Paracetamol versus other analgesia in adult patients with minor musculoskeletal injuries: a systematic review

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ABSTRACT

Objectives Pain treatment in acute musculoskeletal injuries usually consists of paracetamol, non-steroidal antiinflammatory drugs (NSAIDs) or opioids. It would be beneficial to determine whether paracetamol is as effective as other analgesics. The objective of this study was to evaluate available evidence regarding efficacy of paracetamol in these patients.

Methods Embase, MEDLINE, Cochrane and relevant trial registers were searched from inception to 14 February 2018 by two independent reviewers to detect all randomised studies with adult patients with acute minor musculoskeletal injuries treated with paracetamol as compared with other analgesics. There were no language or date restrictions. Two independent reviewers evaluated risk of bias and quality of evidence. Primary outcome was decrease in pain scores during the first 24 hours, and secondary outcomes included pain decrease beyond 24 hours, need for additional analgesia and occurrence of adverse events.

Results Seven trials were included, evaluating 2100 patients who were treated with paracetamol or NSAIDs or the combination of both as comparisons, of which only four studies addressed the primary outcome. No studies were found comparing paracetamol with opioids. There were no differences in analgesic effectiveness within and beyond 24 hours, nor in need for additional analgesia and occurrence of adverse events. Overall, quality of evidence was low. Because of methodological inconsistencies, a meta-analysis was not possible.

Conclusions Based on available evidence, paracetamol is as effective as NSAIDs or the combination of both in treating pain in adult patients with minor musculoskeletal injuries in the acute setting. The quality of evidence is low.

BACKGROUND AND IMPORTANCE

Patients with minor musculoskeletal injuries such as strains, sprains and contusions are frequently treated in the ED as well as in general practice. In Western Europe, the exact incidence is unknown, and in the USA, approximately 66 million ED visits are injury related, of which 25% involve strains, sprains and contusions.[1] These minor injuries are treated with rest, compression and elevation, usually in combination with analgesia, such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) or opioids.[2] Although paracetamol is associated with hepatic failure, prudent use is safe in most instances. Regarding NSAIDs, even short-term treatment has been associated with serious adverse events, especially cardiovascular, renal and gastrointestinal complications.[3 4] Although several studies on the use of paracetamol compared with other analgesics have been published previously, these studies have not been evaluated systematically.

Goals of this study

The purpose of this systematic review was to critically appraise current best evidence regarding relative effectiveness of paracetamol in treating pain in adult patients with acute minor musculoskeletal injuries, compared with other analgesics. The primary outcome was pain decrease within the first 24 hours after initiation of treatment. Secondary outcomes were pain decrease beyond 24 hours, need for additional analgesics and occurrence of adverse events. We hypothesised that pain treatment with paracetamol was at least as effective as pain treatment with other analgesics, such as NSAIDs, opioids or combinations of different analgesic medication.

METHODS

Study design

We systematically reviewed all randomised controlled studies comparing analgesic effectiveness of paracetamol to one or more other analgesic drugs in adult patients with acute minor musculoskeletal injuries. Minor musculoskeletal injuries were defined as strains, sprains or contusions. Strains and sprains are injuries to muscles and ligaments in the absence of a fracture. Contusion is defined as haemorrhage in the soft tissues due to a traumatic force. The study adhered to the guidelines as reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[5]

Search strategy

Eligible studies were searched for, using MEDLINE (Ovid), Embase (Ovid) and the Cochrane database. In order to identify ongoing trials and to compare registered and published studies, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched as well. There were no restrictions in date of publication and language, and when deemed necessary, native speakers were contacted within our centre. A clinical librarian (FVE-J) formulated and performed the search on 29 September 2017, and the search was repeated 14 February 2018. The detailed search strategy can

be found as supplementary digital content (online supplementary figure S1).

Selection of studies

Two reviewers (MLR and JS) independently screened all titles that were identified by the search. When necessary, abstracts were evaluated for eligibility. Only randomised controlled studies were considered for inclusion, and the inclusion criteria were defined beforehand. These criteria were: adult patients; presenting with acute minor traumatic extremity injuries; pharmacological treatment with paracetamol versus one or more comparators; and standardised pain measurement as outcome. An acute injury was defined as occurring within 48 hours before enrolment in the study. Studies addressing patients with fractures; repetitive strain injuries; back pain; delayed onset muscle soreness; and primary inflammatory conditions, such as tendinitis or arthritis, were excluded.[6] Moreover, after having screened all titles and abstracts, articles that did not evaluate pain treatment in adult patients with minor musculoskeletal injuries, and those lacking a comparison between paracetamol and another analgesic drugs were excluded. Full-text articles were obtained of all potentially eligible articles. In case of disagreement between the two independent reviewers concerning eligibility of studies, a third reviewer (HG) was consulted, consensus was reached after discussing the specific article and the inter-rater agreement was calculated. When necessary, corresponding authors were contacted by email in order to clarify methods and to collect original data.

