Oral Paracetamol Versus Combination Oral Analgesics for Acute Musculoskeletal Injuries

Jiayi Gong, MClinPharm; Margaret Colligan, RN; Carl Kirkpatrick, PhD; Peter Jones, PhD*

*Corresponding Author. E-mail: peterj@adhb.govt.nz, Twitter: @nzpetejones.

Study objective: We compare paracetamol with a combination of paracetamol, ibuprofen, and codeine for pain relief in acute minor musculoskeletal injuries.

Methods: This was a prospective, double-blind, randomized, active-controlled, parallel-arm study at an urban tertiary hospital emergency department. Participants were aged 18 to 65 years and had acute (<48 hours) closed limb or trunk injuries with moderate pain (greater than 3/10). A single dose of 1 g of paracetamol, 400 mg of ibuprofen, and 60 mg of codeine was compared with a single dose of 1 g of paracetamol, placebo ibuprofen, and placebo codeine. The minimum detectable difference in pain was taken as 1.3.

Results: Baseline characteristics and pain were similar. There were clinically detectable reductions in pain at rest at 60 minutes for paracetamol: −1.6; 95% confidence interval (CI) −2.2 to −1.1); n=59 and the combination −2.0; 95% CI −2.5 to −1; n=59; difference −0.4; 95% CI −1.1 to 0.29; *P*=.26. At 120 minutes, the reduction in pain was −2.4; 95% CI −3.2 to −1.6 for paracetamol (n=30) and −2.9; 95% CI −3.7 to −2.2 for the combination (n=35); difference −0.5; 95% CI −1.6 to 0.5; *P*=.32. Rescue analgesia was required by 4 of 59 patients in the paracetamol group and 5 of 60 in the combination group (*P*>.99). More participants in the combination group had adverse events: 14 of 60 versus 5 of 59 in the paracetamol group, relative risk 2.8; 95% CI 1.1 to 7.2. No adverse events were serious.

Conclusion: Combining oral paracetamol, ibuprofen, and codeine as the initial treatment for pain associated with acute musculoskeletal injuries was not superior to paracetamol alone for pain reduction at 60 minutes or need for rescue analgesia, with more adverse events in the combination group. [Ann Emerg Med. 2019;74:521-529.]

Please see page 522 for the Editor's Capsule Summary of this article.

Readers: click on the link to go directly to a survey in which you can provide **feedback** to *Annals* on this particular article.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2019.05.030

INTRODUCTION

Background

Prescribing opioids in the acute setting has been identified as a risk for subsequent long-term opioid use.[1] Despite this, the use of opioids is common for the management of moderate to severe pain caused by acute musculoskeletal injuries. A recent audit in our department (unpublished data) found that more than a third of patients were prescribed oral opioids either alone or in combination with nonsteroidal anti-inflammatory drugs and paracetamol for moderate to severe pain related to such injuries. This practice is not supported by the available evidence, with a Cochrane review finding that using oral opioid compared with nonsteroidal anti-inflammatory drugs offered no benefit in terms of pain relief but may have increased the incidence of adverse events. This review also found that the combination of paracetamol and opioid did not provide better pain relief than nonsteroidal anti-inflammatory drugs alone.[2] However, the quality of evidence was very low and few studies contributed to this body of evidence.[2]

Several studies compared paracetamol with a combination of paracetamol and nonsteroidal anti-inflammatory drugs, finding no clinically important differences in analgesic efficacy and adverse events.[3-7] Another study compared the addition of opioids with paracetamol and nonsteroidal anti-inflammatory drugs in this setting, also finding no difference in analgesia.[8]

Importance

To our knowledge, no previous studies have compared the efficacy of paracetamol alone with a combination of paracetamol, nonsteroidal anti-inflammatory drugs, and an opioid for moderate and severe pain in the setting of acute musculoskeletal injury. If there were no difference between

Editor's Capsule Summary

What is already known on this topic

The coadministration of different analgesics may be synergistic.

What question this study addressed

Does the combination of acetaminophen 1,000 mg, ibuprofen 400 mg, and codeine 60 mg provide greater analgesia than acetaminophen 1,000 mg alone?

What this study adds to our knowledge

In this adequately powered, randomized, double-blind trial of 118 adults with acute musculoskeletal pain, pain scores were similar at 60 minutes in both groups. There were more adverse events in the combination group.

