Comparison of intravenous paracetamol (acetaminophen) to intravenously or intramuscularly administered non-steroidal anti-inflammatory drugs (NSAIDs) or opioids for patients presenting with moderate to severe acute pain conditions to the ED: systematic review and meta-analysis

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Handling editor Gene Yong-Kwang Ong

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/emermed-2022-212869).

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Received 28 September 2022
Accepted 17 April 2023
Published Online First 12 May 2023

To cite: Qureshi I, Abdulrashid K, Thomas SH, *et al*. *Emerg Med J* 2023;**40**:499–508.

ABSTRACT

Objective Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates/opioids, administered parenterally via intravenous or intramuscular route, are widely used to provide analgesia for patients with moderate to severe pain. This systematic review and meta-analysis evaluated the level of analgesia provided by intravenous paracetamol (IVP) alone compared with NSAIDs (intravenous or intramuscular), or opioids (intravenous) alone in adults attending the ED with acute pain.

Methods Two authors independently searched PubMed (MEDLINE), Web of Science, Embase (OVID), Cochrane Library, SCOPUS and Google Scholar (3 March 2021–20 May 2022) for randomised trials without any language or date restriction. Clinical trials were evaluated using the Risk of Bias V.2 tool. The primary outcome was mean difference (MD) for pain reduction at 30 min (T30) post analgesia delivery. The secondary outcomes were MD in pain reduction at 60, 90 and 120 min; the need for rescue analgesia; and the occurrence of adverse events (AEs).

Results Twenty-seven trials (5427 patients) were included in the systematic review and 25 trials (5006 patients) in the meta-analysis. There was no significant difference in pain reduction at T30 between the IVP group and opioids (MD −0.13, 95% CI −1.49 to 1.22) or IVP and NSAIDs (MD −0.27, 95% CI −1.0 to 1.54. There was also no difference at 60 min, IVP group versus opioid group (MD −0.09, 95% CI −2.69 to 2.52) or IVP versus NSAIDs (MD 0.51, 95% CI 0.11 to 0.91). The quality of the evidence using Grading of Recommendations, Assessments, Development and Evaluations methodology was low for MD in pain scores.
The need for rescue analgesia at T30 was significantly higher in the IVP group compared with the NSAID group (risk ratio (RR): 1.50, 95% CI 1.23 to 1.83), with no difference found between the IVP group and the opioid group (RR: 1.07, 95% CI 0.67 to 1.70). AEs were 50% lower in the IVP group compared with the opioid group (RR: 0.50, 95% CI 0.40 to 0.62), whereas no difference was observed in the IVP group compared with the NSAID group (RR: 1.30, 95% CI 0.78 to 2.15).

Conclusion In patients presenting to the ED with a diverse range of pain conditions, IVP provides similar

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several clinical trials have been published assessing the efficiency of intravenous paracetamol (IVP) in a diverse set of pain conditions presenting to the ED, but all are small and single centre with no previous meta-analysis. Systematic reviews have suggested similar levels of pain relief are provided by IVP for patients with renal colic as compared with non-steroidal anti-inflammatory drugs (NSAIDs) or opiates/opioids, but with a greater need for rescue analgesia compared with NSAIDs.

WHAT THIS STUDY ADDS

⇒ This systematic review (27 randomised trials, 5427 participants) and meta-analysis of patients presenting to the ED with diverse pain aetiologies found intravenous paracetamol, intravenous or intramuscular NSAIDs and intravenous opiates/opioids to offer similar, clinically significant levels of pain relief at 30, 60 and 90 min post delivery. Considering the significant risk of bias in the included studies and the imprecision of the pooled effect, the quality of the evidence using Grading of Recommendations, Assessments, Development and Evaluations methodology was low for mean difference in pain scores. Rescue analgesia was required less frequently in patients receiving intravenous/intramuscular NSAIDs as compared with intravenous paracetamol (number needed to treat=14), and adverse events (AEs) were less frequent with IVP as compared with opiates (number needed for harm=12).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In patients with no contraindications, NSAIDs may be considered first-choice analgesia in patients with acute pain presenting to the ED, with IVP as a viable alternative. Opiates/opioids do not appear to offer superior analgesia and had risk of more AEs.

levels of pain relief compared with opiates/opioids or NSAIDs at T30 post administration. Patients treated with NSAIDs had lower risk of rescue analgesia, and opioids cause more AEs, suggesting NSAIDs as the first-choice analgesia and IVP as a suitable alternative.
PROSPERO registration number CRD42021240099.

INTRODUCTION

Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates/opioids, administered parenterally via intravenous or intramuscular route, are used to provide analgesia for moderate to severe pain conditions in the ED.[1] While other routes for paracetamol are widely used, intravenous paracetamol (IVP) offers a more rapid onset of analgesia (around 10 min) than by mouth (PO) or by rectum (PR) preparations; however, the analgesia effects at 30 min (T30) post administration are reported to be similar.[2] IVP is associated with higher costs and requires more logistics compared with oral administration. However, IVP has been reported to have fewer side effects compared with parenteral opioids and NSAIDs in equal therapeutic doses.[3]

A 2016 systematic review by Sin *et al*[4] reported on use of IVP in acute pain presentations to the ED; however, the authors did not include a meta-analysis, and 23 relevant trials have been subsequently published. Three systematic reviews have focused on specific aetiologies in the ED; one focused on patients with renal colic[5]; and two focused on patients with musculoskeletal injuries.[6 7] However, these reviews mainly focused on the use of analgesic medication in general or on the use of paracetamol, regardless of route of administration (intravenously and orally administered) as intervention or comparison.

We undertook a systematic review and meta-analysis of randomised controlled trials (RCTs) to evaluate the level of analgesia provided by IVP alone compared with NSAIDs (intravenous or intramuscular) or opioids (intravenous) alone (or as in combination) among adult patients attending the ED with acute pain of various aetiologies.

METHODS

Protocol and registration

The review was designed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The review was registered with the International Prospective Register of Systematic Reviews on 15 April 2021, with registration number CRD42021240099.

Primary and secondary outcomes

The primary outcome was defined as the mean difference (MD) in pain reduction for each group (IVP vs NSAIDS or opiates/opioids) at T30 post analgesia delivery (baseline (T0)). The secondary outcomes were the MD in pain reduction at 60 min (T60), 90 min (T90) and 120 min (T120); the need for rescue analgesia at T30, T60, T90 and T120; and the occurrence of adverse events (AEs) during the trial period.

