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# Comparison of Oral Prednisolone/Paracetamol and Oral Indomethacin/Paracetamol Combination Therapy in the Treatment of Acute Goutlike Arthritis: A Double-Blind, Randomized, Controlled Trial

Chi Yin Man, MD  
Ian T. F. Cheung, MD  
Peter A. Cameron, MD  
Timothy H. Rainer, MD

From the Accident and Emergency Medicine Academic Unit, The Chinese University of Hong Kong, Hong Kong, China (Man, Cheung, Rainer); and Emergency and Trauma Centre, The Alfred Hospital, Melbourne, Victoria, Australia (Cameron).

**Study objective:** We compare the analgesic efficacy and adverse effects of oral prednisolone/acetaminophen and oral indomethacin/acetaminophen combination therapy in the treatment of acute goutlike arthritis in patients presenting to an emergency department (ED).

**Methods:** This is a double-blind, randomized, controlled study in a university hospital emergency department (ED) in the New Territories of Hong Kong. Patients older than 17 years and presenting between February 1, 2003, and June 30, 2004, with a clinical diagnosis of goutlike arthritis were randomized to receive either oral prednisolone/acetaminophen or oral indomethacin/acetaminophen combination therapy. Primary outcome measures were pain scores, time to resolution of symptoms and signs, and adverse effects. Secondary outcome measures were the need for additional acetaminophen and relapse rate.

**Results:** There were 90 patients randomized: 46 patients to the indomethacin group and 44 patients to the prednisolone group. Baseline characteristics, including pain scores, were similar in the 2 groups. Both treatment groups had a similar decrease in pain score in the ED. The mean rate of decrease in pain score with activity for indomethacin was  $-1.7 \pm 1.6$  (SD) mm per day and for prednisolone was  $-2.9 \pm 2.0$  (SD) mm per day (mean difference 1.2 mm/day; 95% confidence interval 0.4 to 2.0 mm/day;  $P = .0026$ ). Although these differences were statistically significant, at no time was the difference in mean pain score greater than 13 mm. Therefore, it is unclear whether these differences are clinically significant. The mean total dose of acetaminophen consumed by the prednisolone group was significantly more than in the indomethacin group (mean 10.3 g, range 1 to 21 g versus mean 6.4 g, range 1 to 21 g). Twenty-nine patients in the indomethacin group and 12 patients in the prednisolone group experienced adverse effects ( $P < .05$ ). The commonest adverse effects in the indomethacin group were nausea, indigestion, epigastric pain, dizziness, and gastrointestinal bleeding (N=5; 11%). None of the patients in the prednisolone group developed gastrointestinal bleeding. The relapse rate for both groups was similar.

**Conclusion:** In the treatment of acute goutlike arthritis, oral prednisolone/acetaminophen combination is as effective as oral indomethacin/acetaminophen combination in relieving pain but is associated with fewer adverse effects. [Ann Emerg Med. 2007;49:670-677.]

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## INTRODUCTION

### Background

Acute gouty arthritis is a crystal-induced inflammation of the joint that primarily affects middle-aged and elderly adults. It is

the commonest cause of inflammatory joint disease in men older than 40 years.<sup>1</sup> It has been estimated that the overall prevalence in the United Kingdom is 10 per 1,000, with men affected more commonly than women.<sup>2</sup> The diagnosis of acute

### Editor's Capsule Summary

#### *What is already known on this topic*

Acute gouty arthritis is typically treated with nonsteroidal antiinflammatory agents, though prednisone has also been recommended. Their relative efficacy is unknown.

#### *What question this study addressed*

The efficacy and adverse effects of oral prednisolone and oral indomethacin in the treatment of acute goutlike arthritis in emergency department patients.

#### *What this study adds to our knowledge*

In this 90-patient randomized controlled trial, the treatments exhibited similar efficacy. Adverse effects were more common in patients given indomethacin, including gastrointestinal bleeding in 11%.

