Randomized Double-Blind Trial Comparing Oral Paracetamol and Oral Nonsteroidal Antiinflammatory Drugs for Treating Pain After Musculoskeletal Injury

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Study objective: We investigate the efficacy and safety of oral paracetamol compared with oral nonsteroidal antiinflammatory drugs or combination therapy in relieving pain after blunt limb injury in an emergency department (ED).

Methods: This was a double-blind, randomized, controlled study in an ED of a university hospital in the New Territories of Hong Kong. Three hundred adult patients with painful isolated limb injuries were enrolled. Primary outcome measures were pain relief at rest and with limb movement, adverse events, and patient satisfaction.

Results: There was no statistical difference in the mean reduction in pain score between any of the combinations at any point, although combination therapy was the first to reach a clinically significant reduction in pain score (<13 mm), and diclofenac-paracetamol combinations consistently produced a greater reduction in mean pain score than either nonsteroidal antiinflammatory drugs or paracetamol alone. All combinations appeared to be safe, although more patients receiving diclofenac-paracetamol combination complained of abdominal pain. The median patient satisfaction scores were poor.

Conclusion: In the doses, frequencies, and routes of administration used for this study, any analgesic benefit of oral paracetamol–nonsteroidal antiinflammatory drug combinations over single nonsteroidal antiinflammatory drugs or paracetamol treatment is small and of doubtful clinical significance. Nonsteroidal antiinflammatory drugs, paracetamol, and diclofenac-paracetamol combinations appeared equally safe in the management of musculoskeletal pain. [Ann Emerg Med. 2005;46:352-361.]

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INTRODUCTION

Background

Nonsteroidal antiinflammatory drugs are widely used. In the western world, it is estimated that almost 10% of the population have used a nonsteroidal antiinflammatory drug at some time and that an average of 11 to 36 people per 1,000 population consume a nonsteroidal antiinflammatory drug each day.[1,2] These drugs have antiinflammatory, analgesic, antipyretic, and antithrombotic effects[3] yet have no known effect on disease processes itself. They are currently indicated for many acute and chronic musculoskeletal problems of mild to moderate pain intensity.

Importance

A recent Cochrane review of randomized clinical trials found little evidence of any difference in efficacy or dose effect between different nonsteroidal antiinflammatory drugs in the management of rheumatoid arthritis, osteoarthritis, or acute musculoskeletal syndrome.[4] No large, double-blind, randomized, controlled trial with more than 100 participants has compared paracetamol with nonsteroidal antiinflammatory drugs in the treatment of pain in acute musculoskeletal syndromes.[4] Our study aimed to recruit a sufficient number of subjects in order to demonstrate the efficacy of nonsteroidal antiinflammatory drugs versus paracetamol. Readers would then have a better guide in choosing analgesics in a more cost-effective manner.

Goals of This Investigation

The aim of this study is to compare the analgesic efficacy and safety of oral nonsteroidal antiinflammatory drugs with oral paracetamol or diclofenac-paracetamol combination therapy in the management of pain after acute musculoskeletal syndrome

Editor's Capsule Summary

What is already known on this topic

Few studies have compared acetaminophen, nonsteroidal antiinflammatory drugs, and combinations of the 2 for the treatment of pain in the emergency department (ED).

What question this study addressed

This double-blinded, randomized, controlled, 4-limb trial compares the efficacy of acetaminophen, diclofenac, indomethacin, and acetaminophen-diclofenac in treating pain resulting from nonpenetrating extremity injuries in the ED and during the first 3 days after injury.

What this study adds to our knowledge

Differences in pain relief were similar in all 4 groups at all points.

How this might change clinical practice

In the doses tested, diclofenac and indomethacin alone or diclofenac in combination with acetaminophen offers little or no benefit over acetaminophen alone for upper extremity musculoskeletal injury. Given the potential adverse effects of these nonsteroidal antiinflammatory drugs, physicians may wish to use acetaminophen as the primary analgesic for such patients.

in an emergency department (ED) setting. We hypothesized that paracetamol would be as efficacious as nonsteroidal antiinflammatory drugs or combination therapy in the management of acute pain and would be associated with fewer adverse events. Participants were randomized into 4 groups, and each received combinations of analgesics or placebo. Pain scores were measured in 2 stages: acutely in the ED (stage 1) and for 3 consecutive days after discharge (stage 2). The occurrence and severity of adverse effect were also recorded at each stage.

MATERIALS AND METHODS

Study Design

This was a randomized, double-blind, controlled trial comparing 3 drugs, namely, paracetamol, indomethacin, and diclofenac potassium. After checking that participants satisfied the predetermined inclusion and exclusion criteria, subjects were randomized into 4 groups. Each group received 2 study drugs (X and Y). Drug X could be either paracetamol or paracetamol-like placebo. Drug Y could be indomethacin, indomethacin-like placebo, or diclofenac potassium. Pain scores were recorded by a dedicated research nurse who was also blinded to the treatment groups. Pain-score measurement was done within the ED (stage 1) and also for 3 consecutive days after discharge (stage 2). The score was reviewed by the same research nurse on follow-up. Any adverse effects were also recorded.

