Feasibility study comparing oral paracetamol and oral non-steroidal anti-inflammatory drugs for treating pain after musculoskeletal injury: a randomised, double blind, controlled trial

一個隨機化雙盲對照試驗：比較口服對乙酰氨基酚與口服非類固醇抗炎藥對治療肌肉骨骼受傷後痛楚之可行性研究

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Objectives: To investigate the efficacy and safety of oral paracetamol compared with oral non-steroidal anti-inflammatory drugs (NSAIDs) or combination therapy in relieving pain after limb injury in an emergency department. ***Design:*** Double blind, randomised, controlled study. ***Setting:*** Emergency department of a university hospital in the New Territories of Hong Kong. ***Subjects:*** 50 adult patients with painful isolated limb injuries. ***Main outcome measures:*** Primary outcome measures were pain relief at rest and with limb movement, and adverse events. ***Results:*** There was no statistical difference in the mean reduction in pain score between oral paracetamol and oral NSAIDs in the first two hours of treatment or over three days. Patients' pain reduced significantly over three days but it was unclear whether this was due to natural healing rather than analgesic medication. There was no significant difference in pain relief between paracetamol and NSAIDs over three days treatment. All combinations appeared to be safe with no major adverse effects reported in the study. ***Conclusion:*** Oral paracetamol may be as effective and as safe as moderate dose of NSAIDs in the management of musculoskeletal pain. A larger study is required to confirm this hypothesis. (*Hong Kong j.emerg.med.* 2004;11:78-84)

目的：研究在急症室因肢體受傷之病者，使用口服對乙酰氨基酚或口服非類固醇抗炎藥或組合治療的止痛功效及安全比較。**設計：**雙盲隨機化對照研究。**環境：**香港新界一所教學醫院的急症室。**研究對象：**五十名因單一肢體受傷而引起痛楚的成年病者。**主要結果測量：**主要的結果測量為休止時的止痛功效，肢體活動時的止痛功效及不良效果。**結果：**於治療最初的兩小時或三天後，口服對乙酰氨基酚與口服非類固醇抗炎藥的止痛計分平均值都沒有統計學上的差別。病者的痛楚在三天後有顯著的減輕，但不清楚這是因為自然的痊癒還是止痛藥的效應。三天的療程中，對乙酰氨基酚與非類固醇抗

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炎藥的止痛功效沒有顯著的差別。這次研究顯示，所有組合都是安全的，及沒有重大的不良副作用事件。**結論：**於治療肌肉骨骼痛症中，口服對乙酰氨基酚與中等劑量的非類固醇抗炎藥同樣有效及安全。但需要一個較大型的研究以証實這假設。

Keywords: Diclofenac, indomethacin, NSAID, wounds and injuries

關鍵詞：雙氯芬酸、吲哚美辛、非類固醇抗炎藥、傷口及創傷

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are commonly used oral analgesics in emergency departments (ED), not only in Hong Kong but throughout the world.[1-3] Every year, much money is spent in prescribing analgesics for soft tissue injuries, and some of this is spent on expensive NSAIDs. Studies have shown that there is little difference in analgesic effect among NSAIDs prescribed orally despite differences in cost, although there may be differences in adverse effects.[4-8] There are no large-scale, prospective, randomised studies comparing paracetamol with NSAIDs in the management of soft tissue injury.[9] As paracetamol is cheaper than most NSAIDs,[10,11] may be as effective in the management of pain and possibly with fewer adverse effects, a large-scale, randomised, controlled trial study is needed to answer questions of relative analgesic efficacy and safety. This has important implications for patients, physicians and health administrators in Hong Kong. As these medications are commonly used in many other countries, this study will also have international relevance.

The aim of this study was to assess the feasibility of comparing the efficacy and safety of oral paracetamol with oral NSAIDs or NSAID/paracetamol combination therapy in the management of painful soft tissue injury within an ED setting and after discharge. We hypothesised firstly that paracetamol, NSAIDs or combination therapy administered orally for soft tissue injuries had equal analgesic efficacy; and secondly that paracetamol had less adverse effects than NSAIDs.