It was anticipated that some potentially eligible studies had included both patients with acute minor musculoskeletal injuries such as strains and sprains and patients with fractures. In this case, we evaluated the study results excluding the patients with fractures. If this was not possible due to lack of specific study results, the corresponding author was contacted and asked for original study data of patients without fractures. When data could not be retrieved and more than 10% of the total study population in the specific study had a fracture, the study was excluded from this review. The same strategy was used in case of a mixed study population of both patients with acute injuries as well as chronic musculoskeletal disorders. We excluded studies that looked at combination preparations of paracetamol with another drug and non-conventional interventions such as herbal medications. We included studies where paracetamol was compared with a combination of analgesics or more than one control intervention, as well as studies that used both oral and intravenous route of paracetamol, as previous studies have shown no significant differences in achieving satisfactory analgesia, both in the perioperative as well as in the acute setting.[7 8]

Data collection and study appraisal

After obtaining the final eligible studies, a standardised, previously piloted, data extraction form was used in which all data were recorded. Both reviewers documented the data independently. Extracted data were not blinded and included author, publication year, funding sources, number and country of recruiting centres, study setting, inclusion and exclusion criteria, study population including loss to follow-up, intervention and comparisons, including dosages and routes of administration, outcome measurements and time points at which these were measured. In order to evaluate the risk of bias of individual studies, the methods according to the Cochrane Handbook were used.[9] This evaluation included random sequence allocation, concealment of allocation, blinding of participants and outcome assessors, incomplete outcome data, selective reporting and sources of other bias. The absence of selective reporting bias could only be established in case there was access to a published study protocol or registration in a trial register.[10] The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used to rate the overall quality of the evidence related to the outcome measures.[10] This approach specifically addresses the following categories with which quality of evidence can be graded down: risk of bias, inconsistency, indirectness, imprecision and publication bias.[11] Moreover, quality of evidence can be graded up using three categories: large effect, dose response and all plausible confounding. Indirectness occurs when population, intervention or outcomes among included studies differ or in case there are no direct, head-to-head comparisons between compared interventions.[12]

Pain scores were analysed as continuous data and extracted from the studies as absolute mean differences compared with baseline measurements including SD or 95% CIs. In case absolute decreases were not reported, the corresponding author was asked for the original study data. If not available, the results as reported were extracted. When no SD of mean decreases in pain scores were available, the SDs were imputed for change from baseline as described in the Cochrane handbook.[9] The primary outcome was presented in a Forest plot with means and SD. The secondary outcomes, need for additional analgesics and occurrence of adverse events,were extracted as absolute numbers and percentages, where possible. The inter-rater agreement between the two independent reviewers was calculated for the final included articles, using kappa statistic. When indicated and deemed appropriate, a meta-analysis would be performed by evaluating Forest plots using Review Manager V.5.3. Statistical heterogeneity between study results would be assessed by calculating I^2.

RESULTS

Search results

The literature search yielded 1769 references of which 1541 references were available for review after removal of duplicate records (figure 1). After title and abstract screening, 38 studies were considered potentially eligible for inclusion and were reviewed in full, including their reference lists in order to identify additional eligible papers. This resulted in further exclusion of 31 articles, of which 10 articles were review articles.[13–22] Three original comparison studies were not eligible due to the use of paracetamol in combination with other analgesics in two studies and the direct comparison of different routes of administration of paracetamol in another study.[23–25] In one study, pain was not measured.[26] Four studies were excluded due to a large proportion of fractures and dislocations within the study population, and original study data could not be obtained after contacting the authors.[27–30] In three studies, both patients with acute and chronic musculoskeletal disorders were evaluated, and due to the publication date, it was not possible to contact the authors.[31–33] The remaining excluded articles did not contain any relevant data.[34–42] No additional studies were found after reviewing the reference lists and eventually, seven studies were included in the qualitative review.[43–49] The inter-rater agreement between the two independent reviewers was 0.73 (kappa statistic), indicating substantial agreement.

Included studies

Within the included studies, a total of 2100 patients received randomised analgesic treatment as allocated (table 1). Three