Setting

This study was conducted in the ED of the Prince of Wales Hospital, Shatin, a 1,400-bed university teaching hospital in the New Territories of Hong Kong. The ED serves a population of approximately 1,500,000 and currently receives 190,000 new patients per annum, of whom approximately 20% are admitted to the hospital. Ethical approval was obtained from the local institutional research ethics committee to conduct a prospective, randomized, double-blind, controlled study comparing oral paracetamol with oral indomethacin, oral diclofenac, and paracetamol-diclofenac combination in the management of pain after limb injury. Informed written consent was obtained from each patient.

Selection of Participants

All patients aged 16 years or older and presenting to the ED between 9 AM and 5 PM Monday to Friday with an isolated painful limb injury after a traumatic mechanism were considered for the study. Because painful injuries should be treated with analgesia before specific diagnoses are made, recruitment inevitably included some subjects with a low clinical probability of a fracture but who subsequently were found to have fractures or dislocations. All patients were studied on an intention-to-treat basis, and in the analysis all 4 groups were compared to ensure that baseline values were similar. Patients were to be excluded if there was a history of substance abuse, dementia, indigestion, peptic ulceration or hemorrhage, recent anticoagulation, pregnancy, adverse reaction to paracetamol or nonsteroidal antiinflammatory drugs, renal or cardiac failure, hepatic problems, rectal bleeding, chronic nonsteroidal antiinflammatory drug consumption, asthma, chronic obstructive airways disease, chronic pain syndromes, or previous treatment with analgesia for the same injury. They were also excluded if they had a physical, visual, or cognitive impairment making use of the visual analog scale unreliable. Within the study period, all patients went through normal registration and triage processes as usual. Consecutive cases with musculoskeletal injuries were identified by the triage nurses, who informed our research nurse. The patient was then approached by the research nurse. The research nurse was responsible for recruiting subjects into the study, for obtaining consent, for randomizing subjects into treatment groups, and for measuring and recording pain scores and adverse events. We did not keep a record of the number of patients who refused to enter the study or the reason for refusing to enter into the study.

Interventions

Patients were randomly allocated to 1 of the 4 treatment groups using a computer-generated randomization list. Every patient took 2 oral tablets X (paracetamol 500 mg or placebo) and 1 oral tablet Y (nonsteroidal antiinflammatory drug or placebo). Group A received oral paracetamol 1 g and oral (indomethacin mimic) placebo. Group B received oral

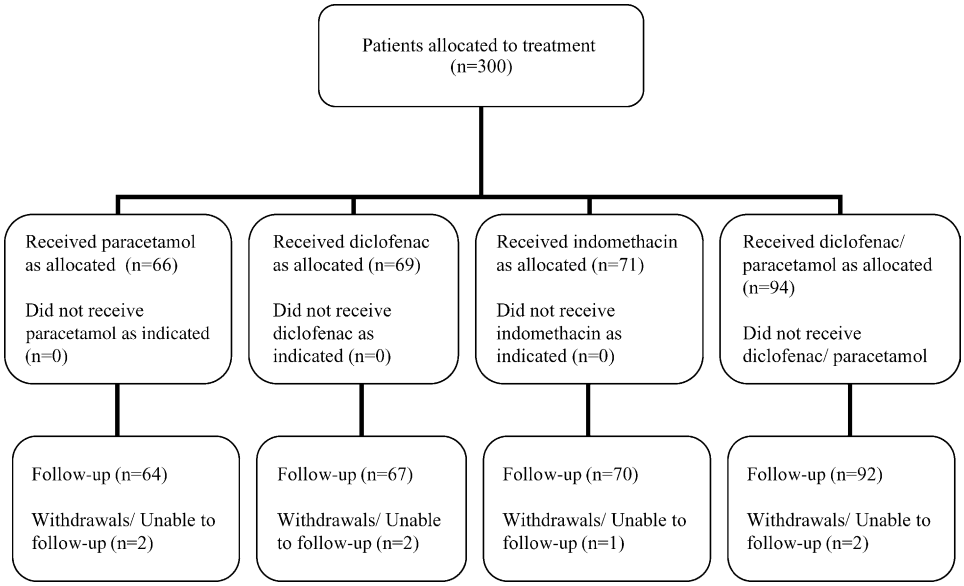

Figure 1. Flow chart describing progress of patients through randomized trial.

(paracetamol mimic) placebo and oral indomethacin 25 mg. Group C received oral (paracetamol mimic) placebo and oral diclofenac 25 mg. Group D received oral paracetamol 1 g and oral diclofenac 25 mg combination therapy. These doses were chosen first because they are in accordance with British National Formulary recommendations[3] and second because they are doses used in emergency physicians' practice in our setting. In our institution, physicians are reluctant to administer maximal recommended doses of nonsteroidal antiinflammatory drugs because of the risk of adverse events, particularly gastrointestinal hemorrhage.

A research nurse opened a precoded envelope that contained the medication and a randomization number. All of the clinicians and nurses on duty, the research nurse, and patients were blinded to the medication. Analgesia was administered in 2 stages.

Stage 1 was conducted in the ED. Baseline visual analog pain scores were recorded before the patient was randomized to 1 of the 4 treatment groups. The patient was then monitored for 2 hours for changes in visual analog pain scores and adverse events. Pain scores were taken at 30, 60, 90, and 120 minutes after the start of analgesia. The research nurse interviewed each patient at these times. Arrangements were then made for specialist referral and follow-up as per normal ED practice.