Methods

This study was conducted in the ED of the Prince of Wales Hospital (PWH), in collaboration with the Accident and Emergency Medicine Academic Unit of the Chinese University of Hong Kong (CUHK). The ED in PWH received 200,000 new patients per annum, served a population of approximately 1,500,000, and admitted 20% of those attending. Ethical approval was received from the local Institutional Research Ethics Committee to conduct a pragmatic, prospective, randomised, double-blind, controlled study comparing oral paracetamol with oral diclofenac, oral indomethacin and diclofenac/paracetamol combination in the management of soft tissue injury. Informed, written consent was obtained from each patient.

Inclusion criteria and exclusion criteria

All patients age 16 years or above presenting to the ED with an isolated soft tissue limb injury following a traumatic mechanism between the hours of 9 am to 5 pm, Monday to Friday, were considered for the study. As painful injuries should be treated with analgesia before specific diagnoses are made, recruitment inevitably included some subjects with minor fractures which were not apparent initially. All patients were studied on an intention-to-treat basis. Patients were excluded if there was a history of peptic ulceration or haemorrhage, recent anticoagulation, pregnancy, adverse reaction to paracetamol, diclofenac or indomethacin, renal or cardiac failure, hepatic problems, rectal bleeding, chronic non-steroidal anti-inflammatory drug consumption, asthma, chronic obstructive airways disease, chronic pain syndromes

or prior 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 analogue scale unreliable.

Randomisation, interventions and preparation of medication

Patients were randomly allocated to one of four treatment groups using a random number table.[12,13] Every patient received either (1) a true analgesic – paracetamol, diclofenac or indomethacin – and one placebo mimicking paracetamol or indomethacin; or (2) two true analgesics – diclofenac and paracetamol. Each patient was randomised to one of four groups. Group 1 received 2x [Paracetamol 500 mg] four times a day and 1x [Indomethacin placebo] three times a day, for 3 days. Group 2 received 2x [Paracetamol placebo] four times a day and 1x [Diclofenac 25 mg] three times a day, for 3 days. Group 3 received 2x [Paracetamol placebo] four times a day and 1x [Indomethacin 25 mg] three times a day, for 3 days. Group 4 received 2x [Paracetamol 500 mg] four times a day and 1x [Diclofenac 25 mg] three times a day, for 3 days (Table 1).

A research nurse opened a pre-coded envelope which contained the drugs and a randomisation number. All of the clinicians and nurses on duty, the research nurse, and patients were blinded to the medication.

Definitions

Soft tissue injuries were defined as simple abrasions, wounds, sprains, contusions, and minor avulsion fractures which were not clinically obvious on first assessment and prior to analgesia and radiography. Contusions were simple injuries involving a bruise. Crush injuries involved swollen tissues caused by blunt pressure rather than distraction forces. For the purpose of this study, wounds included injury by blunt trauma or sharp objects.

Data collection: pain score, observations and symptoms

During the study, analgesia was administrated in two phases. In the first phase, the patients were given the study drugs, and observed over two hours for pain relief and initial adverse effects in the ED. In the second phase, the patients were discharged with a three-day course of study drugs. Patients were asked to record their pain scores and adverse events three times a day for three days. Follow up was arranged in the emergency department five to eight days after the initial presentation. If the patient was not able to attend for follow up, a telephone follow up would then be arranged. A 100 mm, numbered, horizontal, visual analogue pain score (VAPS)[14] was used for baseline measurements (t_0), and at 20 (t_1), 40 (t_2), 60 (t_3), 80 (t_4), 100 (t_5), 120 (t_6) minutes after the first oral medication. Readings were also taken three times a day for the subsequent three days. Readings were taken at rest (e.g. non-weight bearing) and after activity (e.g. full weight bearing). All adverse events were documented. Data were analysed using Statview v5.0 (Abacus Concepts).

Clinical outcome

The primary clinical outcome was the mean reduction in pain score at rest and with movement. The secondary outcomes were adverse events which were assessed for type. The end point of the first phase of the study was set at two hours after the administration of analgesia if the patient was discharged from the emergency department, and for the second phase was set at three days.

