluation of efficacy was based on the visual analogue scale (VAS). The analgesic effects of indoprofen were found to be significantly superior to those of pentazocine, and both drugs had good tolerability[8].

Chang *et al*[9] investigated, in an RCT, the effectiveness of 4 oral analgesics in patients who had acute, moderate-to-severe extremity pain and were admitted to the ED. Patients received one of the following regimens: ibuprofen (IBP) (400 mg)/acetaminophen (APAP) (1000 mg); oxycodone (OXY) (5 mg)/APAP (325 mg); hydrocodone (HYCOD) (5 mg)/

Table 2 Characteristics of the studies included in the qualitative synthesis

Ref.	Country/year	Injury	Opioid(s)-ROA	Nonopioid(s)-ROA	Patients /study type	Outcome (minimum clinically important difference)	Evaluation time	Efficacy result	Safety results
Soave *et al*[8]	Italy/1983	Severe pain due to fractures	Pentazocine-IV	Indoprofen-IV	The 40/pseudo-RCT	Any reduction on VAS	The 0 minute, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours	Pain relief in Pentazocine group	No differences
Chang *et al*[9]	United States/2017	Acute extremity pain	OXY/APAP-PO, HYCOD/APAP-PO, COD/APAP-PO	IBP/APAP-PO	416/RCT	Reduction of 1.3 on the NRS	2 hours	No differences	ADR in opioid
Bijur *et al*[10]	United States/2021	Acute musculo-skeletal pain	OXY/APAP-PO, HYCOD/APAP-PO, COD/APAP-PO	IBP/APAP-PO	600/RCT	Any reduction on NRS	The 0 hour, 1 hour or 2 hours	No differences	ADR in opioid
Buccelletti *et al* [11]	Italy/2014	Acute musculo-skeletal traumatic pain	COD/APAP-PO	Ketorolac-PO	134/pseudo-RCT	Any reduction on NRS	The 0 minute, 30 minutes, 2 hours	Pain relief in COD/APAP group	Not available
Craig *et al*[12]	United Kingdom/2012	Severe traumatic limb pain	MORPH-IV	APAP-IV	55/RCT	≥ 13 mm reduction on VAS	The 0 minute, 5 minutes, 15 minutes, 30 minutes, 60 minutes	No differences	ADR in opioid
Jalili *et al*[13]	Iran/2016	Severe traumatic limb pain	MORPH-IV	APAP-IV	60/RCT	Any reduction on NRS	The 0 minute, 15 minutes, 30 minutes	Pain relief in APAP group	No differences
Farahmand *et al*[14]	Iran/2018	Severe traumatic limb pain	MORPH-IV	Lidocaine-IV	50/RCT	Reduction of 1.3 on the NRS	The 0 minute, 15 minutes, 30 minutes, 45 minutes, 60 minutes	No differences	Heart rate/respiratory rate reduction in opioid
Gurnani *et al* [15]	India/1996	Acute musculo-skeletal traumatic pain	MORPH-IV	KET-subcutaneous	40/RCT	Any reduction on VAS	The 0 minute, 15 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours	Pain relief in KET group	ADR in opioid
Shimonovich *et al*[16]	Israel/2016	Moderate-severe acute traumatic pain	MORPH-IV/MORPH-IM	KET-IN	90/RCT	≥ 15 mm reduction and max pain reduction on VAS	Time to onset in min	No differences	No differences
Tongbua *et al* [17]	Thailand/2022	Moderate-severe Musculo-skeletal pain	MORPH-IV	KET-IN	74/RCT	Reduction of 1.3 on the NRS	The 0 minute, 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes and 120 minutes	No differences	No differences
Kampan *et al* [18]	Thailand/2024	Moderate-severe Musculo-skeletal pain (≥ 65)	MORPH-IV	KET-IN	92/RCT	Reduction of 1.3 on the NRS	The 0 minute, 30 minutes	No differences	ADR in opioid
Esfahani *et al* [19]	Iran/2021	Severe traumatic limb pain	MORPH-IV	KET-IV	76/RCT	Any reduction on NRS	The 0 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes	No differences	ADR in KET
Le Cornec *et al* [20]	France/2024	Out-of-hospital traumatic pain	MORPH-IV	KET-IV	251/RCT	Reduction of 1.3 on the NRS	The 0 minute, 30 minutes	No differences	ADR in KET