Inclusion and exclusion criteria

We included only RCTs performed on adults (≥18 years) in the ED setting reporting Numerical Rating Scale (NRS) or Visual Analogue Scale (VAS) pain scores at T0 and T30 post medication administration. There was no restriction on language. Trials administering medications orally in any arm were excluded. Trials including tramadol as one of the treatments were included under the opioid/opiate arm.

Information sources, databases and search strategy

The initial literature search was conducted between 3 March 2021 and 1 April 2021 using the electronic databases of MEDLINE (through PubMed interface), Web of Science, Embase (OVID) and Cochrane Library and supplemented by hand searching references of relevant articles. The grey literature was accessed using Google Scholar and Trip Medical Databases. A second identical literature search was conducted between 18 May 2022 and 20 May 2022. The Clinical Trials registry (clinicaltrial.gov) was searched for ongoing trials. Non-English language papers were translated to English for review; however, none met the criteria to be included in the review. The Medical Subject Headings used for the search strategy are shown in the online supplemental appendix 1.

Study selection and data extraction

Two reviewers independently (IQ and KA) performed the literature search, selection and quality assessment of papers, and extracted data using a priori defined data collection tools. Any disagreements were resolved by a third reviewer (TH). Data extracted included author; year of publication; country; study design; aetiology of pain; sample size; time; method of pain scores; pain scores at T0, T30, T60 and T120; rescue analgesia at T30, T60 and T120; and all reported AEs. There is no agreed definition of AEs, and these were abstracted directly from reported trial data. Pain scores were recorded exactly as published, with some authors using the VAS and others NRS. After full analysis, 13 trials were excluded (figure 1). Key data were missing from 25 papers, and the lead authors were contacted to request the information.[8–32]

Methodological quality assessment

The quality assessment was performed using the Risk of Bias (ROB V.2) tool[33] (online supplemental appendix 2). The ROB V.2 tool is recommended by Cochrane for the quality assessment of randomised trials. It includes a set of fixed domains to assess bias within a trial design, conduct and reporting. Risk of bias is reported as low risk, some concern or high risk in each domain then summarised for the paper overall. The Grading of Recommendations, Assessments, Development and Evaluations (GRADE) assessment offers a transparent quality assessment framework and a systematic approach for quality recommendations for the primary and secondary outcomes under review. This approach involved consideration of within-study risk of bias (methodological quality), heterogeneity, directness of evidence, precision of effect estimates and risk of publication bias. Recommendations based on the overall quality of the data are described as strong or weak.

Statistical analysis

Stata V.17 software was used to calculate the overall pooled effect size using the inverse variance heterogeneity (IVhet) model.[34] The IVhet model makes no assumption regarding the distribution of the true effects and is a robust model in the presence of both heterogeneity and publication bias. In each trial, the effect size was calculated using the MD in pain scores between the groups compared at T0, T30, T60, T90 and T120. VAS and NRS scores were scaled 0–10 to allow pooling of all data and were presented with 95% CIs. Additionally, for the mean pain reduction outcomes, the treatment effects were reported as standardised MD with 95% CI using the random effects model, and the method of variance estimation was restricted maximum likelihood.

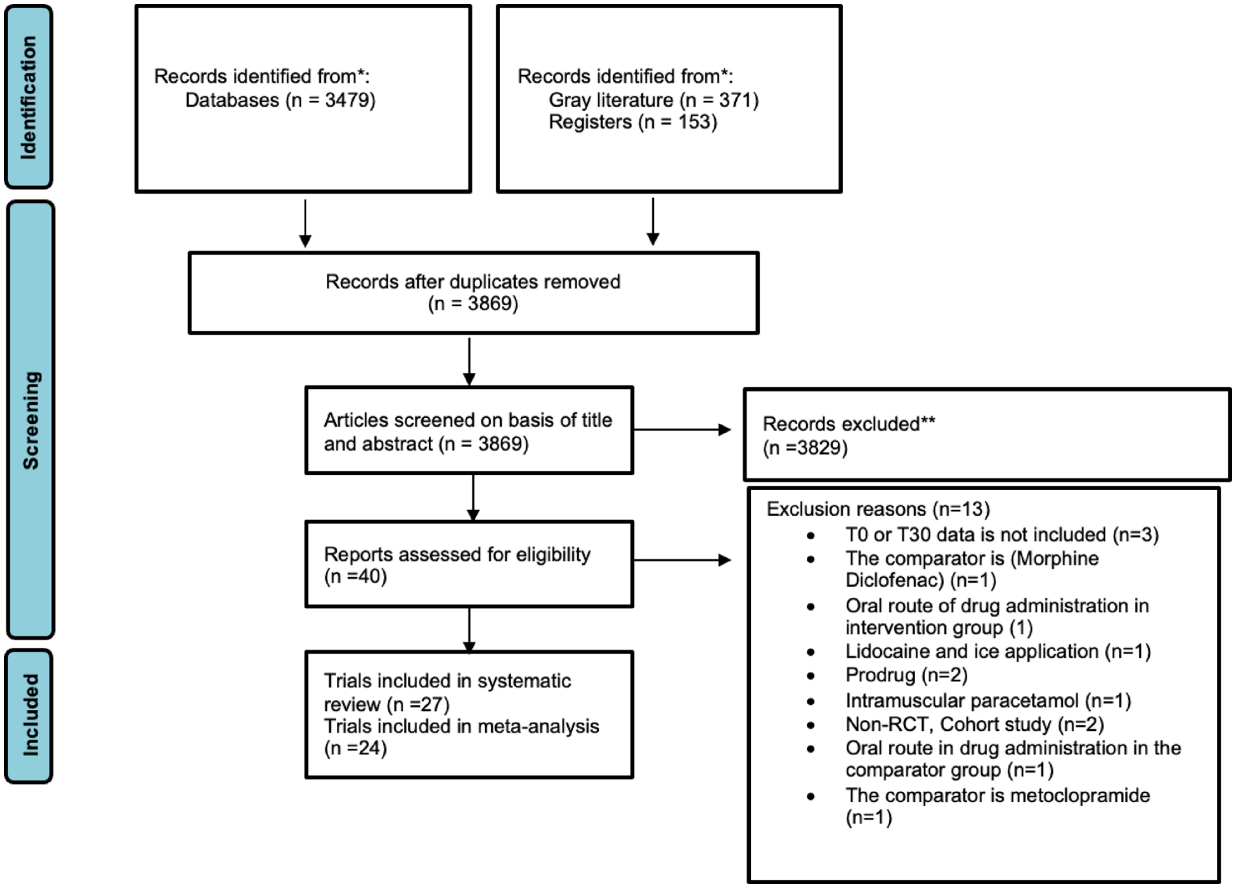

Figure 1 Study flow diagram. RCT, randomised controlled trial.