Statistical analysis

Data were analysed on an intention to treat basis and all statistical analysis involved two-tailed tests. The mean change in pain score from the baseline was computed in the first two hours and the first three days. The first measurements were taken as the baseline

Table 1. Drugs used in the four treatment groups

Group 1	Group 2	Group 3	Group 4
Paracetamol 2 x 500 mg QID	Diclofenac 25 mg TID	Indomethacin 25 mg TID	Paracetamol 2 x 500 mg QID
Indomethacin placebo TID	Paracetamol placebo x 2 QID	Paracetamol placebo x 2 QID	Diclofenac 25 mg TID

either at time zero for the hourly measurements, or on day one for the daily measurements. Comparison of mean change in pain score was analysed by ANCOVA model with the baseline value as the covariate.[15] Any two treatments were said to be equally effective in pain reduction if the 95% confidence interval for the mean fell totally within +/-13 mm.[16,17] Baseline characteristics of categorical data were compared using chi-square test or Fisher's exact test. One-way ANOVA was used for comparing continuous data that conformed to the normal distribution whilst the Kruskall-Wallis test was used for time data which did not conform to a normal distribution. The occurrence of adverse events were compared by estimating the 95% confidence interval for the percentage difference.[12-17]

Results

Between 6th September and 4th October 2001, 50 patients with painful soft tissue injuries were randomised and allocated into four different analgesic groups: 16 patients to group 1; 12 patients to group 2; 11 patients to group 3; and 11 patients to group 4. There were about 3,000 trauma patients, which accounted for 18% of the total attendance, during this period.

Baseline characteristics and clinical outcomes

Baseline characteristics of the four groups (N=50 patients) were similar (Tables 2 & 3). Most of them had sprain injuries. A few patients with minor fractures that did not require operation were also included in the study. None was hospitalised, six needed follow up in orthopaedic outpatient clinic for orthopaedic reasons and not because of adverse events to analgesia. Only one patient developed an adverse effect which was a mild allergic reaction to paracetamol (Table 2). Three patients, each from different groups, requested more analgesic after three days. There was no mix up of treatment. Sixteen patients used herbal medicine in treating their injuries.

Phase 1

The mean change in resting pain score over the initial 2-hour period was less than 13 mm, the minimum difference required for a clinically significant reduction in pain. With activity, the mean change in pain score exceeded 13 mm only in the paracetamol and the paracetamol/diclofenac groups (Table 4). The 95% confidence interval for mean change in pain score both at rest and with activity exceeded 13 mm for all groups suggesting that there was a small possibility that all groups had some clinically significant analgesic effect. However, there was no clinically or statistically significant difference between the four strategies.

Phase 2

During the three-day study, the diclofenac group was the only group in which the mean pain score changed by more than 13 mm at rest (Table 4). With activity, all but the indomethacin group had their mean score change by greater than 13 mm. Again, in all four groups the 95% confidence interval exceeded this critical value, showing no statistical or clinically significant difference.

Discussion

This study showed that in the first two hours after analgesia, there was no statistically significant difference in pain relief between the four groups. Over the three days, diclofenac showed the highest mean pain score reduction both at rest and with activity. However, as the 95% confidence interval overlapped 13 mm reduction in pain score for all four groups, the difference is unlikely to be clinically important. Paracetamol is a less costly option than NSAIDs and it does not appear that NSAIDs offer any advantage at the doses and frequencies tested in this study. The analgesic effect of paracetamol is no different than that of NSAIDs. This finding is of great financial and clinical significance. From a health service perspective, analgesic agents are being prescribed in large quantities which are a considerable drain on the health care budget. Therefore, an inexpensive, effective analgesic with fewer side effects may be welcomed by physicians and health service providers. No patient developed major side effects with NSAIDs in our study. Two reasons may account for this. Firstly, the sample size in this preliminary study might not be large enough. Secondly, we did not use a high dosage of NSAID and therefore the side effects might not be apparent.