How this is relevant to clinical practice

At the standard doses studied, supplementing acetaminophen with ibuprofen and codeine does not enhance analgesia.

paracetamol alone compared with this combination of analgesics for moderate or severe pain, then there would be little reason to prescribe oral opioids in this setting.

Goals of This investigation

The primary aim of this study was to determine whether adding nonsteroidal anti-inflammatory drugs and codeine at routinely prescribed doses to paracetamol provided superior analgesic efficacy in the setting of moderate or severe pain from acute musculoskeletal injury. The primary outcome was difference in pain relief between the groups at 60 minutes for pain at rest. The secondary outcomes were difference in pain relief at 60 minutes for pain on activity, rest and activity pain at 120 minutes, need for rescue analgesia, and the rate of adverse events between the groups.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, double-blind, randomized, active-controlled, parallel-arm study, conducted between September 3 and November 25, 2018, in the adult emergency department (ED) at Auckland City Hospital. The hospital is an academic urban tertiary referral hospital, with an annual census of 72,000 patients aged 15 years and older.

Selection of Participants

We recruited adult patients presenting to the ED between 8 AM and midnight 7 days per week, with at least moderate pain (pain scores >3 of 10). Other inclusion criteria were aged 18 to 65 years, acute closed limb or trunk injury (<48 hours), and suitable for oral analgesia (as determined by the treating clinician).

Patients were excluded if they needed time-critical interventions (such as immediate reduction of dislocated joints or obviously displaced fractures), had digital injuries requiring immediate nerve block, had open injuries (lacerations), were pregnant or breastfeeding, had a contraindication or allergy to one of the study medications (including peptic ulcer disease, asthma, and known hepatic or renal impairment), were acutely intoxicated, had received analgesia within 4 hours before presentation, or were regular users of analgesics for chronic conditions.

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Approval was obtained from the Health and Disability Ethics Committee, the Auckland District Health Board research committee, and the University of Monash ethics review committee. An amendment to the protocol was submitted on August 21, 2018, because of a New Zealand Medicines and Medical Devices Safety Authority restriction on prescribing codeine for patients younger than 18 years,[9] and this was approved on September 6.

Interventions

Participants were randomized either to a combination of 1 g paracetamol, 400 mg ibuprofen, and 60 mg codeine (the combination group) or the active control group, consisting of 1 g paracetamol and placebo ibuprofen and codeine (the paracetamol group). Participants in both groups received 5 capsules identical in appearance. An independent clinical trial pharmacist determined the randomization schedule, using the randomize function in Microsoft Excel (version 2016; Microsoft, Redmond, WA). Patients were randomly assigned to the intervention and control groups through a computer-generated sequence in a 1:1 fashion in blocks of 10. The study medication was provided by the pharmacy in a plain cardboard box, numbered sequentially. Once a participant had consented to the study, he or she was provided with the next box in the sequence. The number on the box became the participant's unique study number. The researchers, research assistants, clinicians, and participants were blinded to both the randomization process and the preparation and allocation of study medications.

Methods of Measurement

Baseline demographics (age, sex, and ethnicity), chief complaint, and baseline pain at rest and activity were collected by a trained research assistant, masked to study assignment with a standard case record form (Appendix E1, available online at http://www.annemergmed.com). Written informed consent was obtained from each participant. Pain was assessed by the research assistants at baseline, using a verbal rating scale. This was a validated 11-item scale from zero to 10,[10] with zero being no pain and 10 being the worst pain imaginable.

Outcome Measures

Pain assessments were repeated by the research assistant at 60 minutes and 120 minutes (if the patient had not been discharged from the ED at that point). A difference of 1.3 of 10 on the verbal rating scale was set as the minimum clinically detectable value.[10,11] Patients were able to access rescue analgesia during the study in the form of intravenous morphine or other as prescribed at the discretion of the treating physician. At the end of the study period, participants were asked whether they experienced adverse events, what that adverse event was, the severity (mild, moderate, or severe), and what action was taken to mitigate the adverse event.

In a previous study, the response within each subject group was normally distributed, with SD of the within-group change of 20 mm on a 100-mm visual analog scale[12] (equivalent to 2 points on the verbal rating scale). If the true difference in the experimental and control means was 13 mm (equivalent to 1.3/10 points on the verbal rating scale), we needed to study 51 participants in each group to be able to reject the null hypothesis that the population means were equal with probability (power) of .9 and type I error probability of .05.[13] We rounded up the number of patients required per arm to 60 to account for potential dropouts.