A previously published systematic review reported the minimum clinically important difference for mild, moderate and severe pain as 6, 13 and 21 mm, respectively, and the mean pain score in that study was 7.6 (NRS).[35] In the current review, we used a median reported score (17 mm) to define a clinically significant reduction in pain.

Subgroups analyses were performed for treatment groups by pain aetiology classified a priori into five defined groups: renal colic, headache, back pain, abdominal pain and musculoskeletal injuries.

To consider the variation in the NSAID drugs, a sensitivity analysis was performed.

The pooled risk ratios (RRs) of AE and patients requiring rescue analgesia at T30, T60 and T120 were estimated between the IVP and comparator groups.[34] The need for rescue analgesia was as reported in the studies. Results of the meta-analysis are graphically presented in forest plots, and potential publication bias was examined by funnel plots.

RESULTS

Characteristics of included studies

Forty RCTs were fully reviewed with 13 excluded, leaving 27 articles involving 5427 patients in the systematic review (figure 1). Characteristics of included studies are shown in table 1. All trials were double-blind RCTs except one, which was not blinded, as acupuncture was one of the comparator arms[8] (online supplemental appendix 2). Included studies' pain scores ranged from 2.7 to 9.2 (mean 7.6). In 24 trials,[9–14 16–30 36–38] the change in pain scores from T0 to T30 was reported, and all trials except one[29] reported that all groups (paracetamol, NSAIDs or opioids) achieved clinically significant reductions in pain scores from T0 to T30. Key data were missing from 25 papers, and the lead authors were contacted to request the information,[8–32] but no authors replied to requests for data.

IVP was administered as a single dose of 1 g in 100 mL NS (100 ml normal saline) in 26 trials[8–13 15–19 21–30 32 36–38] and at a dose of 15 mg/kg in one trial.[20] The infusion rate for the administration of IVP was as a rapid bolus infusion in three trials,[11 12 24] slow infusion over 5–20 min in 16 trials,[8 10 13 16 18 19 21 22 25 26 29–32 36–38] and not mentioned for 8 trials.[9 14 15 17 20 23 27 28] Doses of morphine were 0.1 mg/kg in 12 trials,[9 13 19–23 25–28 37] 5 mg/mL in 1 trial[30] and 10 mg in 2 trials.[18 31]

Of the 27 studies included in the review, 20 trials[8–13 15 17–21 23–28 32 36] were assessed to have a high or unclear risk of bias, and 7 trials[14 16 22 29 30 37 38] were assessed to have a low risk of bias using the ROB V.2 tool. The domains assessed as having some concern or a high risk of bias were randomisation process (22 studies), deviation from intended intervention (19 studies), bias due to missing outcome data (17 studies), bias in the measurement of outcome (18 studies) and bias in the selection of reported outcome (17 studies) (risk of bias table, online supplemental appendix 2).

There was a high degree of missing information: 12 trials[9 13 15 17 21 23–28 31] did not provide information regarding the intention to treat analysis; 5 trials[9–12 24] had missing baseline characteristics; and 5 trials[8 14 18 20 29] did not provide information regarding allocation concealment.

Eleven trials concluded that there was no significant difference in pain scores between IVP and the comparator groups (opioids or NSAIDs) at T30[9–11 15 18 19 24 25 27 29 32] (online supplemental