studies were multicentre studies, recruiting patients in EDs as well as in other clinics or urgent care centres in the USA, Turkey and The Netherlands.[43 45 48] The other studies were from Hong Kong and Greece.[44 46 47 49] Three studies specifically evaluated patients with lateral ankle sprains.[43 45 46] All other studies recruited patients with 'acute limb trauma' or 'soft tissue injuries'.[44 47–49] Although presence of a fracture was an exclusion criterion in all studies, it was deemed inevitable that patients with fractures would have been recruited (as pain treatment is typically initiated before a fracture is excluded) and eventually 86 of the included 2100 patients had a fracture. One study excluded patients with fractures after randomisation and allocation to treatment.[48] Of the 2100 recruited patients, 737 patients received paracetamol and were compared with 820 patients receiving an NSAID and 543 patients receiving paracetamol–NSAID combination treatment. All studies evaluated oral administration routes. Four studies used 1000 mg four times daily, two studies used 500 mg three times daily and one study used 1300 mg extended release three times daily. Duration of treatment varied between 3 and 10 days. Paracetamol was compared with treatment with an NSAID in all studies, and four studies included a treatment arm with a combination of paracetamol and an NSAID as well.[44 47–49] Three different NSAIDs were used in five different dosages as comparison. Only four studies assessed pain in the ED.[44 47–49] In all but one study a 100 mm visual analogue scale (VAS) was used as pain measurement instrument.[48] Due to significant differences in dosing schedules of paracetamol as well as of comparators, use of different NSAIDs and time points during which outcomes were measured, a meta-analysis could not be performed and study results are only synthesised qualitatively.

The risk of bias of individual studies, according to the Cochrane Handbook criteria, is shown in online supplementary table S1. One study[48] had low risk of bias, and two studies[47 49] had high risk of bias, due to non-consecutive patient recruitment.[47–49] All remaining studies scored an unclear risk of bias in at least one item.

Primary outcome

The primary outcome, pain scores during the first 24 hours after treatment initiation, was reported in four studies (table 2). As only the studies by Man *et al*, Hung *et al* and Ridderikhof *et al* reported absolute pain score reductions both in rest and with activity, including CIs, data from these studies could be directly extracted and used in creating Forest plots.[44 47 48] Mean decreases in pain scores were extracted from the reported figures and tables in the study of Woo *et al*.[49] SDs were imputed as described previously. The resulting Forest plots are shown in figure 2.

In the paracetamol treatment arms, Man *et al* and Hung *et al* showed absolute reductions of 9.4 mm and 12 mm in rest and 13.3 mm and 17 mm with movement, respectively.[44 47] They found similar results in all comparison groups as all CIs overlapped, revealing no statistically significant differences between groups. Ridderikhof *et al* reported absolute decreases of 1.23 NRS points and 1.72 NRS points in the paracetamol group in rest and with movement and similar results for the diclofenac group and the combination treatment group.[48] They also reported direct comparisons of paracetamol versus diclofenac and paracetamol versus combination treatment, and as the upper limits of both CIs did not cross a predefined non-inferiority margin of 0.75, they concluded treatment with paracetamol was not inferior to both other treatments, in rest as well as with movement. Table 2 shows that Woo *et al* did not report absolute decreases in pain scores, but direct comparisons were described between paracetamol versus diclofenac, paracetamol versus indomethacin and paracetamol versus paracetamol/diclofenac combination treatment.[49] At rest and with movement, all CIs of these direct comparisons crossed the value zero and fell completely within the predefined minimum clinically relevant difference of 13 mm, indicating there was no statistically significant difference between groups, let alone a clinically relevant difference. Taken together, all four studies showed that pain treatment with paracetamol was equally effective as pain treatment with an NSAID or pain treatment with the combination of both paracetamol and an NSAID.

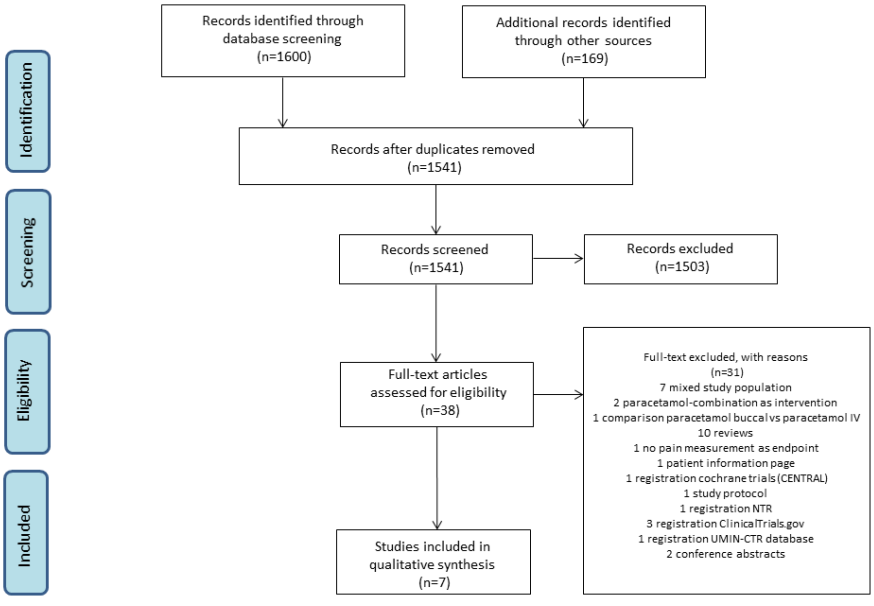

Figure 1 PRISMA flow diagram of systematic review. From a total of 1769 potentially eligible search results, 1541 were screened by the two independent reviewers after removal of duplicates. Full text was acquired of 38 hits, of which 31 were excluded from the review, and eventually seven studies were included in the review. NTR, NetherlandsTrial Register; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Overview of studies