#### *How this might change clinical practice*

A short course of prednisolone is at least as effective as indomethacin and may be safer.

gout is typically made clinically by the presence of rapid onset of severe pain, swelling, and erythema of an affected joint and definitively by demonstrating the presence of negatively birefringent uric acid crystals in aspirated joint fluid. The diagnosis is often made in the absence of joint aspiration because this procedure is painful, poorly tolerated by some patients, and declined by others and is sometimes difficult or inconvenient to perform in a busy emergency department (ED). The treatment of such patients is inconsistent, and evidence-based guidelines to support clinical management are lacking. Gout is an increasingly prevalent condition worldwide and creates a heavy economic burden.<sup>1,3</sup>

### Importance

Oral nonsteroidal antiinflammatory drugs (NSAIDs) administered in high doses are recommended as first-line agents in the management of gout but may be contraindicated because of gastrointestinal hemorrhage or renal failure.<sup>4-12</sup> Oral colchicine may be as effective as NSAIDs but is limited by toxicity at higher doses.<sup>13-15</sup> Intraarticular corticosteroids may also be administered for monoarticular disease and intramuscular corticosteroids for podagra.<sup>4</sup> A few small controlled studies have compared oral NSAIDs with intraarticular or intramuscular steroids and suggest that NSAIDs are as effective as steroids in the treatment of acute gout.<sup>16-18</sup> However, NSAIDs have a significant rate of adverse effects, including gastric irritation, gastrointestinal hemorrhage, and renal failure.<sup>4</sup> Although steroids cause severe adverse events if taken at high doses for long periods, there appear to be few adverse effects if they are taken in low to moderate doses for short periods.<sup>19</sup> The gastrointestinal adverse effects also appear to be less severe than those of NSAIDs.<sup>5</sup> Long-term effects, such

as osteoporosis and muscle wasting, are not relevant to acute gout treatment. Oral NSAIDs have not been compared to oral steroids in the management of acute gout.

### Goals of This Investigation

The objective of this study was to compare the efficacy and adverse effects of oral indomethacin/acetaminophen with oral prednisolone/acetaminophen combination therapy in the treatment of patients presenting to the ED with a clinical diagnosis of acute goutlike arthritis.

## MATERIALS AND METHODS

### Study Design

In this prospective, randomized, double-blind, controlled study, the analgesic efficacy and adverse effects of oral prednisolone/acetaminophen and oral indomethacin/acetaminophen combination were compared in patients presenting to an ED with a clinical diagnosis of acute gouty arthritis (Figure 1). Ethical approval was obtained from the local institutional research ethics committee. Informed written consent was obtained from each patient.