Table 1 Characteristics of included studies

Reference and year	Country	Participants (n)	Pain condition	Pain Analogue Scale	Patients in (paracetamol/ opioids/NSAIDs/ placebo/ other) groups	Intervention (paracetamol) dose and the route of administration	Comparator dose and the route of administration	Timing of pain scores
Far *et al*,[30] 2020	Iran	105	Post-trauma headache	VAS	35/35/35/–/–	Intravenous, 1 g (1000 mg)	Intravenous, ketorolac: 30 mg/mL Intravenous, morphine: 5 mg/mL	T=0, 15, 30 and 60 min
Ghamry *et al*,[16] 2020	Egypt	100	Dysmenorrhoea	VAS	50/50/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, 100 mg tramadol in 100 mL normal saline	T=0, 15, 30, 60 and 120 min
Al-Terki *et al*, [15] 2020	Kuwait	203	Renal colic	VAS	105/–/103/–/–	Intravenous, 1 g (1000 mg)	Intravenous, 40 mg of parecoxib infusion	T=0 and 30 min
Yalçınlı *et al*,[14] 2020	Turkey	172	Soft tissue injury	NRS	86/–/86/–/–	Intravenous, 1 g (1000 mg)	Intravenous, ibuprofen: 400 mg/mL 4 mL	T=0, 15,30 and 60 min
Demirozogul *et al*,[12] 2019	Turkey	200	Non-traumatic musculoskeletal pain	NRS	100/–/100/–/–	Intravenous, 1 g (1000 mg)	Intravenous, dexketoprofen: 50 mg in 150 mL normal saline.	T=0, 15, 30 and 60 min
Cenker *et al*,[17] 2018	Turkey	200	Renal colic	VAS	99/–/97/–/–	Intravenous, 1 g (1000 mg)	Intravenous, ibuprofen: 800 mg in 100 mL normal saline	T=0, 15 and 30 min
Serinken *et al*,[36] 2018	Turkey	100	Dysmenorrhoea	VAS	50/–/49/–/–	Intravenous, 1 g (1000 mg)	Intravenous, dexketoprofen: 50 mg in 100 mL normal saline	T=0, 15 and 30 min
Yazdani *et al*,[18] 2018	Turkey	150	Renal colic	VAS	50/50/50/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 10 mg sulfate in 100 mL normal saline Intravenous, ketorolac: 30 mg in 100 mL normal saline	T=0 and 30 min
Yilmaz *et al*,[24] 2019	Turkey	200	Musculoskeletal trauma	VAS	100/–/100/–/–	Intravenous, 1 g (1000 mg)	Intravenous, dexketoprofen: 50 mg in 150 mL normal saline	T=0, 15, 30 and 60 min
Montazer *et al*,[19] 2018	Iran	355	Renal colic	VAS	152/192/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg in 100 mL normal saline	T=0, 15, 30, 60 and 120 min
Al *et al*,[32] 2017	Turkey	300	Renal colic	VAS	100/100/100	Intravenous, 1 g (1000 mg)	Intravenous, dexketoprofen: 50 mg Intravenous, fentanyl: 2 µg/kg	T=0, 15 and 30 min
Talebi Deloee *et al*,[25] 2017	Iran	50	Isolated long bone fractures	VAS	24/26/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine sulfate: 0.1 mg/kg	T=0, 5 and 30 min
Gülen *et al*,[10] 2016	Turkey	90	Pancreatitis	VAS	30/30/30/–/–	Intravenous, 1 g (1000 mg)	Intravenous, dexketoprofen: 50 mg Intravenous, tramadol: 1 mg/kg in 100 mL normal saline	T=0 and 30 min
Jalili *et al*,[26] 2016	Iran	60	Limb trauma	NRS	30/30/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg in 100 mL normal saline	T=0, 15 and 30 min
Pathan *et al*,[37] 2016	Qatar	1645	Renal colic	NRS	548/549/548/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg Intramuscular injection of diclofenac: 75 mg/3 mL	T=0, 30, 60 and 90 min
Serinken *et al*,[13] 2016	Turkey	300	Sciatica	VAS	100/100/–/100/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg in 100 mL of normal saline Intravenous placebo: 100 mL of normal saline	T=0 and 30 min
Esmailian *et al*,[27] 2015	Iran	54	Rib fracture	NRS	25/29/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg of body weight, single dose	T=0 and 30 min
Kaynar *et al*,[8] 2015	Turkey	121	Renal colic	VAS	42/–/40/–/42	Intravenous, 1 g (1000 mg)	Intramuscular, diclofenac sodium: 75 mg Acupuncture	T=0, 10, 30, 60 and 120 min
Azizkhani *et al*,[20] 2013	Iran	124	Renal colic	VAS	62/62/–/–/–	Intravenous, 15 mg/kg	Intravenous, morphine: 0.1 mg/kg	T=0 and 30 min
Eken *et al*,[9] 2014	Turkey	137	Low back pain	VAS	46/45/46/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine:0.1 mg/kg in 100 mL normal saline Intravenous, dexketoprofen: 50 mg in 100 mL normal saline solution	T=0,15 and 30 min
Masoumi *et al*,[21] 2014	Iran	108	Renal colic	VAS	54/54/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg in 100 mL normal saline	T=0, 15, 30 and 60 min

Continued

Table 1 Continued

Reference and year	Country	Participants (n)	Pain condition	Pain Analogue Scale	Patients in (paracetamol/ opioids/NSAIDs/ placebo/ other) groups	Intervention (paracetamol) dose and the route of administration	Comparator dose and the route of administration	Timing of pain scores
Shams Vahdati *et al*,[28] 2014	Iran	60	Post-trauma headache	VAS	30/30/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg/100 mL/10 min	T=0, 15, 30 min and after 1 week
Turkcuer *et al*,[11] 2014	Turkey	200	Acute migraine	NRS	100/–/100/–/–	Intravenous, 1 g (1000 mg)	Intravenous, dexketoprofen: 50 mg	T=0, 15 and 30 min
Craig *et al*,[29] 2012	US	55	Isolated limb injury	VAS	28/27/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 10 mg	T=0, 5, 15, 30 and 60 min
Serinken *et al*,[22] 2012	Turkey	73	Renal colic	VAS	40/40/–/–/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg in 100 mL normal saline bolus infusion in 4–5 min	T=0, 15 and 30 min
Grissa *et al*,[38] 2011	Tunisia	100	Renal colic	VAS	50/–/50/–/–	Intravenous, 1 g (1000 mg)	Intramuscular injection of piroxicam: 20 mg	T=0, 5, 10, 15, 30, 45 and 90 min
Bektas *et al*,[23] 2009	Turkey	165	Renal colic	VAS	55/55/–/55/–	Intravenous, 1 g (1000 mg)	Intravenous, morphine: 0.1 mg/kg in 100 mL normal saline Intravenous, placebo: 100 mL normal saline	T=0, 15 and 30 min

NRS, Numerical Rating Scale; NSAID, non-steroidal anti-inflammatory drug; T, time; VAS, Visual Analogue Scale.

appendix 2). Seven trials reported that IVP provided superior analgesia to the comparator groups[21–23 26 28 30 38]; in six trials, the comparator was intravenous morphine[21–23 26 28 30]; and in one trial, the comparator was an intramuscular NSAID (piroxicam).[38] Nine trials[8 12–14 16 17 20 36 37] concluded that IVP provided inferior analgesia; seven[8 12–14 17 36 37] compared IVP to NSAIDs and two to opioids (morphine[20] and tramadol[16]). Trials' conclusions are presented in online supplemental appendix 2.

Primary outcome

Pain reduction at T30

Twenty-four RCTs including 5348 patients found no significant difference in mean pain reduction at T30, when IVP was compared with opiate/opioids (MD −0.13, 95% CI −1.50 to 1.14) or to NSAIDs (MD −0.04, 95% CI −0.49 to 0.40) (table 2 and online supplemental appendix 2).[9–14 16–30 36–38]

Significant heterogeneity was observed across the pooled trials (IVP vs opioids, I^2=93.7%, p<0.001; and IVP vs NSAIDs, I^2=65.5%, p<0.001), precluding meta-analysis. Possible sources of heterogeneity were medication type (IVP compared with NSAIDs) and pain aetiology (table 2).

Secondary outcomes

Pain reduction at T60, T90 and 120

Six trials (including 2643 patients) found no difference in mean pain reduction at T60 between the IVP group compared with the opiate/opioid group. Similarly, at T90 and T120, no difference was identified (table 2). Heterogeneity was low–moderate (I^2=49.9%, p<0.09), allowing meta-analysis; for T60 pain reduction comparing between IVP and NSAIDs, there was a statistically but not clinically significant difference favouring NSAIDs (MD 0.22, 95% CI 0.05 to 0.38; p=0.01) (figure 2).