Author, year	Setting	Population	Exclusion criteria	Intervention (patients)*	Comparison (patients)*	Pain measurement and time points
Dalton, 2006[43]	Multicentre in 42 centres in the USA (emergency and urgent care facilities, research facilities, family practices and outpatient clinics).	Adults (18 years and older); grade I or II lateral ankle sprain within 24 hours; initial VAS at least 40/100 mm; had not used NSAIDs, other analgesia or medications that could have confounded assessment of efficacy.†	Second occurrence ankle sprain within 6 months; bilateral ankle injury; ipsilateral knee injury; bed rest, hospitalisation, surgical intervention or casting required; severe or very severe pain at rest; osteoarthritis; rheumatological, gastrointestinal, renal, hepatic or oesophageal disease; hypersensitivity NSAIDs or paracetamol; and use of corticosteroids or hyaluronic acid.	Paracetamol extended release 1300 mg three times a day/9 days (128).‡ Standard care: rest, ice, compression bandages and exercises.	Ibuprofen 400 mg three times a day/9 days (127).‡ Standard care: rest, ice, compression bandages and exercises.	0–100 mm VAS at days 4 and 9.
Hung, 2018[44]	ED, Hong Kong.	Adults (18 years and older); isolated soft tissue injury without suspicion of fracture; non-consecutively during office hours.	Contraindications paracetamol or ibuprofen; chronic pain syndromes; analgesia prior to recruitment; other injuries; and physical, visual or cognitive impairment.	Paracetamol 1000 mg four times a day/3 days (260).§	Ibuprofen 400 mg three times a day/3 days (258).§ Paracetamol 1000 mg four times a day+ibuprofen 400 mg three times a day/3 days (263).§	0–100 mm VAS until 2 hours and during 3 days.
Kayali, 2007[45]	ED and outpatient clinic hospital in Turkey.	Adults (18 years and older); first or second degree lateral ankle sprain within 48 hours; initial VAS at least 45/100 mm with full weight bearing.	Fractures; pregnancy; gastrointestinal, renal or hepatic disorders; systemic inflammatory disease; bilateral ankle sprain; ipsilateral knee injury; third degree sprain; and previous ankle sprain within 6 months previously.	Paracetamol 500 mg three times a day/5 days (50).	Diclofenac 75 mg twice daily/5 days (50).	0–100 mm VAS at days 2 and 10 and at week 6.
Lyrtzis, 2011[46]	ED, Greece.	Adults (18–60 years); second degree lateral ankle sprain within 24 hours.	Other injuries; fractures; pre-existing ankle problem; renal or hepatic insufficiency; analgesia after injury; VAS >45/100 mm; gastric ulcer; lower limb thrombosis; diabetes; pregnancy; psychiatric history; osteoporosis; and chronic alcohol or drug abuse.	Paracetamol 500 mg three times a day/10 days (44).¶	Diclofenac 75 mg twice daily/10 days (42).¶	0–100 mm VAS at days 3 and 10.
Man, 2004[47]	ED, Hong Kong.	Adults (16 years and older); isolated soft tissue limb injury; between 09:00 and 17:00 from Monday to Friday.	Peptic ulceration or haemorrhage; recent anticoagulation; pregnancy; adverse reactions study medication; renal or cardiac failure; hepatic problems; rectal bleeding; chronic NSAID use; asthma; COPD; chronic pain syndromes; prior treatment analgesia for same injury; and physical, visual or cognitive impairment.	Paracetamol 1000 mg four times a day/3 days (16).**	Diclofenac 25 mg three times a day/3 days (12).** Indomethacine 25 mg three times a day/3 days (11). Paracetamol 1000 mg four times a day+diclofenac 25 mg three times a day/3 days (11).**	0–100 mm VAS until 2 hours and during 3 days.
Ridderikhof, 2018[48]	ED of two hospitals and two general practices.	Adults (18 years and older); acute limb trauma within 24 hours.	Previous analgesic treatment for injury; self-inflicted injury; wound; joint dislocation; fracture; more than one injury; daily analgesic use within 2 weeks before presentation; chronic pain; allergies study medication; pregnancy; gastrointestinal haemorrhage or perforation due to NSAID use; active peptic ulceration of bleeding; exacerbation asthma after NSAID use; cardiac, hepatic or renal failure; physical, visual or cognitive impairment; and non-Dutch speaking.	Paracetamol 1000 mg four times a day/3 days (173).††	Diclofenac 50 mg three times a day/3 days (180).†† Paracetamol 1000 mg four times a day+diclofenac 50 mg three times a day/3 days (175).††	0–10 NRS until 90 min and during 3 days.