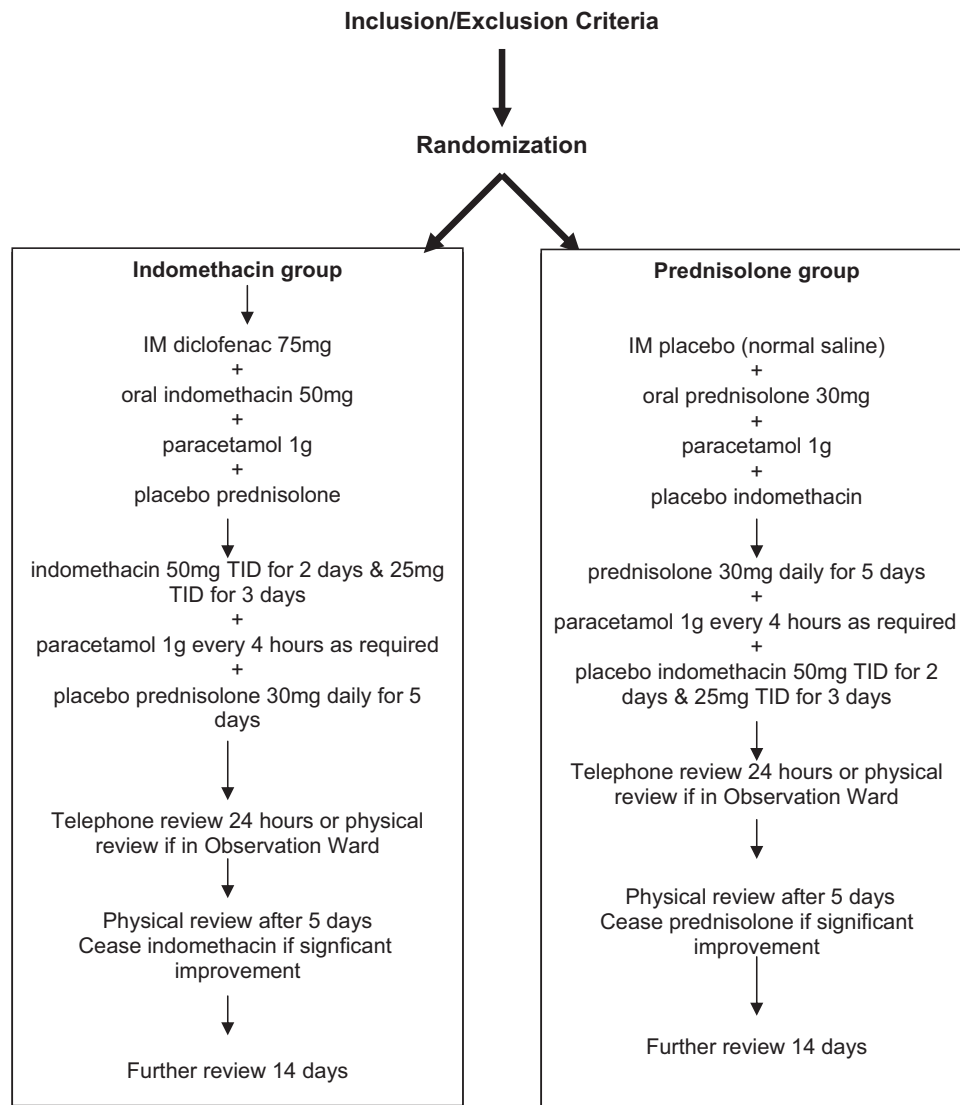
### Setting

The ED of the Prince of Wales Hospital, a 1,400-bed teaching hospital in the New Territories of Hong Kong, receives about 160,000 new patients per annum, of whom about 25% are admitted to the hospital. The hospital serves a population of approximately 1.5 million. Gout is responsible for 1 to 2 patient visits per day at Prince of Wales Hospital ED. Of these patients, up to 15% are admitted to the ED observation ward or a hospital ward, mainly because the patients are elderly and lack social support.

### Selection of Participants

All patients older than 17 years, with an acute arthritis suggestive of gout, and presenting to the ED during designated periods when research staff were on duty between 9 AM and 4 PM, Monday to Friday, from February 1, 2003, to June 30, 2004, were considered for enrollment. Patients were included if they had a clinical diagnosis of acute arthritis suggestive of gout, defined as the presence of pain and warmth in a joint, and presented within 3 days of the onset of pain and also had 1 or more of the following: metatarsal-phalangeal joint involvement; knee or ankle joint involvement and aspirate containing crystals; or typical gouty arthritis, with either gouty tophi present or previous joint aspiration confirming the diagnosis of gout.

Patients were excluded if there was a clinical suspicion of sepsis or other joint disease; if follow-up was impossible because of lack of transport or lack of telephone contact; if there was significant comorbidity that would interfere with assessment; and if patients had dementia, confusion, active gastrointestinal symptoms, renal insufficiency with serum creatinine level greater than 200  $\mu\text{mol/L}$ , bleeding disorder, allergy to a study drug, or joint aspirate that excluded the diagnosis of gout or were taking warfarin.



**Figure 1.** Progress of patients through randomized trial. *TID*, Three times a day.

It is often not possible to definitively separate gout from septic arthritis on clinical grounds alone. In this study, sepsis was considered likely if the patient had a temperature greater than 38°C, chills or rigors, a wound near the affected joint, a history of immunosuppression, erythematous tracking along a lymphatic vessel or vein in the affected limb, lymphadenopathy, or a history of septic arthritis.