Primary Data Analysis

Analysis and reporting were in line with the Consolidated Standards of Reporting Trials[14] guidelines based on a prespecified analysis plan approved by the institutional research committee. Statistical analysis was undertaken before unmasking of the study treatments. The distribution of continuous data was explored with histograms and normality plots. All data were analyzed as intention to treat. The difference in means between the groups at 60 minutes was tested with the independent-samples *t* test. The difference in means between the groups at 120 minutes was tested with a mixed ANOVA test for repeated measures. Counts and proportions with 95% confidence intervals (CIs) were used to describe categoric data. The χ^2 test for proportions or Fisher's exact test as appropriate was used to test for differences in need for rescue analgesia and adverse events between the groups. Statistical analysis was conducted with SPSS (version 24; Armonk, NY). Hybrid parallel line plots were generated with Stata (version 15.1; StataCorp, College Station, TX), using the method described by Schriger.[15]

RESULTS

During the study period, 832 patients were approached in the ED to participate. Seven hundred thirteen were excluded because they did not meet the selection criteria. This included 5 who were missed during screening because of unavailability of research staff and 82 who declined consent. The remaining 626 patients had contraindications to participating in the study (Figure 1).

Sixty participants were enrolled into the combination group and 59 into the paracetamol-only group. One participant in the combination group did not have pain scores documented after receiving nitrous oxide before 60 minutes (missing data). Two participants in the paracetamol group had protocol violations. One had an orbital contusion with minor closed head injury and the other had chronic pain and no acute injury according to the treating clinician. These participants were included in the intention-to-treat analysis. Almost half of the patients dropped out before the 120-minute pain score because of being discharged from the ED, 22 in the combination group and 28 in the paracetamol group. Four and two participants received rescue analgesia before 120 minutes, in the combination and paracetamol groups, respectively. Finally, one participant in the combination group was unable to state the degree of pain on activity at baseline, and one other in this group was unable to state the degree of activity pain at 60 minutes.

Baseline characteristics were similar in the 2 groups, although there were numerically more men in the combination group and more fractures in the paracetamol group. Both groups had similar baseline pain, which was moderate at rest and severe with activity (Table 1).

Table 2 shows the pain reduction and difference between treatments at 60 minutes. At this time, both treatments provided clinically detectable pain relief, with no difference between them. The 95% CIs around the point estimates of difference did not include the clinically detectable difference for either pain at rest or with activity at this point.

Table 3 shows the pain reduction and difference between treatments at 120 minutes. Both treatments provided pain relief at a clinically detectable level. There was no difference between the groups for rest pain, whereas there was a statistically significant difference for activity pain. For this