Continued

Table 1 Continued

Author, year	Setting	Population	Exclusion criteria	Intervention (patients)*	Comparison (patients)*	Pain measurement and time points
Woo, 2005[49]	ED, Hong Kong.	Adults (16 years and older); isolated painful limb injury (18/300 fractures); between 09:00 and 17:00 from Monday to Friday.	Substance abuse; dementia; indigestion; peptic ulceration or haemorrhage; recent anticoagulation; pregnancy; adverse reaction to study drugs; renal or cardiac failure; hepatic problems; rectal bleeding; chronic NSAID use; chronic pain syndromes; previous analgesic treatment for same injury; and physical, visual or cognitive impairment.	Paracetamol 1000 mg four times a day/3 days (66).‡‡	Diclofenac 25 mg three times a day/3 days (69).‡‡ Indomethacine 25 mg three times a day/3 days (71).‡‡ Paracetamol 1000 mg four times a day+diclofenac 25 mg three times a day/3 days (94).‡‡	0–100 mm VAS until 2 hours and during 3 days.

*Medication is administered orally, unless stated otherwise.
†Medications that could have confounded assessment of efficacy: muscle relaxants, neuroleptics, tricyclic antidepressants, sedative hypnotics and anxiolytics.
‡A total of 260 patients were randomised: 132 in the paracetamol group and 128 in the ibuprofen group. Due to lack of postbaseline efficacy assessment (four paracetamol and one ibuprofen), 128 versus 127 patients were included in the intention-to-treat analysis. The per-protocol analysis included 104 patients in the paracetamol group and 100 patients in the ibuprofen group.
§262 Patients were randomised for paracetamol, of whom one patient did not receive allocated treatment due to human error. At the second visit on day 4, 219 patients were analysed in the paracetamol group (18 patients were reported as withdrawn or lost to follow-up, and the remaining 25 patients were not accounted for); 38 patients withdrew/were lost to follow-up in the ibuprofen group and 46 withdrew or were lost to follow-up in the combination group. Patients with fractures were included in the analyses: paracetamol group 21 patients (8%); ibuprofen group 23 (9%) and combination group 19 (7%) had fractures.
¶45 Patients were randomised and allocated to each treatment group. In the paracetamol group, one patient was lost to follow-up, and in the diclofenac group, three patients withdrew because of stomach aches. The study was powered to detect a difference in ankle oedema, not to detect change in pain decrease.
**Two patients in the paracetamol group, one patient in the diclofenac group and two patients in the combination group had a fracture but were included in the analyses.
††In the paracetamol group, nine patients were excluded after randomisation and allocation because of a fracture, in the diclofenac group, two patients were excluded because of a fracture and one because of Achilles tendon rupture, in the combination group, seven patients were excluded because of a fracture. Analysis of pain scores at day 3 included 142 patients in the paracetamol group, 155 in the diclofenac group and 153 in the combination group, leaving the study underpowered to detect non-inferiority at day 3.
‡‡All patients received treatment as randomised and allocated. Two patients were lost to follow-up in the paracetamol group; two in the diclofenac group; one in the indomethacin group; and two in the combination group. A total of 18 patients were included, despite having a fracture: paracetamol group 5 (8%); diclofenac group 3 (4%); indomethacin group 7 (10%) and combination group 3 (3%).
COPD, chronic obstructive pulmonary disease; NRS, Numerical Rating Scale; NSAIDs, non-steroidal anti-inflammatory drugs; VAS, visual analogue scale.

Secondary outcomes

All included studies reported the effect of analgesic treatment beyond 24 hours (online supplementary table S2).[43–49] Absolute reductions in pain scores compared with baseline were reported in four studies, showing no differences between the groups.[43 44 47 48] In a direct comparison, Kayali *et al*[45] found a statistically significant