Need for rescue analgesia

Patients who were treated with IVP required more frequent rescue analgesia compared with patients treated with NSAIDs at T30 (RR=1.5, 95% CI 1.23 to 1.83; p<0.001), with number needed to treat (NNT) of 14 (figure 3). No difference in rescue analgesia needs was identified between IVP and opioid groups (table 2).

Non-specific AEs

The meta-analysis of AEs included 24 trials with 5006 patients).[9–14 16–30 36–38] Patients in IVP group had significantly fewer AEs during the trial time compared with the patients in the opioids group (RR: 0.50; [95% CI: 0.40, 0.62; p<0.001]), with a number needed for harm (NNH) of 12 (figure 4). Nine studies (2093 patients) reported AEs in both IVP and NSAID groups with pooled effect of RR=1.3; however, the CI crossed the line of null effect (table 2).

Pain aetiology subgroup analysis

Twelve trials addressed renal colic (n=3544)[8 15 17–23 32 37 38]; 7 addressed musculoskeletal injuries (n=791)[12 14 24–27 29]; 3 were aimed at headaches (n=365)[11 28 30]; 3 addressed abdominal pain (n=289)[10 16 36]; and 2 addressed back pain (n=437)[9 13] (table 1).

Subgroup analysis was conducted by pain aetiology. No difference was found between IVP and NSAID or opioid groups at T30 in patients with renal colic, headache, musculoskeletal injuries and back pain (table 2). Sensitivity analyses are also presented in table 2. For subgroup analysis, please see forest plot in online supplemental appendix 2.

Headache

Three trials evaluated treatment with intravenous paracetamol in patients presenting to the ED with headaches.[11 28 30] Two trials recruited patients with post-traumatic headache and reported statistically significant differences in favour of IVP at T30.[28 30] However, these differences were not clinically significant. The third trial compared IVP to dexketoprofen (NSAID) in patients with migraine and showed no statistically significant difference at T30.[11]

Renal colic

Twelve trials assessed IVP in patients presenting to the ED with renal colic.[8 15 17–23 32 37 38] Eleven trials[8 15 17–23 37 38] used

Table 2 Effect estimates, heterogeneity and 95% CIs

Drugs			Trials (n)	Estimates		Heterogeneity (I^2 (%), P value)
				MD¶ between intervention and comparator (95% CI)	Standardised MD (95% CI)	
Paracetamol compared with opioids*		T=30†	17	−0.13 (−1.49 to 1.22)	−0.06 (−0.67 to 0.55)	93.7, <0.001
		T=60	6	−0.09 (−2.69 to 2.52)	−0.04 (−1.21 to 1.13)	97.1, <0.001
		T=120	2	1.25 (−7.33 to 9.82)	0.56 (−3.29 to 4.41)	98.9, <0.001
Paracetamol compared with NSAIDs*		T=30†	14	0.27 (−1.0 to 1.54)	0.12 (−0.45 to 0.69)	94.2, <0.001
		T=60	6	0.51 (0.11 to 0.91)	0.22 (0.05 to 0.38)	49.9, 0.09
Paracetamol compared with the placebo*		T=30†	2	−2.18 (−4.08 to −0.29)	−0.98 (−1.83 to −0.13)	91.5, 0.02
Paracetamol compared with opioids in subgroup analysis	Renal colic	T=30	7	−0.31 (−0.82 to 0.20)	−0.14 (−0.37 to 0.09)	62.4, <0.001
	Musculoskeletal injuries	T=30	4	0.09 (−2.07 to 2.25)	0.04 (−0.93 to 1.01)	91.7, <0.001
	Back pain	T=30	2	0.85 (0.13 to 1.60)	0.38 (0.06 to 0.71)	42.6, <0.001
	Abdominal pain	T=30	2	3.25 (−7.97 to 14.48)	1.46 (−3.58 to 6.50)	99.0, <0.001
	Renal colic	T=60	3	−0.28 (−1.29 to 0.71)	−0.13 (−0.58 to 0.32)	88.2, 0.14
Paracetamol compared with NSAIDs in subgroup analysis	Headaches	T=30	2	0.04 (−1.63 to 1.73)	0.02 (−0.73 to 0.78)	84.5, <0.001
	Renal colic	T=30	4	0.18 (−1.05 to 1.43)	0.08 (−0.47 to 0.64)	90.6, <0.001
	Abdominal pain	T=30	3	2.16 (3.50 to 7.79)	0.97 (−1.57 to 3.50)	98.2, <0.001
	Musculoskeletal injuries	T=30	3	0.22 (−0.53 to 1.0)	0.10 (−0.24 to 0.45)	76.9, 0.02
	Musculoskeletal injuries	T=60	3	0.53 (−0.07 to 1.14)	0.24 (−0.03 to 0.51)	63.4, 0.06
Paracetamol compared with NSAIDs	Ketorolac	T=30	2	−0.70 (1.40 to 0.00)	−0.31 (−0.63 to 0.00)	7.5, 0.32
	Ibuprofen	T=30	2	1.52 (0.31 to 2.70)	0.68 (0.14 to 1.21)	84, 0.02
	Dexketoprofen	T=30	6	0.13 (−0.42 to 0.67)	0.06 (−0.19 to 0.30)	65.6, 0.02
	Dexketoprofen	T=60	2	0.27 (−0.16 to 0.71)	0.12 (−0.07 to 0.32)	0.0, 0.33
Paracetamol compared with dexketoprofen in subgroup analysis	Musculoskeletal injuries	T=30	2	−0.04 (−0.84 to 0.76)	−0.02 (−0.38 to 0.34)	I^2=70.5%, p=0.08
	Musculoskeletal injuries	T=60	2	0.27 (−0.16 to 0.71)	0.12 (−0.07 to 0.32)	0.0, 0.33
RR of adverse events	**Trials (n)**	**Estimates RR (95% CI)**		**Heterogeneity (I2, P value)**		
Paracetamol compared with opioids	13	0.50 (0.40 to 0.62)		0.0, 0.59		
Paracetamol compared with NSAIDs	9	1.30 (0.78 to 2.15)		0.0, 0.83		
Paracetamol compared with placebo	2	1.23 (0.29 to 5.27)		29.93, 0.23		
RR§ of rescue analgesia	**Trials (n)**	**Estimates RR (95% CI)**		**Heterogeneity (I2, P value)**		
Paracetamol compared with opioids	T30=10	1.07 (0.67 to 1.70)		66, <0.001		
Paracetamol compared with NSAIDs	T30=8	1.50 (1.23 to 1.83)		2.37, 0.37		
	T60=2	2.42 (1.51 to 3.86)		0, 0.65		