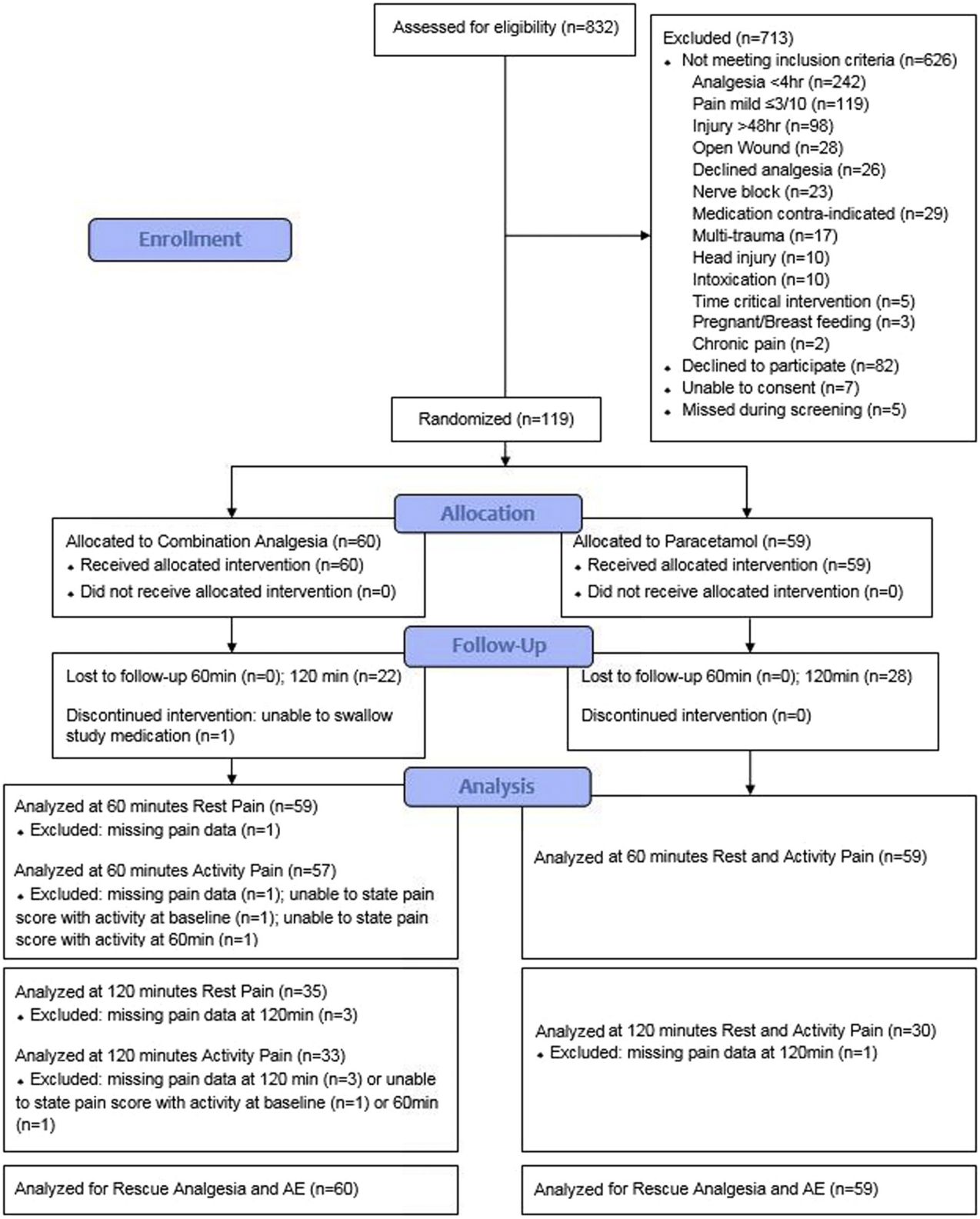


Figure 1. CONSORT diagram. *AE*, Adverse events.