Lim *et al*[21]	Singapore/ 2021	Out-of-hospital traumatic pain	Tramadol-IM	MTX-inhalation	369/RCT	≥ 3-point reduction in NRS	The 0 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes	Pain relief in MTX group	ADR in MTX

APAP: Acetaminophen; ADR: Adverse drug reaction; COD: Codeine; HYCOD: Hydrocodone; IBP: Ibuprofen; IN: Intranasal; KET: Ketamine; MORPH: Morphine; MTX: Methoxyflurane; NRS: Numerical rating scale; OXY: Oxycodone; RCT: Randomized controlled trial; ROA: routes of administration; PO: *Per os*; IV: Intravenous; VAS: Visual analogue scale.

APAP (300 mg); or codeine (COD) (30 mg)/APAP (300 mg). The pain intensity was assessed using an 11-point numerical rating scale (NRS), ranging from the number 0, which indicates no pain, to the number 10, which indicates the most severe pain. The primary outcome was the difference in pain reduction between the groups at 2 hours after administration of medication. According to the NRS, the MCID was 1.3. There were no significant or clinical differences in pain reduction at 2 hours observed between IBP and APAP treatment or 3 different opioid and APAP combination analgesics. The use of opioids resulted in a higher prevalence of nausea and vomiting in patients[9].

Bijur *et al*[10] compared the efficacy and adverse effects of five oral analgesics in an RCT comprising 600 patients presenting to the ED with acute musculoskeletal pain. Patients received one of the following regimens: IBP (400 mg)/APAP (1000 mg), IBP (800 mg)/APAP (1000 mg), COD (30 mg)/APAP (300 mg), HYCOD (5 mg)/APAP (300 mg), or OXY (5 mg)/APAP (325 mg). The main outcome was a difference in pain on NRS before drug administration (defined as the baseline) as compared with that at 1-hour post-baseline. At 1-hour and 2-hours post-baseline, both rescue medication and adverse effects were included in secondary outcomes. The authors concluded that no analgesic was more effective after 1-hours or 2-hours following baseline, while patients treated with opioids experienced a significant increase in nausea and vomiting[10].

In a cross-sectional, observational, prospective, cohort study (pseudo-randomized), Buccelletti *et al*[11] evaluated two oral analgesics in 134 patients presenting to the ED with acute traumatic musculoskeletal pain. The oral analgesics provided were APAP/COD at the dosage of 1000 mg/60 mg and ketorolac administered at the dosage of 15 mg. Seventy-six of the patients received ketorolac and 58 received APAP/COD. The NRS was recorded at 30 minutes and at 2 hours after the administration of the analgesic therapy. Patients with fractures and muscular pain were found to experience significantly higher analgesic relief when given the combination of APAP and COD compared with those who received ketorolac[11].

Craig *et al*[12] evaluated the effectiveness of 1 g IV APAP compared to 10 mg IV morphine (MORPH) in an RCT of 55 patients with moderate-to-severe traumatic limb pain. Using a VAS, the pain score was assessed at 0 minute, 5 minutes, 15 minutes, 30 minutes, and 60 minutes following administration of medication as the primary outcome measure. The frequency of adverse reactions and the need for rescue analgesia were also documented. There were no significant differences in analgesic effect of APAP and MORPH at any time interval. The rescue analgesia administered did not significantly differ between the two groups. However, the MORPH group experienced significantly more adverse reactions compared with the non-opioid group[12].