Table 2 Study results of pain score reduction during the first 24 hours

Study	Measurement	Outcomes	Authors comments/conclusions
Hung *et al*[44]	Decrease in 100 mm VAS at 2 hours compared with baseline – mean (95% CI).	At rest: paracetamol −12 (−14 to −10) versus ibuprofen −12 (−15 to −10) versus combination −13 (−15 to −11). With activity: paracetamol −17 (−19 to −15) versus ibuprofen −17 (−20 to −14) versus combination −15 (−17 to −12).	All treatments were clinically effective without significant differences at rest (p=0.68) or activity (p=0.22).
Man *et al*[47]	Decrease in 100 mm VAS at 2 hours compared with baseline – mean (95% CI).	At rest: paracetamol −9.4 (−13.4 to −5.4) versus diclofenac −8.7 (−13.3 to −4.1) versus indomethacin −8.6 (−13.4 to −3.7) versus combination −9.5 (−14.2 to −4.7). Direct comparisons: paracetamol versus diclofenac −0.7 (−9.0 to 7.6) and paracetamol versus indomethacine −0.8 (−9.4 to 7.7) and paracetamol versus combination 0.1 (−8.4 to 8.6). With movement: paracetamol −13.3 (−19.5 to −7.1) versus diclofenac −7.4 (−14.6 to −0.3) versus indomethacin −9.4 (−16.9 to −1.9) versus combination −14.5 (−21.9 to −7.0). Direct comparisons: paracetamol versus diclofenac −5.9 (−18.8 to 7.0) and paracetamol versus indomethacine −3.9 (−17.3 to 9.5) and paracetamol versus combination 1.1 (−12.1 to 14.4).	No clinically or statistically significant difference between the groups at 2 hours, 95% CI exceeded minimum clinically relevant decrease of 13 mm in all groups.
Ridderikhof 2018[48]	Decrease in 11-point NRS pain scores at 90 min compared with baseline – mean (95% CI).	At rest: paracetamol −1.23 (−1.50 to −0.95) versus diclofenac −1.20 (−1.44 to −0.96) versus combination −1.18 (−1.41 to −0.94). Direct comparisons: paracetamol versus diclofenac −0.027 (−0.45 to 0.39) and paracetamol versus combination −0.052 (−0.46 to −0.36).* With movement: paracetamol −1.72 (−2.01 to −1.44) versus diclofenac −1.52 (−1.77 to −1.26) versus combination −1.33 (−1.55 to −1.12). Direct comparisons: paracetamol versus diclofenac −0.20 (−0.64 to 0.23) and paracetamol versus combination −0.39 (−0.80 to 0.018).*	As upper limits of CIs of direct comparisons were less than predefined non-inferiority margin of 0.75, paracetamol was considered to be non-inferior to both other treatments both at rest and with movement.
Woo *et al*[49]	Between-group difference in 100 mm VAS at 2 hours compared with baseline at rest and with movement – mean (95% CI)	At rest, only direct comparisons were reported: paracetamol versus diclofenac −1.0 (−4.2 to 2.2) paracetamol versus indomethacin −0.6 (−3.7 to 2.6) paracetamol versus combination 0.0 (−3.0 to 3.0). With movement, only direct comparisons were reported: paracetamol versus diclofenac 1.0 (−3.3 to 5.2) paracetamol versus indomethacin 1.6 (−2.6 to 5.8) paracetamol versus combination 3.3 (−0.6 to 7.3).	In all direct comparisons, paracetamol was equally effective as 95% CI fell totally within 13 mm (defined as minimum change in pain score to achieve clinical significance).

*Between-group differences in a pairwise comparison with paracetamol with a 97.5% CI, because of a Bonferroni adjustment.
NRS, Numerical Rating Scale; VAS, visual aalogue scale.

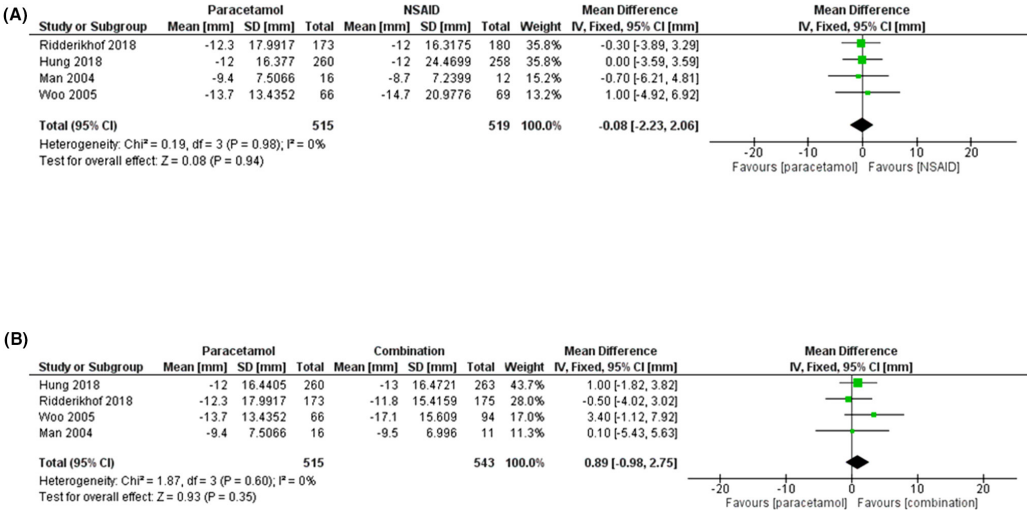

Figure 2 (A) Forest plot of pain score reduction in rest, paracetamol versus NSAIDs. Only comparisons in rest are shown for all relevant included studies. Regarding the study of Man *et al*[47], data of the diclofenac group were used in the NSAID treatment arm. Data from Hung *et al*[44] were used to calculate correlation coefficients, which were imputed in order to calculate an SD of mean decreases in pain scores in the data of Woo *et al*.[49] (B) Forest Plot of pain score reduction in rest, paracetamol versus combination treatment. Only comparisons in rest are shown for all relevant included studies. Data from Hung *et al*[44] were used to calculate correlation coefficients, which were imputed in order to calculate an SD of mean decreases in pain scores in the data of Woo *et al*.[49] NSAIDs, non-steroidal anti-inflammatory drugs.