### Interventions

Patients were allocated with a random-number table generated from StatView for Windows, version 5.0 (Abacus Concepts, SAS Institute, Inc., Cary, NC). The random allocation sequence was implemented with numbered sealed envelopes, such that the sequence was concealed until interventions were assigned. A nurse with clinical responsibilities opened a pre-coded envelope with details of the

drug and a randomization number. The oral preparations of indomethacin 25 mg, acetaminophen 500 mg and prednisolone 5 mg, and identical placebos were all prepacked and placed inside the envelope. Diclofenac was prepared as a solution at 25 mg/mL, and placebo (normal saline solution) as a 1-mL solution was prepared in the ED. This nurse was not involved in the administration of analgesia, the assessment of the patient, or the treatment of adverse effects. The code was only to be broken if a physician or other nurse with clinical duties was concerned about severe adverse effects. Both the research nurse with nonclinical duties and the patient were blinded to the medication.

In the indomethacin group, each patient initially received diclofenac (3 mL; 75 mg) intramuscularly, indomethacin 50 mg orally, acetaminophen 1 g orally, and 6 tablets of prednisolone-like placebo orally and was observed for 120 minutes. The

patient was then given a 5-day prescription of indomethacin (50 mg orally every 8 hours for 2 days, followed by indomethacin 25 mg every 8 hours for another 3 days), 6 tablets of prednisolone-like placebo once a day, and acetaminophen 1 g every 6 hours as required.

In the prednisolone group, each patient initially received an intramuscular placebo injection (3 mL), prednisolone 30 mg (6 times 5 mg) orally, acetaminophen 1 g (2 tablets) orally, and indomethacin-like placebo (2 tablets) orally, and was then observed for 120 minutes. The patient was then given a 5-day prescription of indomethacin-like placebo, prednisolone 30 mg orally once per day, and acetaminophen 1 g every 6 hours as required. Both acetaminophen and intramuscular injection were given in accordance with common local practice. Many patients in Hong Kong believe that symptomatic relief will be faster if an injection is administered. The physician on duty was free to give extra doses or alternative analgesic if clinically required, and this was documented.

### Methods of Measurement

Assessment included demographic data, assessment on scheduled intervals of pain scores at rest and with activity, the occurrence of adverse effects, and the time of symptom resolution. The pain scores were assessed with a visual analogue scale from 0 (absence of pain) to 10 (the most severe pain the patient has ever experienced). A 10-cm, numbered, horizontal, visual analogue pain score was used for baseline measurements ( $t_0$ ) and at subsequent intervals after the first injection.<sup>20</sup> Pain scores and adverse effects were recorded every 30 minutes for 2 hours after drug administration. Patients were aware of their previous scores at all stages of recording.

Research staff contacted the patient by telephone at 24 hours (or physical assessment if the patient was admitted to the observation ward), at 5 days, and also by telephone at 14 days, unless symptoms were not resolved. Patients recorded data daily for 5 days at home.

The type, number, duration, and severity of adverse effects were documented. Specific questions for each adverse event were asked each day in the collection of adverse event data, eg, "Did you experience nausea today?"

The primary clinical outcome measures were pain relief, measured as changes in pain score at rest and with activity, and adverse events. Both the change in the score and absolute value were measured. Activity involved the research nurse gently moving the joint involved in a standardized manner to assess pain. Adverse events were assessed for number, duration, and severity (where applicable). Secondary outcome measures were time to complete resolution of pain, stiffness and joint swelling, supplementary acetaminophen, and relapse rate. Data collection ceased at day 14, and nonresolution of symptoms or recurrence of symptoms at this time was regarded as a treatment failure.