Jalili *et al*[13] evaluated, in an RCT, the effectiveness of APAP (1000 mg) relative to MORPH (0.1 mg/kg) in patients with acute limb trauma and a reported NRS of > 3/10. The primary outcome measure was the change in pain score of the NRS at 0 minute, 15 minutes and 30 minutes after medication administration. The frequency of adverse reactions and the need for rescue analgesia were also documented at 0 minute and 30 minutes after administration of medication. There were no significant differences in analgesic effect for APAP and MORPH at any time interval. The rescue analgesia administered did not differ significantly between the two groups. The MORPH group experienced significantly more adverse reactions. The authors found that the APAP group experienced significantly more pain relief than the MORPH group. The difference in the use of rescue analgesia between the APAP and MORPH groups was significant: The APAP

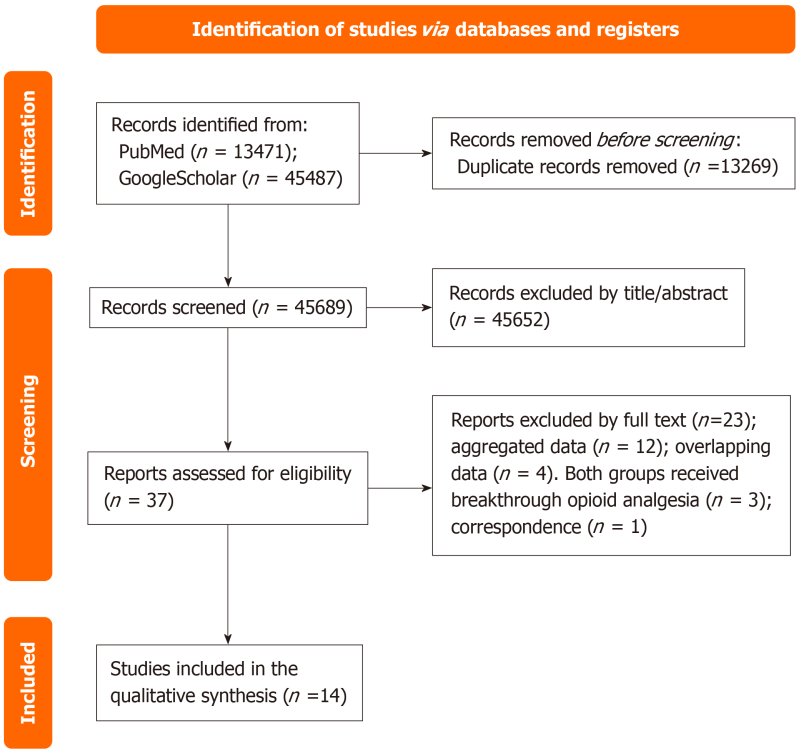

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection.

group had 4 patients who need rescue analgesia, while the MORPH group had 15 patients who need rescue analgesia. There was no significant difference in the number of patients who experienced adverse effects between the two groups [13].

Farahmand *et al*[14] enrolled 50 patients with acute limb trauma in an RCT designed to compare intravenous lidocaine and MORPH for superiority in pain management (25 in each group). Lidocaine (1.5 mg/kg) was administered *via* IV to one group and MORPH (0.1 mg/kg) was administered *via* IV to the other group. At 15 minutes, 30 minutes, 45 minutes, and 60 minutes, the patients' reported pain scores and adverse effects were documented, with their satisfaction with the pain control being assessed 2 hours later. According to the NRS, the MCID was 1.3. There were no clinically or statistically significant differences between two groups, although the pain score decreased significantly in both groups. In the MORPH group, compared with the group receiving lidocaine, the heart rate and the respiratory rate exhibited a statistically significant decrease. In both groups, only one subject reported adverse effects, *i.e.*, nausea and vomiting[14].