larger decrease in pain scores in paracetamol compared with diclofenac at the 2nd and the 10th day. Although it was statistically significant, there was no clinically relevant difference, as the difference was 8.8 and 3.7 mm, respectively. Lyrtzis *et al*[46] reported pain scores at baseline, day 3 and day 10 without absolute decreases and corresponding measures of distribution. No differences between pain scores at these time points were detected. Only direct comparisons were reported in the study by Woo *et al*, showing no differences with CIs including the value zero indicating no effect of any studied intervention.[49]

Need for additional analgesics was reported in four studies of which only one specified methodology of measurement in the methods section (online supplementary table S3).[44 47–49] No differences in need for additional analgesics were found between the paracetamol treatment groups and the comparison treatment groups. In most studies, type and dosages of additional analgesics were not reported.

Six studies reported occurrence of adverse events (online supplementary table S4). Within the 2100 patients who were recruited, a total of 830 adverse events occurred divided among the different groups as follows: 310 in the paracetamol group; 271 in the NSAID group and 249 in the combination treatment group. There were no serious adverse events reported.

Recommendations and level of evidence

Table 3 shows all outcomes of this systematic review and its quality of evidence graded. Regarding the primary outcome of pain treatment during the first 24 hours, it can be concluded that paracetamol is as effective as pain treatment with an NSAID or a combination of both analgesics. Despite the fact that this was shown in four studies with a total of 1659 participants, the level of evidence was low. The main reasons for this were high risk of bias in two studies and indirectness of treatment among all studies because of significant methodological differences.

All seven studies, except for one study, found no differences in pain treatment after 24 hours; however, the quality of evidence was graded low. Need for additional analgesia was not different among paracetamol and comparison groups as well. The quality of evidence was low. Six studies in almost 2000 patients showed no differences in occurrence of adverse events; however, the quality of evidence was very low, due to risk of bias, indirectness and inconsistency.

Limitations

Using the Cochrane Handbook and GRADE system in evaluating the risk of bias of included studies, simplicity is emphasised. Neither system weigh the studies relative to each other, and therefore using the risks of bias does not provide a quantitative rating.[10] More specifically, as two studies were rated with a high risk of bias, quality of evidence was graded down in all outcomes. It is disputable whether the weight of these two studies should be that large, compared with the other included studies.

Although methodologically well designed, several studies had to be excluded from the review because of a mixed study population including less than 90% non-fracture, acute musculoskeletal injuries. Consequently, a significant number of patients could not be included in this review.

Only studies evaluating NSAIDs were included eventually, as eligible studies employing opioids included mixed populations. Therefore, no conclusions regarding relative effectivity of paracetamol and opioids can be drawn.

Due to significant clinical heterogeneity between the studies, a meta-analysis was not possible. The most critical differences among included studies were absence of a standardised dosing regimen of both intervention and comparison treatment groups as well as lack of standardised outcome measurements.

DISCUSSION

In this systematic review, we found that treatment with paracetamol was as effective as treatment with NSAIDs or the combination of both in treating pain during the first 24 hours in adult patients with acute minor musculoskeletal injuries. Moreover, pain treatment beyond 24 hours was identical among treatment strategies, as were need for additional analgesia and occurrence of adverse events. However, the level of evidence was low for the first three outcomes and very low for the latter, mainly due

Table 3 Summary of findings of paracetamol use in minor musculoskeletal injuries

Patient or population: adult patients with acute minor musculoskeletal injuries
Setting: acute care (ie, ED or general practice)
Intervention: paracetamol
Comparison: NSAIDs and/or paracetamol–NSAID combination and/or opioids

Outcomes	Effect	Number of patients (studies)	Quality of evidence*
Pain reduction first 24 hours	All trials reported that paracetamol was equal to NSAIDs or paracetamol–NSAID combination analgesia (as two studies included a treatment arm with combination of both drugs), measured at 90–120 min after drug administration.	1659 (4)	⊕⊕OO Low†
Pain reduction after 24 hours	Although one trial found better pain relief in ankle sprains at the 2nd and 10th day, all other trials found paracetamol to be equal to NSAIDs or paracetamol–NSAID combination treatment measured at days 3, 4, 9 and week 6.	2100 (7)	⊕⊕OO Low‡
Need for additional analgesia	A total of 337 patients who required additional analgesia were reported without differences between intervention and comparison groups. Only one trial described type of rescue analgesia, without dosages.	1730 (4)	⊕⊕OO Low§
Occurrence of adverse events	Six studies reported a total of 830 adverse events, of which none were serious adverse events requiring hospital admission. One study found more adverse events in the paracetamol group compared with NSAIDs or paracetamol–NSAID combination group.	1920 (6)	⊕OOO Very low¶