Table 2. Patients characteristics (n=50)

Variable		Drug				
		Paracetamol and Placebo (n=16)	Diclofenac and Placebo (n=12)	Indomethacin and Placebo (n=11)	Paracetamol and Diclofenac (n=11)	P value*
Sex	F	7 (44)	1 (8)	3 (27)	5 (45)	0.15
	M	9 (56)	11 (92)	8 (73)	6 (55)	
Type of injury	Contusion	2 (13)	3 (25)	1 (9)	3 (27)	-
	Crush	3 (19)	1 (8)	2 (18)	3 (27)	
	Cut	3 (19)	0 (0)	2 (18)	0 (0)	
	Sprain	8 (50)	8 (67)	6 (55)	5 (45)	
Site of injury	Ankle	2 (13)	2 (17)	4 (36)	2 (18)	-
	Arm	1 (6)	0 (0)	0 (0)	1 (9)	
	Elbow	0 (0)	1 (8)	0 (0)	0 (0)	
	Foot	4 (25)	1 (8)	1 (9)	2 (18)	
	Hand	2 (13)	3 (25)	2 (18)	3 (27)	
	Knee	2 (13)	1 (8)	1 (9)	1 (9)	
	Leg	1 (6)	0 (0)	0 (0)	0 (0)	
	Shoulder	1 (6)	1 (8)	1 (9)	2 (18)	
	Wrist	3 (19)	3 (25)	2 (18)	0 (0)	
X-ray (ED)	0	6 (38)	5 (42)	3 (27)	2 (18)	0.65
	1	10 (63)	7 (58)	8 (73)	9 (82)	
X-ray result (ED)	Normal	8 (80)	6 (86)	8 (100)	7 (78)	0.68
	Fracture	2 (20)	1 (14)	0 (0)	2 (22)	
Fracture (ED X-ray)	0	8 (80)	6 (86)	8 (100)	7 (78)	0.68
	1	2 (20)	1 (14)	0 (0)	2 (22)	
Took analgesic before ED >3 hr.	0	15 (94)	12 (100)	11 (100)	11 (100)	1.00
	1	1 (6)	0 (0)	0 (0)	0 (0)	
Adverse effect -ED	0	15 (94)	12 (100)	11 (100)	11 (100)	1.00
	1	1 (6)	0 (0)	0 (0)	0 (0)	
Antibiotic	0	15 (94)	12 (100)	11 (100)	11 (100)	1.00
	1	1 (6)	0 (0)	0 (0)	0 (0)	
Finish Med A (24 tablets)	0	5 (33)	2 (20)	6 (55)	1 (10)	0.15
	1	10 (67)	8 (80)	5 (45)	9 (90)	
Finish Med B (9 tablets)	0	5 (33)	2 (20)	6 (55)	1 (10)	0.15
	1	10 (67)	8 (80)	5 (45)	9 (90)	
F/U OT (PWH)	0	14 (100)	7 (88)	6 (60)	8 (89)	0.03†
	1	0 (0)	1 (13)	4 (40)	1 (11)	
Extra analgesic	0	14 (100)	8 (89)	7 (70)	9 (100)	0.06
	1	0 (0)	1 (11)	3 (30)	0 (0)	
Chinese medicine	0	9 (64)	2 (25)	8 (80)	6 (67)	0.13
	1	5 (36)	6 (75)	2 (20)	3 (33)	
Physiotherapy	0	12 (86)	7 (88)	8 (80)	9 (100)	0.70
	1	2 (14)	1 (13)	2 (20)	0 (0)	
Wound	0	10 (71)	6 (75)	7 (70)	8 (89)	0.83
	1	4 (29)	2 (25)	3 (30)	1 (11)	
Wound clean/dry (F/U)	0	0 (0)	1 (50)	0 (0)	0 (0)	-
	1	4 (100)	1 (50)	3 (100)	1 (100)	
Sprain injury	0	5 (36)	2 (25)	3 (30)	1 (11)	0.71
	1	9 (64)	6 (75)	7 (70)	8 (89)	
Move function (F/U)	0	1 (7)	0 (0)	4 (40)	2 (22)	0.11
	1	13 (93)	8 (100)	6 (60)	7 (78)	
More analgesic (F/U)	0	13 (93)	8 (100)	9 (90)	8 (89)	1.00
	1	1 (7)	0 (0)	1 (10)	1 (11)	
Sick leave	0	9 (64)	7 (70)	3 (27)	5 (56)	0.22
	1	5 (36)	3 (30)	8 (73)	4 (44)	

*Fisher's exact tests.