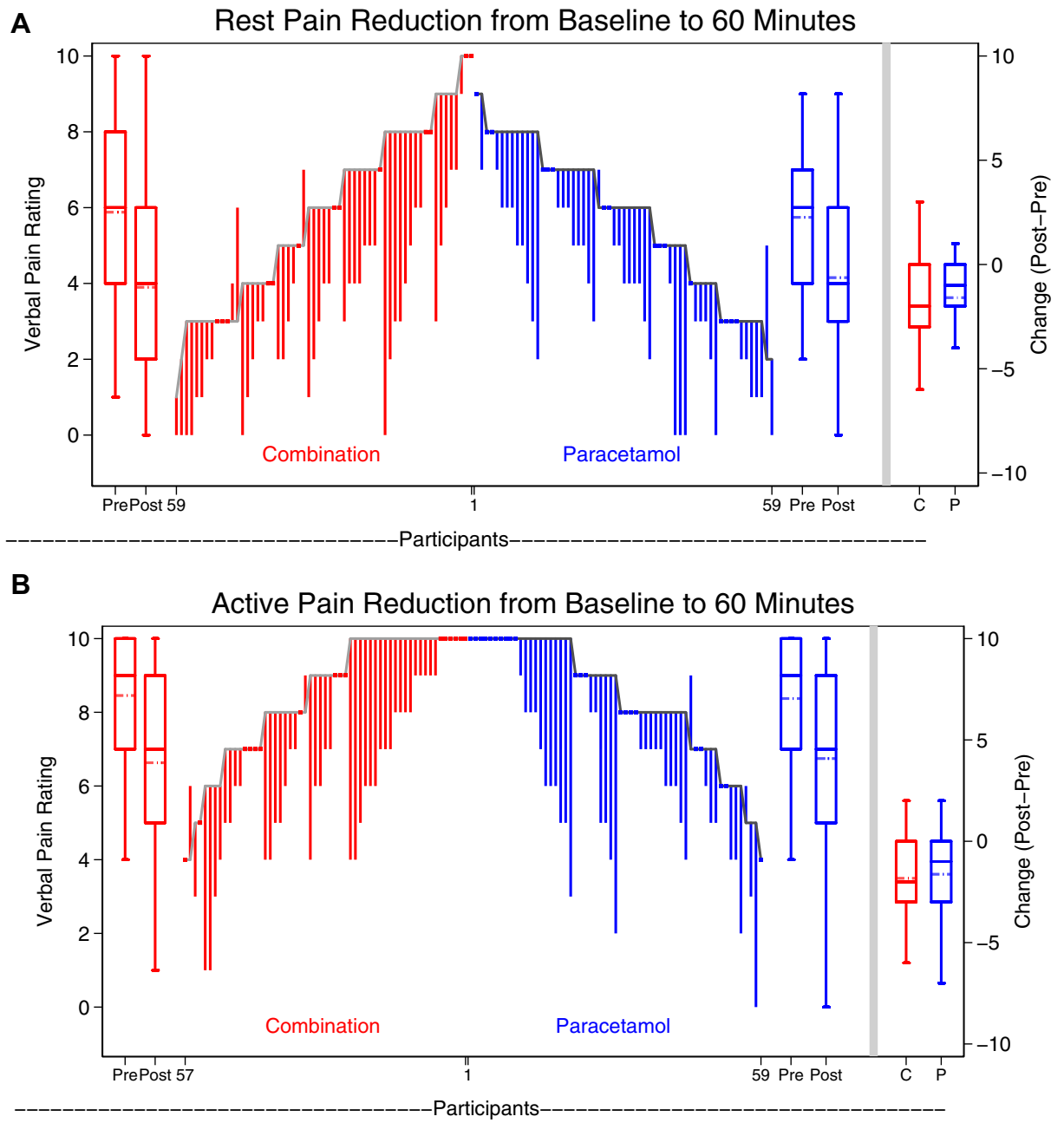


Figure 2. Pain reduction at 60 minutes. *A*, Reduction in rest pain. *B*, Reduction in pain on activity. *C*, Combination; *P*, paracetamol.

outcome, the point estimate of the difference was below the clinically detectable level, although the 95% CIs of the difference included a clinically detectable difference: –1.1 (95% CI –2.3 to 0.1).

Figure 2 shows the change in pain scores for each participant in each group, along with group averages summarized as box plots.

The drop lines show the baseline and 60-minute pain scores on the verbal rating scale (0 to 10). The box plots beside the drop lines summarize the pain at each point for the group as a whole, whereas the box plots to the right of the graph summarize the change in pain for each group.

Table 4 shows adverse events and the need for rescue analgesia. There was no difference between the groups in the number needing rescue analgesia (relative risk 1.2, 95% CI 0.35 to 4.4) for the combination group compared with paracetamol. The combination group had significantly more adverse events in total compared with the paracetamol group (RR 2.8; 95% CI 1.1 to 7.2), although all adverse events were mild. The number needed to harm

Table 1. Baseline characteristics.

Variable	Combination (n=60)	Paracetamol (n=59)
Median (IQR) age, y	28.5 (22–43.5)	30 (23–38)
Men, No. (%)	40 (66.7)	29 (49.2)
Ethnicity, No. (%)		
Asian	17 (28.3)	9 (15.8)
European	28 (46.7)	32 (54.2)
Maori	4 (6.7)	10 (16.9)
Pacific Islander	6 (10.0)	3 (5.1)
Other	5 (8.3)	5 (8.5)
Types of injury, No. (%)		
Sprain	40 (66.7)	31 (52.5)
Fracture	7 (11.7)	14 (23.7)
Contusion	13 (21.7)	12 (20.3)
Other (1 burn; 1 not acute injury)	0	2 (3.3)
Site of injury, No. (%)		
Lower limb	41 (68.3)	39 (66.1)
Upper limb	18 (30)	15 (26.3)
Trunk	1 (1.7)	4 (6.8)
Other (face)	0	1 (1.7)
Mean baseline pain score at rest out of 10 (95% CI)	5.8 (5.2–6.4)	5.8 (5.2–6.3)
Mean baseline pain score with activity out of 10 (95% CI)	8.4 (8.0–8.9)	8.4 (8.0–8.9)

for any adverse events in the combination group compared with the paracetamol group was 7 (95% CI 4 to 50).