I^2 represents the per cent of variation across the studies that is due to heterogeneity rather than chance.
*Paracetamol compared to each drug group separately.
†The main outcome at T=30.
‡Indicates the changes in the analogue scale; the interpretation depends on the direction of the sign (negative sign: in favour of paracetamol; positive sign: in favour of the comparator group).
§RR of rescue analgesia.
¶The presented results were estimated using the inverse variance heterogeneity model.
MD, mean difference; NSAID, non-steroidal anti-inflammatory drug; RR, risk ratio; T60, 60 min; T, time; T30, 30 min.

intravenous morphine and 1 trial used intravenous fentanyl (2 µg/kg).[32] Four trials[21–23 38] reported IVP provided a greater reduction in pain scores than comparators at T30; of those, two showed clinically significant differences, one comparing IVP to morphine[21] and the other to an NSAID (piroxicam).[38]

Five trials reported IVP having a smaller reduction in pain scores than the comparators at T30.[8 17 20 32 37] The four trials comparing IVP with NSAIDs showed statistically significant greater reductions of pain at T30 in favour of NSAIDS, all clinically significant.[9 26 33 38] Three trials reported equivalent levels of analgesia for IVP and comparator groups at T30 (IVP vs morphine,[19] IVP vs NSAIDs,[15] and IVP vs both intravenous morphine and intramuscular ketorolac).[18]

Musculoskeletal injuries

Seven trials assessed IVP in patients with musculoskeletal injuries.[12 14 24–27 29] Two trials[27 30] comparing IVP to intravenous morphine showed a statistically significant greater reduction in pain at T30, favouring IVP; however, only one was clinically significant.[29] Two trials[22 32] comparing IVP to intravenous NSAID showed a statistically significant greater reduction in pain at T30, favouring NSAIDs; with one also clinically significant.[29]

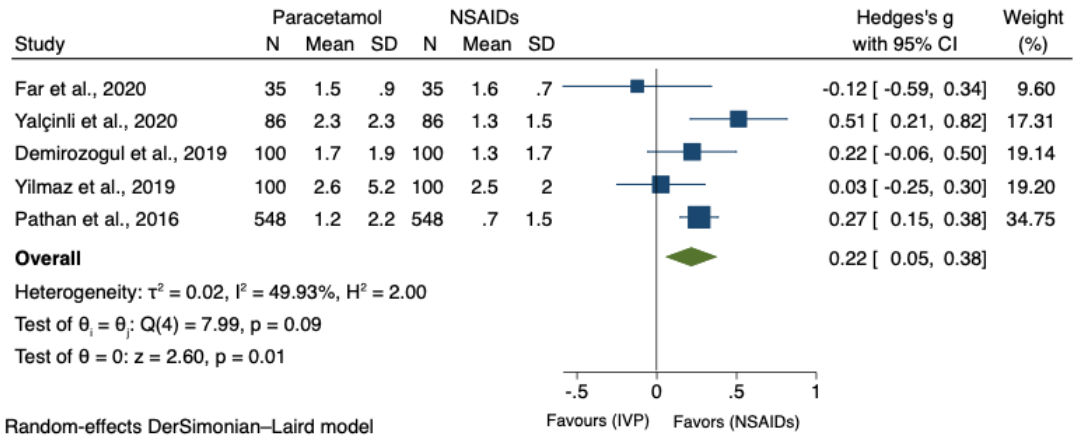

Figure 2 Forest plot: pain reduction and paracetamol (IVP) compared with NSAIDs at 60 min. IVP, intravenous paracetamol; NSAID, non-steroidal anti-inflammatory drug.

Three trials, IVP versus NSAIDs[12 14 24–27] and IVP or intravenous morphine,[12 14 24–27] showed no difference between the groups.

Abdominal pain

Three trials were conducted among patients presenting with abdominal pain, two involved patients with dysmenorrhoea[16 36] and one patients with acute pancreatitis.[14] One of the trials[10–13 16 36] involving patients with dysmenorrhoea reported patients treated with IVP had clinically and statistically significant greater reduction in pain scores than those treated with tramadol at T30.[36] The other dysmenorrhoea trial reported no significant difference in pain scores between IVP and dexketoprofen groups at T15 and T30.[16] The trial recruiting patients with non-traumatic acute pancreatitis concluded IVP, dexketoprofen and tramadol offered similar levels of analgesia.[10]

Back pain

Two trials recruited patients with non-traumatic back pain.[9 13] One trial concluded that intravenous morphine provided statistically, and clinically significant greater pain relief compared with IVP at T30.[13] The other trial concluded IVP, dexketoprofen and morphine offered similar pain relief.[9]

Publication bias and grading the evidence

Funnel plots generated for the primary outcome suggested minor publication bias (online supplemental appendix 2). The quality of evidence following GRADE methodology was low quality for MD in pain scores, as a result of the high risk of bias in the included trials and imprecision of the pooled effect. (online supplemental appendix 2) There was moderate quality of evidence for AEs for IVP compared with opioids, whereas the evidence was low quality for comparison with NSAIDs. There was low quality evidence for the requirement of rescue analgesia with all treatments due to the inconsistencies observed in the treatment effect and the quality of included studies.