Stage 2 continued from stage 1 but was conducted outside the hospital. Patients continued with the same medication that they received in stage 1 but now received a 3-day course of 2 oral tablets X 4 times a day and 1 oral tablet Y 3 times a day. Our research nurse explained the visual analog pain score method to patients and gave them a follow-up form to take home with them. Each form had a separate visual analog pain score line for each time of day and for each of the 3 days. Patients were instructed to self-record their pain scores and adverse events 3 times a day for the 3 days. Follow-up was arranged in the ED 5 to 8 days after initial presentation. If the patient was not able to attend for follow-up, then a telephone follow-up call was arranged. Pain scores in the clinic at the time of follow-up were not assessed. The research nurse reviewed only the home record.

Methods of Measurement

A 10-cm, numbered, horizontal, visual analog pain score was used for baseline measurements (t_0) and at subsequent intervals.[5] In stage 1, visual analog pain scores and adverse effects were recorded every 30 minutes for 2 hours, whereas in stage 2, similar data were recorded 3 times a day. Patients were aware of their previous scores at all stages of recording. The physician on duty was free to give extra or alternative doses of analgesia if clinically required, and this was documented.

The primary clinical outcome was the mean reduction in visual analog pain scores at rest and with activity during the study period. "Activity" for the purpose of this study involved either the research nurse gently moving the injured limb in a standardized method to assess pain or a clinical or investigative procedure that is part of standard practice in these patients. For stage 2, the outpatient phase, activities refer to usual daily activities, eg, walking, bathing, and toileting. Secondary outcomes were number and type of adverse events. The humanistic outcome measures were patient satisfaction with pain relief.

The endpoint was defined as time at follow-up clinic or at last telephone call. However, to exclude any late effects, discharged patients were encouraged to return to the department if they had any adverse events, and computerized records were scanned for returns for up to 4 weeks after the initial attendance. Four weeks was an arbitrary period, after which any related effects were extremely unlikely. For patients admitted to the hospital, the endpoint was set at hospital discharge.

Table 1. Participants' characteristics (n=300). Values are numbers (percentages*) of participants unless stated otherwise.

Variable	Paracetamol and placebo group (n=66)	Diclofenac and placebo group (n=69)	Indomethacin and placebo group (n=71)	Diclofenac and paracetamol group (n=94)
Mean (SD) age (years)†	35.6 (12.2)	38.2 (13.1)	34.2 (11.0)	38.3 (12.7)
No (%) of men‡	44 (67)	33 (48)	45 (63)	55 (59)
Median (interquartile range) time (minutes):				
Between injury and arrival at hospital§	289 (85 to 1136)	714 (98 to 1749)	793 (120 to 1364)	907 (95 to 1391)
Between arrival at hospital and analgesia§	40 (25 to 67)	36 (21 to 55)	41 (28 to 55)	36 (21 to 55)
Between injury and analgesia§	335 (119 to 1213)	742 (149 to 1783)	830 (150 to 1385)	938 (143 to 1419)
Cause of injury:				
Falls‡	30 (45)	29 (42)	27 (38)	37 (39)
Lifting	13 (20)	12 (17)	14 (20)	26 (28)
Falling Objects	5 (8)	16 (23)	16 (23)	20 (21)
Sport	9 (14)	9 (13)	6 (9)	7 (8)
Motor Vehicle Crash	6 (9)	1 (1)	4 (6)	3 (3)
Other‖	3 (5)	2 (3)	4 (6)	1 (1)
X-Ray requested‡	51 (77)	46 (67)	44 (62)	66 (70)
Type of Injury:¶				
Sprain‡	43 (65)	39 (57)	37 (52)	62 (66)
Contusion‡	13 (20)	23 (33)	27 (34)	21 (22)
Wounds‡	9 (14)	11 (16)	13 (18)	12 (13)
Crush‡	7 (11)	3 (4)	5 (7)	7 (8)
Fractures‡	5 (8)	3 (4)	7 (10)	3 (3)
Site of Injury:‡				
Upper limb	21 (32)	23 (33)	31 (44)	26 (28)
Lower Limb	26 (39)	24 (35)	27 (38)	33 (35)
Back	15 (23)	21 (30)	11 (16)	32 (34)
Neck	4 (6)	1 (2)	2 (3)	3 (3)
Analgesic taken >3 hr before arrival at hospital‡	4 (6)	3 (4)	4 (6)	6 (6)
Initial mean (SD) pain score:				
At rest†	19.8 (16.9)	23.8 (18.6)	22.3 (15.3)	25.9 (19.9)
With activity†	63.2 (13.5)	65.9 (14.8)	64.2 (11.6)	68.8 (14.6)
Prophylactic antispasmodic prescribed‡	6 (11)	5 (6)	5 (5)	14 (13)
Prophylactic antibiotics prescribed‡	1 (2)	1 (1)	1 (1)	5 (5)
Referred for orthopaedic assessment‡	5 (8)	6 (9)	9 (13)	10 (11)
Admitted to hosptial‡	0 (0)	1 (1)	0 (0)	3 (3)
Referred for orthopaedic follow up‡	4 (6)	9 (13)	10 (14)	13 (14)

*Percentages may not sum to 100 because of rounding.
†One-way ANOVA.
‡χ^2 test or Fisher's exact test.
§Kruskal-Wallis test. One-way ANOVA.
‖includes domestic accidents and assaults.
¶Numbers may exceed the total because some patients have more than one type of injury.