LIMITATIONS

Our study has several limitations. Not recruiting participants overnight meant that the sample was not consecutive. In the audit that preceded this study, we found that approximately 90% of potentially eligible patients presented during study hours, and it would not have been cost-effective to employ research staff overnight because of high likelihood of low recruitment. We believe this did not bias the study in favor of a particular group and will not limit the generalization of the results to all eligible patients. Our results cannot be extrapolated to patients with open wounds or head or facial injuries because we excluded patients with these injuries. Because of our age restriction, the findings may not be applicable to people younger than 18 years or older than 65 years. Our results may also not apply to other centers, which may treat different patients or use different analgesic agents. The medications chosen and doses were based on our local prescribing patterns at recommended doses. Earlier studies in this setting used either subtherapeutic[3,4,7] or therapeutic doses of nonsteroidal anti-inflammatory drugs[5,6] in combination with paracetamol. Not including a placebo group means that we cannot be sure that the study medications were any better than placebo alone. We considered it unethical not to provide analgesia to patients in moderate or severe pain, and the efficacy of the study medications above placebo has been long established.[16]

Our primary endpoint of 60 minutes was chosen because it is appropriate to attempt to relieve moderate to severe pain quickly, and patients with the types of injuries we were interested in are often discharged within 1 to 2 hours of arrival in our ED. This assumption was confirmed in the study by a high proportion of discharges before 120 minutes, which was at the discretion of the treating clinicians. A condition of our institutional approval was that participation in the study not result in longer stays in the ED than were clinically indicated. The study was therefore underpowered for the 120-minute analysis because nearly half of patients had been discharged by this time and lost to follow-up. More participants in the paracetamol group were discharged before 120 minutes, which may bias toward finding higher pain scores in the paracetamol group, if pain was higher in patients who were not discharged, although we cannot assume this.

The study was also not powered to detect the observed small difference in the number needing rescue analgesia between the groups.

Our results suggest that it may take 120 minutes for clinically important analgesia to be achieved by the oral route. A previous study using patient-reported pain perception showed that the onset of analgesic effect through oral paracetamol tablets was approximately 45

Table 2. Pain reduction and differences between treatments in change of mean pain scores (out of 10) at 60 minutes.

Reduction in Pain	Combination (n=59)	Paracetamol (n=59)	Mean Difference	*P* Value*
Pain at rest (95% CI)	−2.0 (−2.5 to −1.5)	−1.6 (−2.0 to −1.1)	−0.4 (−1.1 to 0.3)	.26
Pain with activity (95% CI)	−1.8 (−2.3 to −1.3)†	−1.6 (−2.1 to −1.1)	−0.2 (−0.9 to 0.5)	.58

*Independent-samples *t* test.
†n=57 Because one participant was unable to state baseline activity pain and one was unable to state activity pain at 60 minutes.

Table 3. Pain reduction and differences between treatments in change of mean pain scores (out of 10) at 120 minutes.

Reduction in Pain	Combination (n=35)	Paracetamol (n=30)	Mean Difference	*P* Value*
Pain at rest (95% CI)	−2.9 (−3.7 to −2.2)	−2.4 (−3.2 to −1.6)	−0.5 (−1.6 to 0.5)	.36
Pain with activity (95% CI)	−3.0 (−3.8 to −2.2)†	−1.9 (−2.8 to −1.0)	−1.1 (−2.3 to 0.1)	.04

*Mixed between-within ANOVA for repeated measures.
†n=33 Because one participant was unable to state baseline activity pain and one was unable to state activity pain at 60 minutes.

minutes,[17] whereas another study showed paracetamol by the oral route to reach maximum cerebral and plasma serum levels after 2 hours.[18] This has implications for the future design of trials of oral analgesics in this setting.

Despite randomization, there were numerically (but not statistically) more male patients in the combination group, although it is not clear how this would bias the results. Conversely, there were more fractures in the paracetamol group, which also inadvertently included a patient with chronic pain reported as severe at all points. These factors may have biased toward finding better analgesic efficacy for combination therapy.

In our hospital, codeine is the most commonly prescribed opioid in this setting, which is why it was chosen for this study. We recognize that because of genetic polymorphism, approximately 10% of people will be nonresponders to codeine,[19] so it is not considered the opioid of choice in many other hospitals. However, previous studies directly comparing codeine with oxycodone or hydrocodone in a setting similar to ours found no difference in analgesic efficacy between them.[8,20]

Last, there may be other bias that we failed to account for, such as the use of nonpharmacologic treatments such as ice, compression, elevation, splints, plaster of paris, and slings. Randomization should have mitigated such bias, but because this was not recorded we cannot be certain that the 2 groups were similar in this respect.

Table 4. Rescue analgesia and adverse effects.