### Primary Data Analysis

Data were analyzed on an intention-to-treat basis, and all statistical analyses involved 2-tailed tests using StatView for

Windows, version 5.0 Statistical Analysis Software (Abacus Concepts, SAS Institute).  $P < .05$  was considered as statistically significant. Because pain score and time data did not conform to the Gaussian distribution, nonparametric tests were used to analyze data.<sup>21</sup> Baseline characteristics of the 2 treatments were analyzed using the  $\chi^2$  test or Mann-Whitney U test.<sup>22</sup> A regression line indicating the change in visual analog scale pain score over time was found, and its slope was therefore a summary measure for each patient.<sup>23</sup> The distribution of coefficients followed a normal distribution, and so the mean slope for the coefficients of each treatment group was compared and analyzed using the  $t$  test. A previous study has shown that a difference in visual analog pain scores of less than 13 mm is unlikely to be clinically relevant.<sup>24</sup> Therefore, unless the upper limits of the confidence intervals (CIs) were less than 13 mm, we assumed that the results were inconclusive.

To detect a clinically significant difference between the mean pain score of the 2 groups of 15 mm, each with an SD of 20 mm, with an estimated power of 90% and at the 5% significance level, 37 patients were required for each group.

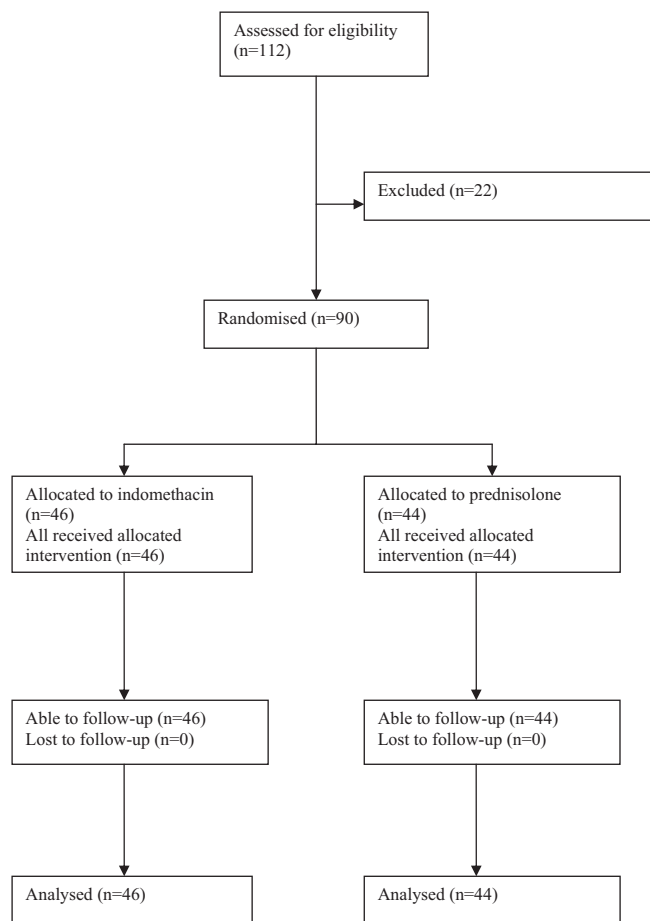
### RESULTS

During the study period, 112 patients presented with a clinical diagnosis of probable acute gout, of whom 22 were excluded because of acute gastroduodenal ulcer ( $n=1$ ), trauma ( $n=3$ ), serum creatinine level greater than 200 nmol/L ( $n=3$ ), bleeding disorders ( $n=3$ ), history of adverse reactions to NSAID ( $n=5$ ), and suspicion of infectious cause ( $n=6$ ). The remaining 90 patients were randomized, 46 patients to the indomethacin group and 44 patients to the prednisolone group (Figure 2).

The demographic and other baseline characteristics of the 2 groups were similar (Table 1). There was no significant difference in initial mean pain score at rest or with activity between the 2 treatment groups. Five patients in the prednisolone group and 2 patients in the indomethacin group agreed to allow joint aspiration. All were positive for urate crystals and negative for bacterial culture.