Previous studies have shown that a difference in visual analog pain scores of less than 13 mm is unlikely to be clinically relevant.[6] Therefore, unless there were mean differences of greater than 13 mm, we assumed that the various groups would be equivalent. A pilot study of 50 patients showed a within-subject SD of 7.32 mm. Using power analysis and sample size 2000,[7] a sample size of at least 58 patients per group was required to detect any group differences at a power of 80%, with type I error at 5%. Using a simple randomization sequence, and to allow that some patients might leave the study, we aimed to recruit 300 subjects to the study.

Primary Data Analysis

Data were analyzed on an intention-to-treat basis, and all statistical analyses involved 2-tailed tests. Any 2 treatments were said to be equally effective in pain reduction if the 95% confidence interval (CI) for the mean difference fell totally within $\pm$13 mm. The value of 13 mm was chosen because studies suggest that this is the minimum change in pain score necessary to achieve clinical significance.[6,8] Pain reduction between the 4 groups was assessed by comparing the mean change in pain score in the first 2 hours or the first 3 days from the baseline. Then analysis of covariance models with the baseline values as the covariate were fitted.

Baseline characteristics were compared using χ^2 test or Fisher exact test for categorical data. One-way analysis of variance was used for comparing continuous data that conformed to the normal distribution, whereas the Kruskal-Wallis test was used for time data that did not conform to a normal distribution. The occurrences of adverse events were compared by estimating

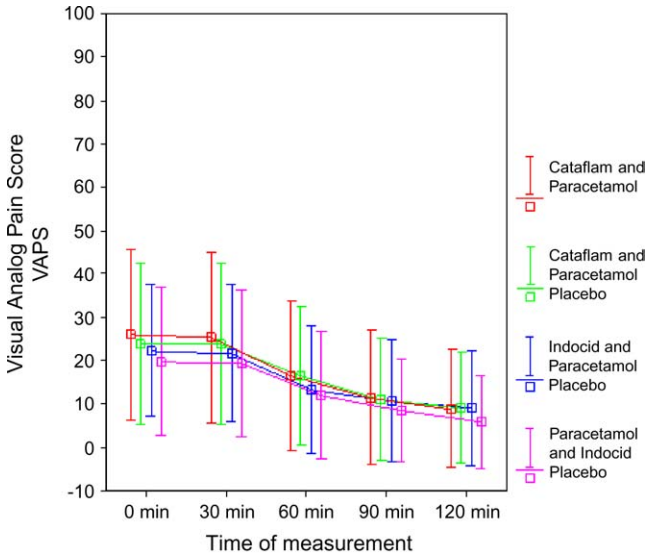

Figure 2. Visual analog pain score at rest during the emergency department (ED) phase. Pain was assessed at pain score at rest at baseline, 30 minutes, 60 minutes, 90 minutes, and 120 minutes. Data are presented as means (error bars are 95% confidence intervals [CI]). The arrowed line shows the 13-mm range, which is the minimum CI required for a clinical difference. There were no statistically or clinically significant differences between any of the groups at any point.

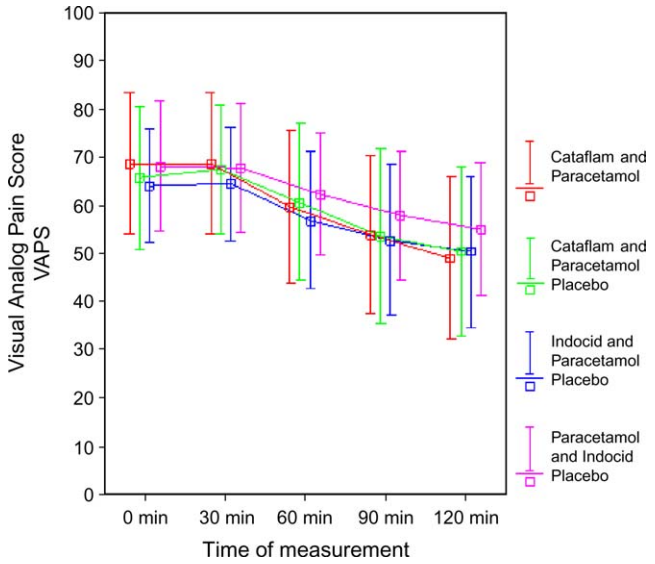

Figure 3. Visual analog pain score with activity during the ED phase. Pain was assessed at pain score with activity at baseline, 30 minutes, 60 minutes, 90 minutes, and 120 minutes. Data are presented as means (error bars are 95% CI). The arrowed line shows the 13-mm range, which is the minimum required for a clinical difference. There were no statistically or clinically significant differences between any of the groups at any point.

the 95% CI for the percentage difference. Data were analyzed using Statview for Windows, version 5.0 Statistical Analysis Software (Abacus Concepts, SAS Institute, Inc., Cary, NC).