Outcome	Combination (n=60)	Paracetamol (n=59)	Relative Risk (95% CI)
Received rescue analgesia, No. (%)	5 (8.3)	4 (6.8)	1.2 (0.4–4.4)
Adverse effects, No. (%)			
Nausea or vomiting	2 (3.3)	0 (1.7)	Not calculable
Drowsiness, dizziness, or light-headedness	10 (16.7)	5 (8.5)	2.0 (0.7–5.4)
Other*	4 (6.7)	0	Not calculable
Total†	14 (23.3)	5 (8.5)	2.8 (1.1–7.2)

*Three patients reported feeling hot and one reported shortness of breath, but none had objective signs of hypersensitivity or required specific treatments for the adverse events.
†Two patients in the combination group had 2 adverse events, so the total is not the sum of individual adverse events.

DISCUSSION

We report the first study in the literature, to our knowledge, comparing a combination of paracetamol, ibuprofen, and codeine with paracetamol alone for the management of pain related to acute musculoskeletal injuries. There were no statistically significant or clinically important differences between the groups in pain reduction at rest or activity at 60 minutes. Although a slight difference in favor of the combination group approached the minimum clinically detectable threshold for activity pain at 120 minutes, the CIs around the point estimate of the difference were wide. The high number of dropouts before this time means that the study was underpowered to detect the observed difference at this point, so this finding is at high risk of bias. There were more adverse events in the combination group, with 1 extra adverse event for every 7 patients given the combination. The results of our study add to the body of evidence that multiple analgesics given together provide no additional benefit to paracetamol given alone in the setting of acute musculoskeletal injury, and that the addition of opioid may increase the risk of adverse events.[2,8]

To our knowledge, no previous studies have compared paracetamol to paracetamol with nonsteroidal anti-inflammatory drugs and opioid in this setting. However, previous studies have found that opioids may have more adverse events compared with nonsteroidal anti-inflammatory drugs[2] and that the combination of paracetamol and nonsteroidal anti-inflammatory drugs does not provide superior analgesia to paracetamol alone for pain from acute musculoskeletal injury.[3-7] Adding oxycodone or codeine to the combination of paracetamol and nonsteroidal anti-inflammatory drugs also did not improve analgesic efficacy,[8] findings that are consistent with those of our study.

In our study, the degree of pain reduction observed was less than may be considered ideal for both groups. Despite this, less than 10% of participants requested rescue analgesia, the reasons for which are unclear. Our results are

similar to those reported previously in this setting,[3-8] suggesting that oligoanalgesia remains an issue in the ED, despite the addition of oral opioid to analgesic regimens.

In conclusion, we found no statistically significant or clinically important difference between the groups for pain reduction or need for rescue analgesia at 60 minutes, whereas there were more adverse events in the combination group. The practice of combining oral paracetamol, ibuprofen, and codeine as the initial treatment for moderate to severe pain associated with acute musculoskeletal injuries is not supported by this study.

The authors acknowledge the Department of Adult Emergency Medicine and the Department of Pharmacy, Auckland City Hospital.

Supervising editor: Steven M. Green, MD. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Pharmacy (Gong) and the Department of Emergency Medicine (Colligan, Jones), Auckland City Hospital, Auckland, New Zealand; Centre for Medicine Use and Safety, Monash University, Melbourne, Victoria, Australia (Kirkpatrick); and the Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, New Zealand (Jones).

Author contributions: PJ conceived the study. PJ, JG, MC, and CK designed the trial and obtained research funding. JG, MC, and PJ supervised the conduct of the trial and data collection. JG and MC undertook recruitment of patients and together with PJ, managed the data, including quality control. PJ and CK provided statistical advice on study design and PJ analyzed the data. JG and PJ drafted the manuscript, and all authors contributed substantially to its revision. PJ takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. The study was funded by grants from the Auckland District Health Board A+ (study 7983), Auckland, New Zealand, and the Australasian College for Emergency Medicine Morson-Taylor Research Award 2018, Melbourne, Victoria, Australia

Publication dates: Received for publication March 8, 2019. Revision received May 15, 2019. Accepted for publication May 21, 2019.