DISCUSSION

This systematic review and meta-analysis provides evidence for the efficacy of IVP in a wide range of conditions with acute pain. The review found no significant difference between medication

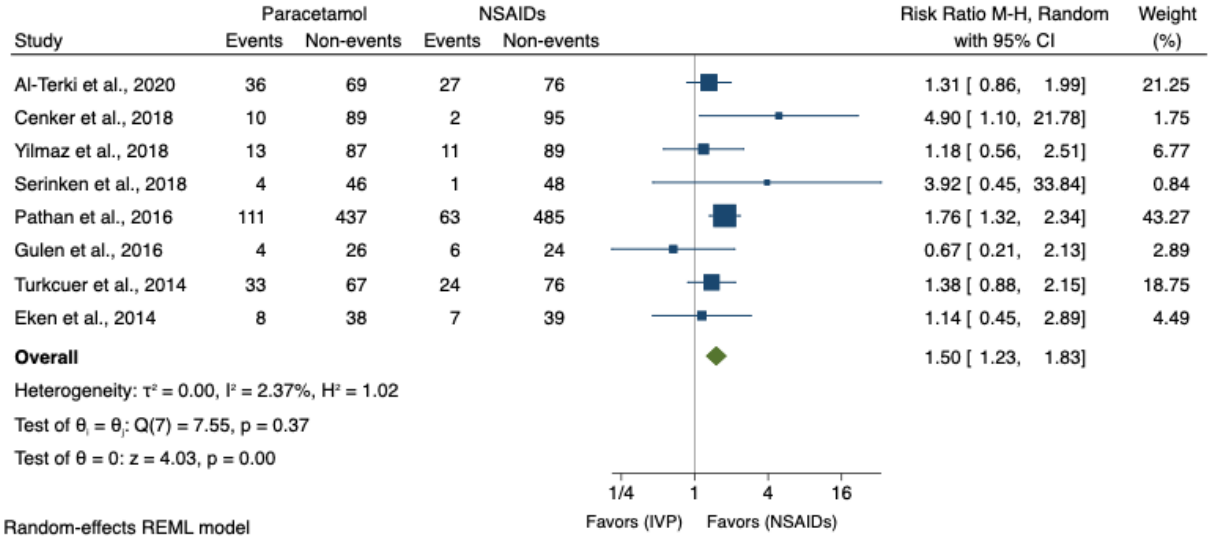

Figure 3 Forest plot: need for rescue analgesia, paracetamol (IVP) compared with NSAIDs at 30 min. IVP, intravenous paracetamol; NSAID, non-steroidal anti-inflammatory drug; REML, restricted maximum likelihood; M-H, Mantel–Haenszel test.

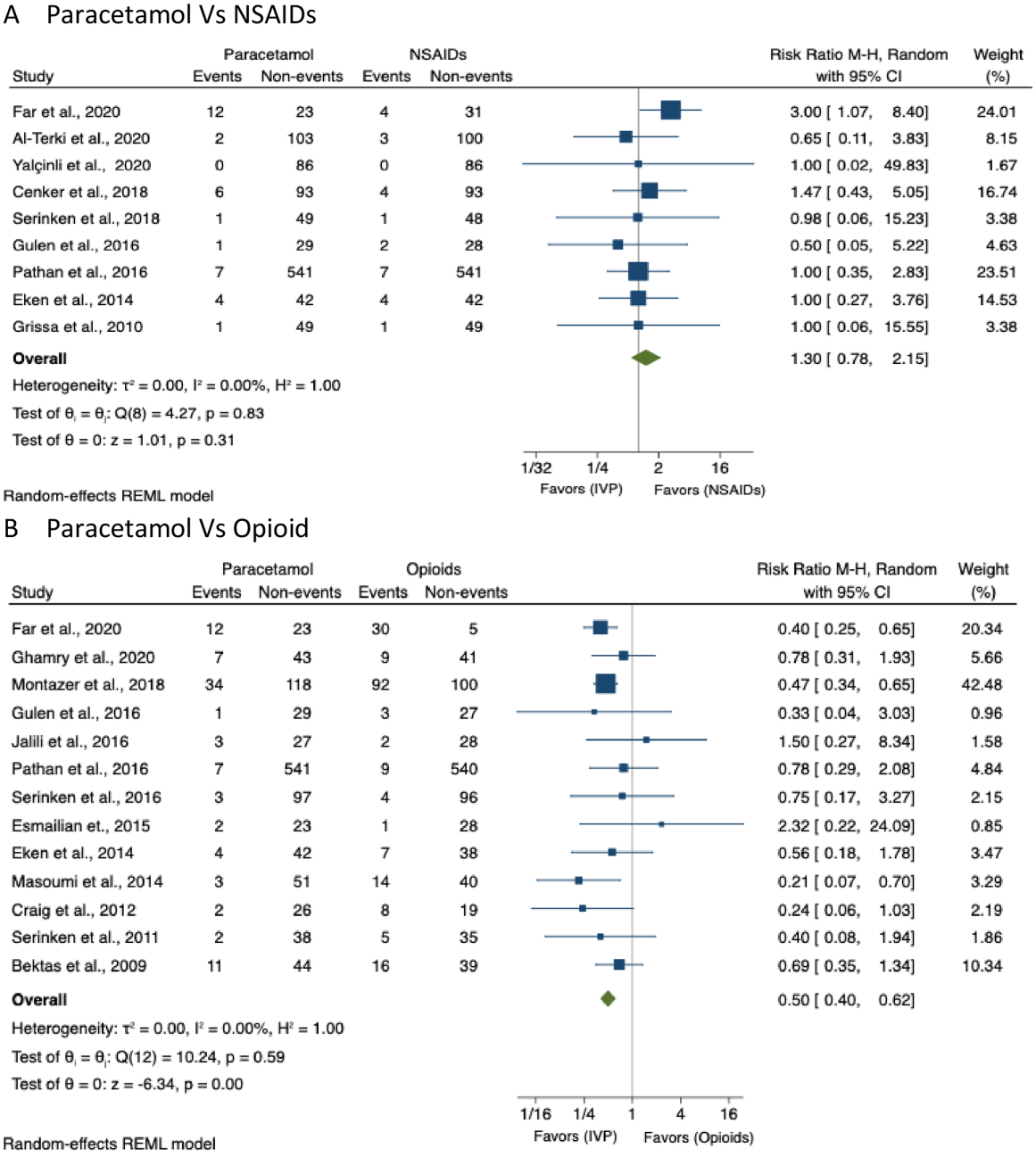

Figure 4 Forest plot: adverse events. IVP, intravenous paracetamol; NSAID, non-steroidal anti-inflammatory drug; REML, restricted maximum likelihood.

groups (IVP, NSAIDs, or opioids) for the analgesic effect at T30, T60, T90 or T120 post analgesia administration. There were 50% fewer AEs reported in patients receiving IVP compared with those receiving opioids. The NSAIDs were found superior to both IVP and opioids in terms of providing sustained analgesia reflected by lower needs for rescue treatments. All analgesia types provided clinically significant reductions in pain at each time point with no benefit for opiates/opioids identified (online supplemental figure 1A). The quality of evidence following GRADE methodology was found to be very low for the outcomes such as difference in pain relief and for the requirement of rescue analgesia, mostly owing to the inconsistencies observed in the treatment effect and the quality of studies included. Evidence for NSAID benefit of lower vomiting rates was of moderate quality. There was high-quality evidence for NSAID benefit over paracetamol for the requirement of rescue treatments.