Table 2. Comparison between groups of mean difference (95% CI) in pain score from baseline in the first 2 hours after receipt of analgesia.*

	Pairwise Comparisons		
Activity Level	**Diclofenac and Placebo Group**	**Indomethacin and Placebo Group**	**Diclofenac and Paracetamol Group**
At rest			
Paracetamol group	−1.0 (−4.2 to 2.2)	−0.6 (−3.7 to 2.6)	0.0 (−3.0 to 3.0)
Diclofenac group	–	0.4 (−2.7 to 3.5)	1.0 (−1.9 to 3.9)
Indomethacin group	–	–	0.5 (−2.3 to 3.4)
With activity			
Paracetamol group	1.0 (−3.3 to 5.2)	1.6 (−2.6 to 5.8)	3.3 (−0.6 to 7.3)
Diclofenac group	–	0.7 (−3.5 to 4.8)	2.4 (−1.5 to 6.3)
Indomethacin group	–	–	1.7 (−2.2 to 5.6)

*Pain score measured at time 0 was taken as the baseline; –indicates column group has a lesser mean difference than the row group.

RESULTS

Between January 7, 2002, and June 24, 2003, 300 patients attended the ED between 9 AM and 5 PM, Monday to Friday, with acute painful musculoskeletal injuries were allocated to receive blinded analgesia (Figure 1). Baseline characteristics of the participants in the 4 groups were similar (Table 1). Because of the triage and consenting processes involved in the study, 35 to 40 minutes passed between arrival at the department and initiation of analgesia. Initial mean pain scores at rest were mild (<30 mm), whereas mean pain scores with activity were moderate (<70 mm).

For stage 1 of the study, the mean change in visual analog pain scores at rest (Figure 2) and with activity (Figure 3) was less than 13 mm in all groups for the first hour. The

Table 3. Numbers (percentages) of participants with adverse events in the ED.

Adverse Events	Paracetamol and Placebo Group (n=66)	Diclofenac and Placebo Group (n=69)	Indomethacin and Placebo Group (n=71)	Diclofenac and Paracetamol Group (n=94)
Total	4 (6)	3 (4)	3 (4)	6 (6)
Dizziness	1 (2)	2 (3)	1 (1)	1 (1)
Indigestion	1 (2)	2 (3)	2 (3)	3 (3)
Other*	2 (3)	0	0	3 (3)

*See text. Pain score measured at time 0 in the ED was taken as the baseline.

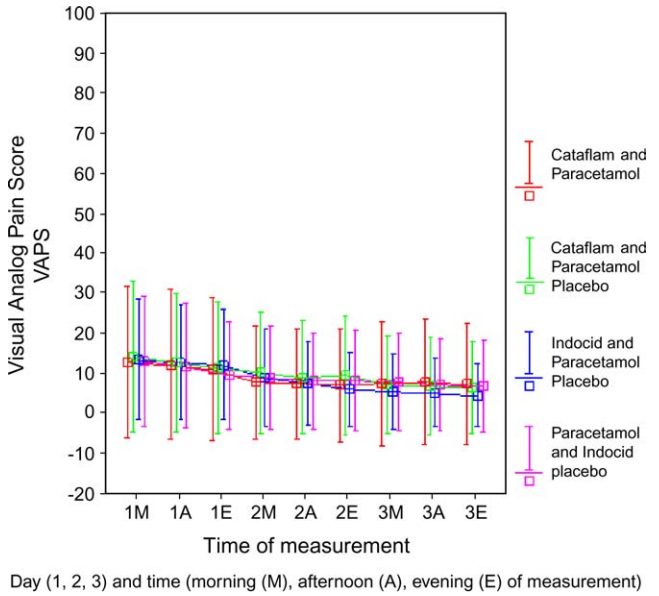

Figure 4. Visual analog pain score at rest during the follow-up phase. Pain was assessed at rest during the morning (M), afternoon (A), and during the evening (E) for days 1 to 3. Data are presented as means (error bars are 95% CI). The arrowed line shows the 13-mm range, which is the minimum required for a clinical difference. There were no statistically or clinically significant differences between any of the groups at any point.

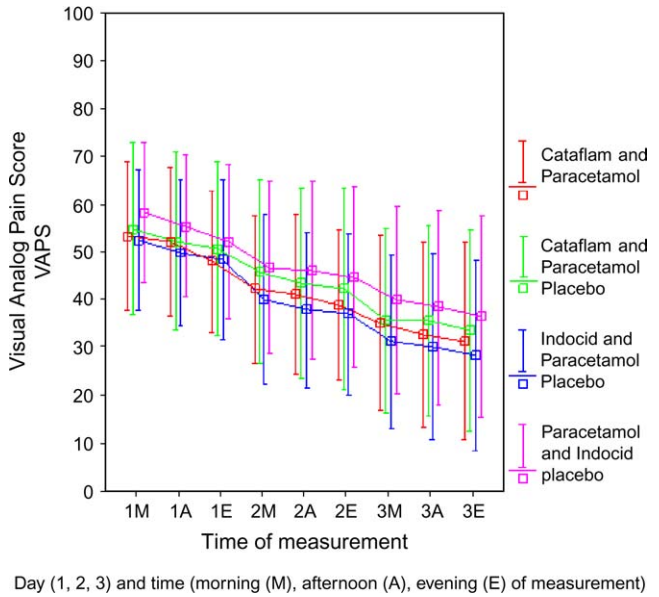

Figure 5. Visual analog pain score with activity during the follow-up phase. Pain was assessed with activity during the morning (M), afternoon (A), and during the evening (E). Data are presented as means (error bars are 95% CI). The arrowed line shows the 13-mm range, which is the minimum required for a clinical difference. There were no statistically or clinically significant differences between any of the groups at any time point.

diclofenac-paracetamol group was first to achieve a difference of greater than 13 mm at 90 minutes after ingestion and also the group to achieve the greatest reduction in pain score at 2 hours.