Trial registration number: ACTRN 12618000020280

The researchers had complete independence from funders. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

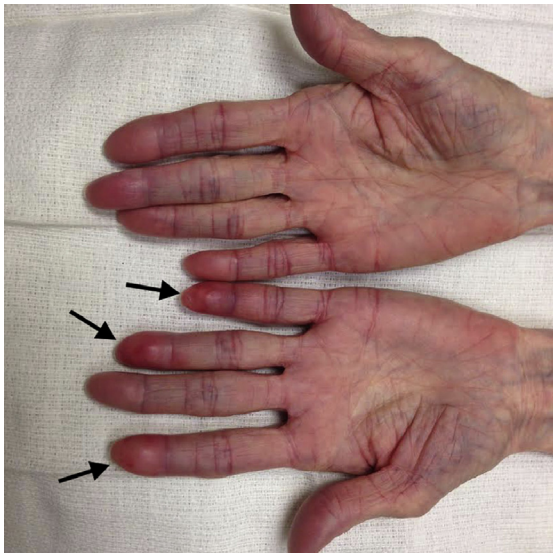
REFERENCES

1. Barnett ML, Olenski AR, Jena AB. Opioid-prescribing patterns of emergency physicians and risk of long-term use. *N Engl J Med*. 2017;376:663-673.
2. Jones P, Dalziel SR, Lamdin R, et al. Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. *Cochrane Database Syst Rev*. 2015;7:CD007789.
3. Man SY, Woo WWK, Lam PKW, et al. Feasibility study comparing oral paracetamol and oral non-steroidal anti-inflammatory drugs for treating pain after musculoskeletal injury: a randomised, double blind, controlled trial. *Hong Kong J Emerg Med*. 2004;11:78-84.
4. Woo WWK, Man SY, Lam PKW, et al. Randomized double-blind trial comparing oral paracetamol and oral nonsteroidal antiinflammatory drugs for treating pain after musculoskeletal injury. *Ann Emerg Med*. 2005;46:352-361.
5. Bondarsky EE, Domingo AT, Matuza NM, et al. Ibuprofen vs acetaminophen vs their combination in the relief of musculoskeletal pain in the ED: a randomized, controlled trial. *Am J Emerg Med*. 2013;31:1357-1360.
6. Ridderikhof ML, Lirk P, Goddijn H, et al. Acetaminophen or nonsteroidal anti-inflammatory drugs in acute musculoskeletal trauma: a multicenter, double-blind, randomized, clinical trial. *Ann Emerg Med*. 2018;71:357-368.
7. Hung KKC, Graham CA, Lo RSL, et al. Oral paracetamol and/or ibuprofen for treating pain after soft tissue injuries: single centre double-blind, randomised controlled clinical trial. *PLoS One*. 2018;13:e0192043.
8. Graudins A, Meek R, Parkinson J, et al. A randomised controlled trial of paracetamol and ibuprofen with or without codeine or oxycodone as initial analgesia for adults with moderate pain from limb injury. *Emerg Med Australas*. 2016;28:666-672.
9. Medsafe. Spotlight on codeine. *Prescriber Update*. 2018;39:18-19.
10. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Acad Emerg Med*. 2003;10:390-392.
11. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med*. 1996;27:485-489.
12. Clark E, Plint A, Correll R, et al. A randomized controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics*. 2007;119:460-467.
13. Dupont WD, Plummer WD. Power and sample size calculations: a review and computer program. *Control Clin Trials*. 1990;11:116-128.
14. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med*. 2010;152:726-732.

15. Schriger DL. Graphic portrayal of studies with paired data: a tutorial. *Ann Emerg Med*. 2018;71:239-246.
16. Moore RA, Derry S, Aldington D, et al. Single dose oral analgesics for acute postoperative pain in adults—an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2015;9:CD008659.
17. Moller PL, Norholt SE, Ganry HE, et al. Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double-blind, randomized, placebo-controlled study. *J Clin Pharmacol*. 2000;40:370-378.
18. Lanford RA, HM, Bjorksten AR, Williams DL, et al. Comparative plasma and cerebrospinal fluid pharmacokinetics of paracetamol after intravenous and oral administration. *Anesth Analg*. 2016;123:610-615.
19. Rogers JF, Nafziger AN, Bertino JS Jr. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450–metabolized drugs. *Am J Med*. 2002;113:746-750.
20. Chang AK, Bijur PE, Esses D, et al. Effect of a single dose of oral opioid and nonopioid analgesics on acute extremity pain in the emergency department: a randomized clinical trial. *JAMA*. 2017;318:1661-1667.

Images in Emergency Medicine

The *Annals* Web Site (*www.annemergmed.com*) contains a collection of hundreds of emergency medicine related-images, complete with brief discussion and diagnosis, in 18 categories. Go to the Images pull-down menu and test your diagnostic skill today. Below is a selection from the Dermatology Images.



"Elderly Woman With Painful Swollen Fingers" by Bickel et al, March 2017, Volume 69, #3, pp. 297, 314.