Headache

Prior data support the use of IVP as a suitable analgesic in acute headaches, consistent with the findings of this meta-analysis, where oral medications are contraindicated or unavailable. In this review, we found that both IVP and comparators (NSAIDs or opioids) provided adequate analgesia for headache at T30. A narrative review (2018), including data from published reviews, meta-analysis, RCTs and clinical trials of acute migraine treatments,[39] concluded that oral paracetamol and oral NSAIDs were suitable first line treatment for mild to moderate migraine. A 2015 review[40] assessing the evidence of migraine pharmacotherapies

suggested there was inadequate evidence to refute the efficacy of IVP. Another (2015) systematic review[41] evaluated 44 RCTs involving the use of a wide range of therapies in adults with migraine recommending against the use of IVP, based on only one moderate quality trial. A 2016 systematic review, including 8079 participants with recurrent tension headache, concluded that oral paracetamol 1000 mg (compared with placebo) was associated with a higher proportion of patients pain free at 2 hours (NNT=10).[42]

Renal colic

IVP and comparators (NSAIDs or opioids) all provided adequate analgesic for renal colic patients by T30 and rescue analgesia was required significantly less often in patients treated with NSAIDS. These findings support earlier analyses of 2018 systematic review[5] of 36 trials (4887 patients) and 2017 systematic review and meta-analysis,[43] including 20 trials (3852 patients); both comparing IVP, NSAIDs and opiates/opioids in ED patients, suggesting that NSAIDS are the first-choice analgesic for renal colic.

Musculoskeletal injuries

Meta-analysis suggests IVP offered similar levels of analgesia as compared with NSAIDs or opioids for MSK conditions at T30. Overall rescue analgesia was required less frequently for patients treated with NSAIDs, reaching statistical and clinical significance at T60, suggesting they be considered as first-choice medications. IVP is a suitable alternative where NSAIDs are contraindicated. A 2022 systematic review and meta-analysis[7] reported similarly, with opiates/opioids proving statistically but not clinically significantly better analgesia at 2 hours, while no statistical or clinical difference was reported for NSAIDs versus opiates/opioids. The authors also reported possible higher AE associated with opiates/opioids with high levels of uncertainty.[7]

Abdominal pain

Meta-analysis suggested IVP offered similar analgesia as compared with opiates/opioids or NSAIDs. A 2002 meta-analysis in women with primary dysmenorrhoea comparing trials of PO paracetamol with PO NSAIDs concluded naproxen 400 mg provided statistically significant greater pain relief than 1000 mg of paracetamol at T30.[44] A Cochrane review of 80 RCTs (5820 patients)[45] assessed the effectiveness of PO NSAIDs compared with placebo, other PO NSAIDs or PO paracetamol, strongly supporting PO NSAIDs as first-line treatment for primary dysmenorrhoea.

Back pain

Meta-analysis suggested no difference in analgesia offered by IVP as compared with opioids. A 2008 systematic review of seven trials aimed to assess the efficacy of paracetamol in the treatment of pain and disability in patients with non-specific low back pain. The review failed to find evidence to support the widely held view that oral paracetamol is effective in the treatment of non-specific low back pain. The authors called for further trials to provide reliable evidence for IVP and to establish the validity of the recommendations, with the small sample sizes of most published data contributing to imprecise estimates.[46] A 2018 clinical practice guideline supported the use of weak opioids for short periods in acute low back pain if NSAIDS were contraindicated or not effective.[47] Overall (limited) data suggest NSAIDs as first-choice analgesics, but IVP is a suitable alternative analgesic for back pain in the ED, with further trials required.

Limitations

The systematic review restricted the route of drug administration to the intravenous route for paracetamol, and findings cannot be extrapolated to oral dosing. There was considerable heterogeneity in the trials included in the analysis. There were variations in pain aetiology, participant characteristics, medication and doses between trials and the methods of reporting pain scores. Most of the trials were small and single centre. The high degree of heterogeneity precluded meta-analysis of the primary outcome, MD pain scores T30. Key trial data were missing from 25 trials, but no authors replied to requests for data. There was no standardised reporting of AE, with only 21 trials[9–11 13–23 26 27 29 30 36–38] reporting these. Finally, we were unable to perform a multivariate meta-analysis that incorporates correlation with the pain at different time point outcomes as only two with a low level of evidence measured pain scores at T90 and T120.

CONCLUSION

In this systematic review of adults presenting to the ED with diverse pain aetiologies IVP, intravenous/intramuscular NSAIDs and intravenous opiates/opioids offered clinically meaningful reductions in pain at T30 and similar analgesic effect for each at T60 and T90. However, NSAIDs offered sustained analgesia as compared with IVP by requiring fewer rescue analgesia (NNT=14), and the IVP group observed fewer AEs compared with opioids (NNH=12). Therefore, in an ED adult patient population requiring parental analgesia for acute pain management, NSAIDs (intravenous or intramuscular) may be regarded as first-choice analgesics for patients with no contraindications and IVP as a suitable alternative or second-choice strategy. This approach provides adequate analgesia with lesser need for rescue analgesia and fewer AEs.

Contributors IQ: searching of databases, trial selection, data extraction, trial quality assessment and manuscript writing; KA: searching of databases, trial selection, data extraction, trial quality assessment, data analysis, manuscript writing, and generation of graphs and tables; SHT: study concept and design and manuscript preparation; MEA-R: statistical analysis and preparation and review of the manuscript; SAP: manuscript preparation, analysis and trial quality assessment; TH: study concept and design, direct supervision of database searches, trial selection, data extraction, trial quality assessment and manuscript review. TH is the article guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data available upon request.

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