Table 4. Comparison between groups of mean difference (95% CI) in pain score from baseline in the first 3 days after attending the ED.*

	Pairwise Comparisons†		
Activity Level	**Diclofenac and Placebo Group**	**Indomethacin and Placebo Group**	**Diclofenac and Paracetamol Group**
At rest			
Paracetamol group	0.8 (−4.3 to 5.9)	1.5 (−3.5 to 6.6)	2.0 (−2.8 to 6.7)
Diclofenac group	–	0.8 (−4.2 to 5.7)	1.2 (−3.5 to 5.9)
Indomethacin group	–	–	0.4 (−4.2 to 5.0)
With activity			
Paracetamol group	1.6 (−5.6 to 8.8)	5.7 (−1.5 to 12.8)	4.9 (−1.8 to 11.6)
Diclofenac group	–	4.1 (−3.0 to 11.1)	3.3 (−3.4 to 10.0)
Indomethacin group	–	–	−0.7 (−7.3 to 5.9)

*Pain score measured on the morning of day 1 was used as the baseline measurement for the first 3 days; – indicates column group has a lesser mean difference than the row group.
†Analysis of covariance model.

At 90 minutes, the 95% CI for the difference in pain score in all groups exceeded 13 mm. However, there was no statistical difference between the groups at any time (Table 2).

Adverse effects occurred in less than 7% of cases and were not severe (Table 3). There was only 1 case of nausea and vomiting (diclofenac-paracetamol), 1 case of drowsiness (paracetamol), 2 cases of allergy (paracetamol and diclofenac-paracetamol), and no cases of gastrointestinal hemorrhage or renal damage.

For stage 2 of the study, 98% of participants were followed up within a median of 6 days. Figures 4 and 5 show changes in visual analog pain scores at rest and with activity after 24 hours. The combination therapy group was the only one to achieve a mean reduction in pain score greater than 13 mm with activity on the first morning. This group achieved the greatest reduction in pain score at every time at rest and with activity. However, there was no obvious clinical or statistical difference in mean pain reduction between the 4 groups at any point (Table 4).

The highest proportion of participants with adverse events occurred in the diclofenac-paracetamol group, but none of these were severe (Table 5). Diclofenac-paracetamol combination produced a higher proportion of participants with abdominal pain, and this was significantly higher than that of the indomethacin group.

The difference between the groups in the number of tablets ingested and in the proportion of participants who completed the course of analgesia, were treated by a general practitioner, took

Table 5. Comparison of the percentage difference (95% CI) of adverse events in the 3 days between different drugs.