*Quality of evidence is graded using the Grading of Recommendations Assessment, Development and Evaluation system of rating quality of evidence.
†The quality of evidence was rated down due to high risk of bias among two studies and because of indirectness in treatment due to use of different NSAIDs and use of different dosages of both paracetamol and NSAIDs.
‡The quality of evidence was rated down due to high risk of bias among two studies and because of indirectness in both treatment (drug regimens and dosages of paracetamol and comparisons) and outcome measurements (timing of measurement and standardised method of measurements). Two studies only mentioned direct comparisons and absolute reductions in pain scores among groups could not be recovered.
§The quality of evidence was rated down because of high risk of bias among two studies and because of indirectness. Moreover, additional analgesia was not explicitly described in two studies. It was unclear whether additional analgesia was used during the study medication course or after this course.
¶The quality of evidence was graded down due to high risk of bias among two studies, inconsistency and indirectness in outcome standardisation. There were significant methodological differences in timing of measurement among all studies and lack of standardised measurement of (predefined) adverse events in two studies. Moreover, in the study of Ridderikhof *et al*,[48] all participants used a proton pump inhibitor, and therefore, the occurrence of adverse events could not be assessed properly. Woo *et al* reported patients with adverse events in the acute phase and only percentages of adverse events at follow-up. As absolute numbers were unavailable, these adverse events could not be added up to the total sum of adverse events.
NSAIDs, non-steroidal anti-inflammatory drugs.

to high risk of bias in two studies, as patients were recruited non-consecutively during office hours.[47 49] This could have introduced bias, as patients presenting outside regular office hours could have had different levels of pain severity or different injuries (eg, higher incidence of sports injuries in weekends). General practitioner access during week days versus weekends could have played a role as well.

Besides risk of bias, indirectness in treatment, comparison and outcome measurement was significant as well. According to the GRADE approach, the quality of evidence decreases in case substantial differences exist between the study population, the intervention or the outcome measured.[12] Although the intervention of interest was clearly defined in our eligibility criteria, the dosing regimens of paracetamol differed significantly among the various studies included. The same was applicable for the comparison treatment arms, as ibuprofen, diclofenac and indomethacin were used as comparison in five different dosing regimens. Moreover, combination treatment arms comprised of three different dosing regimens.

Indirectness in outcome measurements was detected, as there was lack of standardised outcome measurements. In the acute phase, within 24 hours, this was not regarded as a major issue, as all four studies evaluated pain in rest and with movement explicitly between 90 min and 120 min. However, regarding the outcome measurements of pain treatment beyond 24 hours, some studies evaluated pain scores while weight bearing and not at rest. More importantly, pain was measured at time points varying between 2 days to 6 weeks after recruitment.

Use of different pain scales—one study used 0–10 Numerical Rating Scale (NRS) and the other six studies used 0–100 mm VAS—was not regarded as an important shortcoming. Both instruments are valid, reliable and appropriate to use in the acute setting and have similar sensitivity.[50 51] Previous authors have concluded that both NRS and VAS seem to have a strong correlation and can be used interchangeably in acute pain measurement in adult patients. The cut-off for a minimum clinically significant difference in pain intensity is 1.3 points on the NRS and 10–14 mm on the VAS, depending on pain severity, without significant differences between both instruments.[52–55]

Most studies did not specify standardised measurements for additional analgesia and occurrence of adverse events in their methods section. Finally, in the study of Ridderikhof *et al*, the patients who received paracetamol reported more adverse events than the patients treated with diclofenac or the combination of both study drugs.[48] As mentioned by the authors, this might have been due to the protective use of a proton pump inhibitor, which were administered to recruited patients in all three study arms in order to maintain complete blinding of the study drugs.

This is the first systematic review comparing paracetamol as intervention to other analgesics in pain treatment in adult patients with acute minor musculoskeletal injuries. Although all included studies found no difference in analgesic effectiveness compared with NSAIDs or the combination of both drugs, the quality of evidence is low, mainly due to significant methodological differences among the available studies. In daily clinical practice, it seems reasonable to start analgesic treatment in minor musculoskeletal injuries with paracetamol.

Contributors MLR, HG, SVD, PL, JCG and MH designed the study. MH and JCG supervised the conduct of the study. FVE-J formulated the search strategy, performed the search and supplied the reviewers with the search results. MLR and JS evaluated the search results independently, and HG acted as a referee in case of disagreement. SVD formulated the statistical analyses plan. MLR drafted the manuscript, and all authors contributed substantially to its revisions. MLR takes responsibility for the paper as a whole.

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