†Significant difference was found between drug 1 and drug 3 (P=0.0359). Group comparisons were further made by using logistic regression.
F/U=Follow up; OT=Orthopaedic; PWH=Prince of Wales Hospital; Med A=Paracetamol/Paracetamol placebo; Med B=NSAID/NSAID placebo; Percentages in brackets.

Table 3. Patients characteristics (n=50)

	Drug				
	Paracetamol and Placebo (n=16)	Diclofenac and Placebo (n=12)	Indomethacin and Placebo (n=11)	Paracetamol and Diclofenac (n=11)	P value*
Age – mean (SD)	36.3 (14.6)	27.9 (7.2)	35.9 (11.2)	36.6 (15.6)	0.28
Time injury to ED (mins) – median (IQR)	421.0 (73.8 to 1032.3)	736.5 (62.5 to 995.5)	44.0 (33.0 to 950.0)	806.0 (57.0 to 1263.0)	0.33
Time ED to time drug (mins) – median (IQR)	74.5 (50.3 to 94.0)	56.5 (34.0 to 104.3)	87.0 (39.0 to 103.0)	62.0 (49.0 to 106.0)	0.89
Time injury to time drug (mins) – median (IQR)	500.0 (127.5 to 1117.5)	782.5 (191.3 to 1100.0)	210.0 (105.0 to 1090.0)	900.0 (150.0 to 1380.0)	0.48
Systolic blood pressure-t_0 – mean (SD)	137.8 (13.5)	134.0 (10.8)	144.5 (20.2)	137.5 (18.6)	0.47
Diastolic blood pressure-t_0 – mean (SD)	74.9 (9.4)	72.0 (12.3)	83.3 (10.2)	79.5 (9.5)	0.06
Pulse rate-t_0 – mean (SD)	79.6 (13.3)	85.0 (11.5)	78.5 (14.1)	81.6 (12.8)	0.63
Pain score at rest-t_0 – mean (SD)	27.3 (24.8)	28.1 (20.9)	18.5 (25.5)	23.5 (12.7)	0.71
Pain score with activity-t_0 – mean (SD)	68.6 (12.9)	61.7 (13.8)	66.4 (16.1)	73.0 (14.8)	0.30
Pain score at rest-Day 1 – mean (SD)	17.8 (22.5)	29.9 (20.2)	9.9 (14.6)	19.4 (15.7)	0.19
Pain score with activity-Day 1 – mean (SD)	53.1 (22.1)	60.3 (17.8)	48.2 (18.4)	61.2 (19.0)	0.44
No. of tabs/A – median (IQR)†	24.0 (20.5 to 24.0)	24.0 (24.0 to 24.0)	20.0 (9.5 to 24.0)	24.0 (24.0 to 24.0)	0.02
No. of tabs/B – median (IQR)†	9.0 (7.5 to 9.0)	9.0 (9.0 to 9.0)	8.0 (4.5 to 9.0)	9.0 (9.0 to 9.0)	0.02

*One-way ANOVA for variables expressed in mean (SD) and Kruskal-Wallis tests for those expressed as median (IQR).
†No significant pairwise group difference found after Hochberg step-up procedure (Hochberg & Benjamini 1990).
ED=Emergency department; IQR=Interquartile range; A=Paracetamol/Paracetamol placebo; B=NSAID/NSAID placebo.