Adverse Events	With Adverse Events, %	Pairwise Comparisons		
		Diclofenac and Placebo Group	Indomethacin and Placebo Group	Diclofenac and Paracetamol Group
Total				
Paracetamol group	15.6 (7.8–26.0)	3.7 (−8.4 to 15.9)	5.6 (−5.9 to 17.6)	−2.9 (−14.3 to 9.8)
Diclofenac group	11.9 (5.3–21.9)	–	1.9 (−8.9 to 13.1)	−6.5 (−17.3 to 5.4)
Indomethacin group	10.0 (4.8–18.9)	–	–	−8.5 (−18.9 to 2.9)
Diclofenac-paracetamol group	18.5 (11.7–27.3)	–	–	–
Headache				
Paracetamol group	1.6 (0.1–7.8)	−2.9 (−10.9 to 4.5)	−1.3 (−8.4 to 5.8)	0.5 (−4.5 to 7.3)
Diclofenac group	4.5 (1.2–11.9)	–	1.6 (−6.0 to 9.8)	3.4 (−2.3 to 11.3)
Indomethacin group	2.9 (0.5–9.2)	–	–	1.8 (−3.5 to 8.8)
Diclofenac-paracetamol group	1.1 (0.1–5.3)	–	–	–
Dizziness				
Paracetamol group	7.8 (3.1–16.4)	4.8 (−3.7 to 14.3)	6.4 (−1.3 to 15.7)	3.5 (−4.2 to 13.0)
Diclofenac group	3.0 (0.5–9.6)	–	1.6 (−5.0 to 8.9)	−1.4 (−8.0 to 6.4)
Indomethacin group	1.4 (0.1–7.1)	–	–	−2.9 (−9.3 to 3.8)
Diclofenac-paracetamol group	4.3 (1.5–10.3)	–	–	–
Nausea				
Paracetamol group	1.6 (0.1–7.8)	1.6 (−4.0 to 8.3)	−1.3 (−8.4 to 5.8)	−3.9 (−10.7 to 3.6)
Diclofenac group	0.0 (0.0–5.3)	–	−2.9 (−9.8 to 2.9)	−5.4 (−12.1 to 0.8)
Indomethacin group	2.9 (0.5–9.2)	–	–	−2.6 (−9.6 to 5.1)
Diclofenac-paracetamol group	5.4 (2.2–12.0)	–	–	–
Allergy				
Paracetamol group	0.0 (0.0–5.6)	0.0 (−5.4 to 5.7)	0.0 (−5.2 to 5.7)	−1.1 (−5.8 to 4.7)
Diclofenac group	0.0 (0.0–5.3)	–	0.0 (−5.2 to 5.4)	−1.1 (−5.8 to 4.4)
Indomethacin group	0.0 (0.0–5.1)	–	–	−1.1 (−5.8 to 4.2)
Diclofenac-paracetamol group	1.1 (0.1–5.3)	–	–	–
Indigestion				
Paracetamol group	7.8 (3.1–16.4)	1.8 (−7.7 to 11.7)	−0.8 (−10.7 to 9.5)	−0.9 (−9.6 to 9.2)
Diclofenac group	6.0 (2.1–14.3)	–	−2.6 (−12.2 to 7.0)	−2.7 (−11.1 to 6.7)
Indomethacin group	8.6 (3.8–17.2)	–	–	−0.1 (−8.9 to 9.7)
Diclofenac-paracetamol group	8.7 (3.8–15.8)	–	–	–
Abdominal pain				
Paracetamol group	0.0 (0.0–5.6)	−3.0 (−10.2 to 3.1)	0.0 (−5.2 to 5.7)	−6.5 (−13.5 to 0.1)
Diclofenac group	3.0 (0.5–9.6)	–	3.0 (−2.6 to 10.2)	−3.5 (−10.8 to 4.5)
Indomethacin group	0.0 (0.0–5.1)	–	–	−6.5 (−13.5 to −0.3)
Diclofenac-paracetamol group	6.5 (2.9–13.1)	–	–	–

extra analgesia, tried additional Chinese rather than western medicines, or who reattended an ED within 30 days (Table 6) was not clinically or statistically significant. Wound healing within 6 days appeared no different between the 4 groups, and return to normal function was also similar.

Median (interquartile range) patient satisfaction scores (out of 10) with the oral analgesic treatment were 3.0 (3.0 to 4.0; P=.39) and with the study in general were 3.0 (3.0 to 4.0; P=.25).

LIMITATIONS

The strengths of the study lie in its randomized, controlled design; its simple, practical, safe method of delivery of analgesia; and in its attempt to reflect the real world as far as reasonably possible. The doses of nonsteroidal antiinflammatory drugs used in this study reflected normal prescribing practice in our department. We have sought to reflect our real world, but these doses may be lower than those used in other health care settings. It is possible that higher doses produce a greater analgesic effect, but other studies will be required to address this issue.

Our study did not include a pure placebo arm because we did not consider it appropriate to deny some patients some form of accepted analgesia, which is a difficult dilemma because we cannot be sure whether the reduction in pain score during 3 days was a result of natural healing or partial placebo effect rather than a true analgesic effect of the medication.

This study differs from our normal ED practice in the following respects. In the study, a mean delay in administering analgesia of between 36 and 41 minutes occurred as a result of triage procedures, patient information, and consent procedures. In normal practice, we would hope that the delay would not be so long. The delay in this study was kept to an absolute minimum, and no complaints were subsequently received from patients or relatives. Second, in normal practice, analgesia will not be given in a blinded regimen, patients will not be observed

Table 6. Initial follow-up. Values are numbers (percentages) of participants unless otherwise stated.*

Variable†	Paracetamol and Placebo Group (n=66)	Diclofenac and Placebo Group (n=69)	Indomethacin and Placebo Group (n=71)	Diclofenac and Paracetamol Group (n=94)
Completed course of analgesia				
Paracetamol or placebo	49 (77)	54 (81)	47 (67)	62 (67)
Nonsteroidal antiinflammatory drug or placebo†	50 (78)	54 (81)	50 (71)	66 (72)
Reason for not completing course				
Forgot	1 (7)	1 (8)	4 (17)	5 (17)
Pain relief complete	6 (43)	9 (75)	14 (61)	15 (52)
Adverse event	7 (50)	2 (17)	2 (9)	5 (17)
Adverse event and pain relief	0 (0)	0 (0)	2 (9)	1 (3)
Tablets too large to swallow	0 (0)	0 (0)	1 (4)	1 (3)
Chinese alternative medicine	0 (0)	0 (0)	0 (0)	1 (3)
Did not like medication	0 (0)	0 (0)	0 (0)	1 (3)
Treated by general practitioner	1 (2)	4 (6)	1 (1)	0 (0)
Extra analgesic prescribed before follow-up	1 (2)	6 (9)	4 (6)	4 (4)
Chinese medication prescribed before follow-up	24 (38)	16 (24)	21 (30)	24 (26)
Chinese treatment (eg, massage, manipulation) prescribed before follow-up	18 (28)	9 (13)	16 (23)	15 (16)
Wound clean and dry at follow-up	8 (89)	11 (100)	12 (86)	11 (85)
Return to normal function at follow-up	35 (55)	42 (63)	44 (63)	56 (61)
Required more analgesic at follow-up	18 (28)	18 (27)	13 (19)	21 (23)
Required more sick leave at follow-up	38 (59)	47 (70)	44 (63)	59 (64)
Reattendance within 30 days	6 (9)	8 (12)	3 (4)	13 (14)
Reason for reattendance				
Required oral analgesia	5 (8)	7 (10)	2 (3)	11 (12)
Required intramuscular analgesia	1 (2)	2 (3)	0 (0)	1 (1)
Required orthopedic follow-up	0 (0)	1 (2)	0 (0)	4 (4)
Required physiotherapy	0 (0)	1 (2)	0 (0)	1 (1)