Gurnani *et al*[15] compared the effectiveness of pain control between ketamine (KET) and MORPH in a pilot study of 40 ASA-I adults after acute musculoskeletal trauma. In 20 patients, an initial loading dose of KET (0.25 mg/kg) was given slowly *via* IV followed by low-dose KET *via* Subcutaneous (0.1 mg/kg/hour). In the control group, 20 patients received MORPH (0.1 mg/kg intravenously, every four hours). The VAS was used to assess pain at 0 minute, 1 minute, 2 minutes, 4 minutes, 8 minutes, 12 minutes, 15 minutes, and 24 hours. Vital parameters and patient acceptability for supplementary analgesia, drowsiness score, and early mobilization were also assessed. The authors found that KET infusion provided better pain relief than intermittent MORPH, with no need for additional analgesia for the patients in the KET group. Compared with patients in the MORPH group, it was easier to physically move the patients receiving KET. The drowsiness score showed that patients were more awake and alert after receiving KET infusion. In the MORPH group, there was a high rate of nausea and vomiting[15].

Shimonovich *et al*[16] evaluated the efficacy and adverse effects of intranasal (IN) KET compared with those of IV and IM MORPH in an RCT. Ninety patients with moderate-to-severe acute traumatic pain (> 80 mm on 100 mm VAS) were randomly assigned either 1.0 mg/kg IN KET, 0.1 mg/kg IV MORPH, or 0.15 mg/kg IM MORPH. The drug was given, and pain relief and adverse events were assessed for an hour. The 'time-to-onset' was used to determine effectiveness—which was defined as a 15 mm reduction in pain on VAS—and also the duration and level of maximum pain relief. Clinically, IN KET had similar results to MORPH in terms of efficacy (onset of reduction of pain and maximum reduction time) and safety[16].

Tongbua *et al*[17] evaluated the pain-relieving effectiveness and safety of IN KET relative to IV MORPH in patients aged 65 years or older attending the ED with acute moderate-to-severe pain (score higher than 5 on an 11-point NRS). A decrease in NRS pain scores was the primary outcome, after 30 minutes of treatment; both rescue medication and the incidence of adverse effects were included in the secondary outcomes. The number of patients enrolled was 72, with 37 in the IN-KET group and 37 in the IV-MORPH group. At 30 minutes, the mean pain score for both groups did not differ significantly. Nausea and vomiting were present in one patient in the IN- KET group and in two patients of the IV-MORPH group, and only one patient in the IV-MORPH group subsequently received treatment with an anti-emetic drug [17].

Kampan *et al*[18] investigated the analgesic efficacy of nebulized KET relative to IV MORPH in older patients (aged 65 years and older) admitted to the ED with acute moderate-to-severe musculoskeletal pain (defined as a pain score of 5 or more on NRS). The outcomes were a decrease in NRS 30 minutes after treatment with nebulized KET or IV MORPH, as well as in the frequency of adverse events and the need for rescue therapy. The authors enrolled 92 patients, divided equally into each group. The nebulized KET and IV MORPH groups showed no significant difference in mean NRS at 30 minutes. The groups did not exhibit a difference in their rates of rescue therapy. The incidence of nausea in the MORPH group was significantly higher than in the KET group. None of the patients in the KET group reported nausea, whereas in the MORPH group, 8 patients experienced nausea[18].

An RCT conducted by Esfahani *et al*[19] compared the efficacy and safety of KET relative to MORPH in the reduction of pain associated with isolated traumatic limb injuries in patients referred to the ED. The number of patients enrolled was 73, with the KET group receiving 0.1 mg/kg of KET and the MORPH group receiving 0.05 mg/kg of MORPH. NRS and adverse drug reactions (ADRs) were recorded at baseline and every 5 minutes, for 30 minutes in total. At each assessed timepoint, the KET group had a significantly lower mean pain score than the MORPH group. Additionally, the KET group had significantly higher overall ADRs than the MORPH group[19].