Table 4. Mean change in pain score from baseline* (n=50)

		Estimated mean change (95% CI)	Pairwise comparisons [mean difference (95% CI)]		
			Diclofenac and Placebo	Indomethacin and Placebo	Paracetamol and Diclofenac
At rest (first 2 hours)	Paracetamol & Placebo	-9.4 (-13.4 to -5.4)	-0.7 (-9.0 to 7.6)	-0.8 (-9.4 to 7.7)	0.1 (-8.4 to 8.6)
	Diclofenac & Placebo	-8.7 (-13.3 to -4.1)	-	-0.1 (-9.3 to 9.0)	0.8 (-8.3 to 9.9)
	Indomethacin & Placebo	-8.6 (-13.4 to -3.7)	-	-	0.9 (-8.4 to 10.2)
	Paracetamol & Diclofenac	-9.5 (-14.2 to -4.7)	-	-	-
With activity (first 2 hours)	Paracetamol & Placebo	-13.3 (-19.5 to -7.1)	-5.9 (-18.8 to 7.0)	-3.9 (-17.3 to 9.5)	1.1 (-12.1 to 14.4)
	Diclofenac & Placebo	-7.4 (-14.6 to -0.3)	-	2.0 (-12.3 to 16.3)	7.0 (-7.1 to 21.2)
	Indomethacin & Placebo	-9.4 (-16.9 to -1.9)	-	-	5.1 (-9.4 to 19.6)
	Paracetamol & Diclofenac	-14.5 (-21.9 to -7.0)	-	-	-
At rest (first 3 days)	Paracetamol & Placebo	-5.5 (-10.0 to -1.0)	10.4 (0.1 to 20.7)	-1.9 (-11.6 to 7.7)	2.9 (-7.0 to 12.8)
	Diclofenac & Placebo	-15.9 (-21.9 to -10.0)	-	-12.3 (-23.4 to -1.2)	-7.5 (-18.8 to 3.8)
	Indomethacin & Placebo	-3.6 (-9.0 to 1.7)	-	-	4.8 (-5.8 to 15.5)
	Paracetamol & Diclofenac	-8.4 (-14.1 to -2.8)	-	-	-
With activity (first 3 days)	Paracetamol & Placebo	-18.3 (-25.5 to -11.2)	5.2 (-11.2 to 21.7)	-11.9 (-27.2 to 3.5)	-2.4 (-18.2 to 13.4)
	Diclofenac & Placebo	-23.6 (-33.1 to -14.0)	-	-17.1 (-34.8 to 0.6)	-7.7 (-25.7 to 10.4)
	Indomethacin & Placebo	-6.5 (-15.0 to 2.1)	-	-	9.4 (-7.6 to 26.4)
	Paracetamol & Diclofenac	-15.9 (-24.8 to -6.9)	-	-	-

*For the data collected in the first 2 hours, pain score measured at time 0 was taken as the baseline. Data obtained at the morning of Day 1 was the baseline measurement for the first 3 days.

Strengths and weaknesses

The strengths of the study lie in its randomised, controlled design that will enable the analgesic efficacy and safety of paracetamol, indomethacin and diclofenac in the management of soft tissue limb injury to be established. It was not possible to completely blind the diclofenac arm as an identical placebo was not available to us. Nevertheless, blinding the paracetamol arm introduced an uncertainty such that patients and staff were never sure what they were prescribing. Staff who were involved in managing patients, opening packages, prescribing study medications and recording follow up data were not involved in preparing packages of drugs. For ethical reasons, our study did not include a pure placebo arm. Therefore we cannot be sure whether the pain reduction over three days was a result of analgesic effect or natural healing. Also, the use of herbal medicine in treating soft tissue injury is very common in Chinese. This may affect our result especially if our sample size is small. The major criticism in this study is its small sample size which makes its validity questionable. Therefore, we need a large-scale trial to verify these findings in the pilot study.

We did not record whether data collected was by telephone follow up or by emergency department attendance. Gender and some types of injury might be over-represented in some treatment arms.

Purpose and potential for implementation of results

This study shows that with the methods used in this study, paracetamol may be as effective as diclofenac, indomethacin and combination therapy in the management of minor to moderate musculoskeletal injury. A large-scale trial is required to verify these findings.

Competing interests

None declared.

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