*Percentages may not sum to 100 because of rounding.
†χ^2 Test or Fisher exact test.

and questioned closely by a research nurse for 2 hours, and patients may be discharged sooner than in the study. Some degree of artificiality has to be accepted if vital data are to be recorded. However, because the study was randomized and double blind, any deviations from normal practice should at least be the same for all groups, leaving the effect of the analgesics as the only difference in outcomes.

We used a Statview statistical package to generate the simple randomization sequence, and, by chance, it assigned a markedly disproportionate number of cases to one group. We accepted the randomization protocol and assignment as generated because each group was assigned the minimum required numbers as recommended by our prestudy sample size calculations.

DISCUSSION

These results show that at the doses, frequencies, and routes of administration used in this study, oral paracetamol appears to be as effective as oral indomethacin, oral diclofenac, and oral diclofenac-paracetamol combination in the management of pain in musculoskeletal syndrome of minor to moderate severity. At the doses, frequencies, and durations used in the treatment of these participants, there were no severe adverse events and no significant differences in the proportion of patients with adverse events in the first 2 hours of treatment. However, during 3 days, the combination group had significantly more patients with abdominal pain than the group receiving indomethacin.

This study sought to address a deficiency previously noted by the Cochrane collaboration that there is no reasonably large study comparing the analgesic efficacy and safety of nonsteroidal antiinflammatory drugs with paracetamol in the management of musculoskeletal syndrome.[4] In a 2-part study, we investigated these aspects not only in the ED phase of managing acute pain but also the longer-term phase of managing pain throughout 3 days.

During the ED phase, there was no obvious statistically significant difference in mean reduction in resting or activity pain score between the groups. With activity, all groups showed a reduction in mean change in pain score, which was clinically and statistically significant. However, at no point was the mean difference in pain score between the groups clinically or statistically significant. Therefore, although pain reduction was noted in all groups, no group was dramatically superior.

There were few adverse events in the first few hours of treatment, and none were serious. Less than 20% of participants experienced adverse events during 3 days' treatment, and none were serious. The proportion of participants with adverse events was greatest in the diclofenac-paracetamol combination group. This group had a statistically higher proportion of adverse events compared with the indomethacin group.

Several small randomized trials have addressed the combined analgesic efficacy of paracetamol and opioids in patients with pain in general,[8] acute low back pain,[9] soft tissue strains and sprains,[10-12] and postarthroscopy analgesia,[13] but few have compared it with nonsteroidal antiinflammatory drugs. Of these studies, only 1 recruited more than 100 participants.[9] One double-blind, randomized study (>200 participants) compared a nonsteroidal antiinflammatory drug with placebo and showed no statistical difference in pain relief between the 2 regimens in the first 2 days of treatment.[14] Another single-blind, randomized study trial (160 subjects) compared intravenous propacetamol (a prodrug of paracetamol) with nonsteroidal antiinflammatory drugs and showed that the prodrug was at least as efficacious as nonsteroidal antiinflammatory drugs in the emergency treatment of peripheral injury.[15] Nonsteroidal antiinflammatory drugs have been shown to cause more gastroduodenal injury than paracetamol or placebo.[16]

At follow-up, there appeared to be no difference in wound healing between the different groups, no difference in return to normal function, no difference in requirement for absence from work, no difference in reattendance rates to the ED, and no difference in the use of nonconventional medicines between the 4 groups. Sample size was calculated for primary outcome but not for each of these secondary outcomes, so we cannot determine whether negative differences were due to genuine equality or to insufficient numbers. However, these outcomes were not primary endpoints in our study.

Reasons for the poor patient satisfaction scores are not given, but clearly patients were not satisfied with the effect of the analgesia or with study process in general. However, the main purpose of the study was to compare groups, and no group stood out from any of the others with particularly good or poor scores. The follow-up failure rate was very low and between 67% and 81% of subjects completed the whole course of analgesia. It is possible that higher doses or stronger analgesics would have been preferred, and between 8% and 12% participants returned for further medication. Some patients reflected that they would prefer injectable routes of analgesia because they believed that they were more effective. Also, the medications used in this study can be bought over the counter from any pharmacy in Hong Kong, and so some patients may have thought that the hospital was not offering them any advantage that they could not achieve by their own design. The study could have been strengthened if we had been able to include a diclofenac-like placebo as one of the study arms.

In conclusion, at the doses, routes, and frequencies of delivery of analgesia used in this study, no single strategy distinguished itself as providing better analgesic than any other strategy.

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