The Intravenous Sub-dissociative-Dose Ketamine Versus Morphine for Prehospital Analgesia study is a recently published multicenter RCT assessing the non-inferiority of KET (dosed initially at 20 mg and followed by 10 mg every 5 minutes) compared with MORPH sulfate (2 mg or 3 mg administered every 5 minutes) to alleviate pain in adults with out-of-hospital traumatic pain (NRS > 5). A total of 251 patients were enrolled (KET being administered to 128 patients and MORPH administered to 123 patients). The primary outcome was the difference in NRS measured before medication administration (defined as the patient's baseline pain level) and after 30 minutes, with an MCID of 1.3. KET and MORPH showed no difference in pain reduction in patients with out-of-hospital traumatic pain. More adverse events were observed in the KET group, although no patient was required to withdraw from the study and no intervention was needed to manage ADRs[20].

Another study regarding the treatment of out-of-hospital traumatic pain (NRS > 3) conducted by Lim *et al*[21] compared inhalational methoxyflurane and intramuscular tramadol in an RCT enrolling 343 patients (methoxyflurane, 167 and tramadol, 176). The main outcomes: (1) Decreased pain, as assessed by the decrease in NRS at 5 minutes, 10 minutes, 15 minutes, and 20 minutes following administration of medication; (2) The amount of time taken to administer treatment from arriving at the scene; and (3) The amount of time required for effective analgesia to start (a drop of 3 points in NRS). The occurrence of adverse events was among the numerous secondary outcomes. Although methoxyflurane had better efficacy, speed of onset, and administration than tramadol, it was also associated with more numerous minor adverse events[21].

DISCUSSION

Most studies on the use of non-opioids have concluded that these drugs are non-inferior to opioids for the control of acute pain associated with acute musculoskeletal injury. Therefore, the use of non-opioids can be considered as an alternative to opioids for pain management in acute musculoskeletal injuries. Only two studies[8,11] (those that represented the only non-RCT included in the qualitative synthesis) report opioids to have higher efficacy than the control/non-opioid in pain management. The results are unanimous in the traditional RCT studies that were conducted.

The major limitation of our systematic review is the heterogeneity of the studies regarding the measured outcomes and the opioids and non-opioids that were utilized. This heterogeneity made it infeasible to conduct a meta-analysis. Only the studies of Tongbua *et al*[17] and Kampan *et al*[18] are homogeneous in regard to the type of study conducted, the opioid used (IV MORPH), its comparator (IN KET), and the outcome explored. A meta-analysis of the two studies, that together comprised 166 patients (Tongbua 74, Kampan 92), was not conducted because the studies' results were similar in terms of drug efficacy, and we concluded that it did not provide any additional information.

Another limitation of our systematic review is that the outcomes of the included studies were focused on the immediate, short-term response to medication. Thus, the data have limited applicability for use in consideration of longitudinal treatment of pain or discussion of long-term medication effects. The other limitation is that most of the studies were conducted in the ED. Therefore, we can only state that the use of non-opioids can be considered as an alternative to opioids in the ED for short-term pain management in acute musculoskeletal injuries.

Of all the discussed non-opioid drugs, intravenous KET and methoxyflurane were associated with higher adverse events than opioids. Specifically, only intravenous KET was linked with more adverse events than MORPH[19,22], while inhaled or subcutaneous KET did not elicit more adverse events than MORPH. KET is commonly used as an analgesic in emergency medicine[20], and, according to the literature, intravenous administration of KET could cause more adverse events than other routes of administration (ROA).

In the latest 2022 Clinical Practice Guideline for Prescribing Opioids for Pain of the CDC, non-opioid therapies are recommended for many common minor orthopedic acute pain conditions such as sprains, strains, tendonitis, and bursitis [4]. Our systematic review shows that treatment with non-opioid medications can be effective even in major trauma.

CONCLUSION

The findings of this systematic review should be treated with discretion, owing to the heterogeneity of the studies included in the qualitative synthesis. Overall, for short-term pain management of acute musculoskeletal injuries in the ED,

non-opioid medications may provide a viable substitute for opioids. IV administration of KET may cause more adverse events than other ROA. There is a need for additional high-quality RCTs that provide consistency in the target population, interventional components, methodology in reporting outcomes, follow-up periods, and full cost analysis.

FOOTNOTES

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