During the ED phase, the rate of decrease in mean pain score over time both at rest and with activity (Figure 3) was similar for both groups. The mean rate of decrease in pain score at rest for indomethacin was  $-6.4 \pm 8.3$  (SD) mm per hour and for prednisolone was  $-9.5 \pm 10.5$  (SD) mm per hour (mean difference 3.2 mm/hour; 95% CI  $-0.78$  to 7.14 mm/hour;  $P = .12$ ). The mean rate of decrease in pain score with activity for indomethacin was  $-20.3 \pm 9.1$  (SD) mm per hour and for prednisolone was  $-19.2 \pm 11.2$  (SD) mm per hour (mean difference  $-1.0$  mm/hour; 95% CI  $-5.34$  to 3.24 mm/hour;  $P = .63$ ).

During the follow-up phase, the rate of decrease in mean pain score over time at rest and with activity (Figure 4) was greater in the prednisolone group than the indomethacin group. The mean rate of decrease in pain score at rest for indomethacin was  $-0.3 \pm 0.7$  (SD) mm per day and for prednisolone was  $-0.7 \pm 1.2$  (SD) mm per day (mean difference 0.5 mm/day;



**Figure 2.** Interventions given to patients randomized into the 2 study groups.

95% CI 0.03 to 0.89 mm/day;  $P=.04$ ). The mean rate of decrease in pain score with activity for indomethacin was  $-1.7 \pm 1.6$  (SD) mm per day and for prednisolone was  $-2.9 \pm 2.0$  (SD) mm per day (mean difference 1.2 mm/day; 95% CI 0.44 to 2.00 mm/day;  $P=.0026$ ). Although these differences in activity were statistically significant, at no time was the difference in mean pain score greater than 13 mm. At day 14 (the last follow-up day), the same end points were reached by the 2 groups.

Both treatment groups showed improvement in the joint swelling and stiffness, but there was no difference in improvement between the 2 groups.

In the indomethacin group, 29 (63%) patients experienced adverse effects compared with 12 (27%) patients in the prednisolone group ( $P<.05$ ; Table 2). Nausea, indigestion, epigastric pain, and dizziness were significantly more common in the indomethacin group than the prednisolone group. The most common adverse effects in the steroid group were dry mouth and dizziness.

Seven patients had adverse effects that were serious enough to require treatment or hospital admission; all were in the indomethacin group ( $P=.007$ ). Five (11%) patients developed

**Table 1.** Baseline characteristics of patients between the 2 groups.

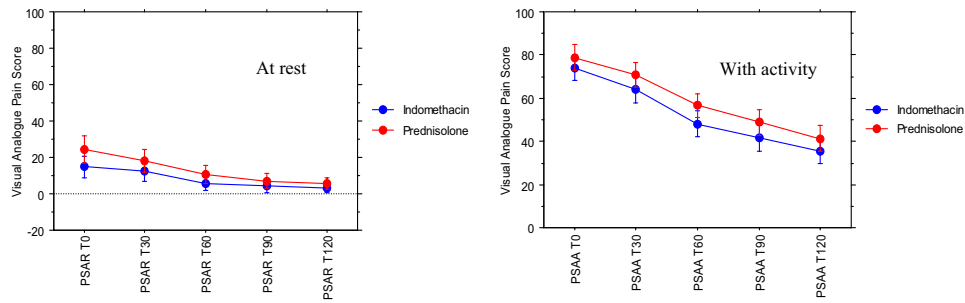
Variable	Indomethacin Group, N=46	Prednisolone Group, N=44
Age, y, mean (SD)	66 (16)	64 (15)
Male patients (%)	39 (85)	35 (80)
History of gout, No. (%)	45 (98)	42 (95)
Duration of symptoms, d, mean (SD)	2.3 (0.6)	2.2 (1.1)
Pain score at rest (pretreatment), mm, mean (SD)	15 (20.8)	24 (25.2)
Pain score with activity (pretreatment), mm, mean (SD)	74 (20.3)	78 (19.7)
Single joint involved, patients (%)	45 (98)	41 (93)
>1 Joint involved, No. (%)	1 (2)	3 (7)
Lower limb involved, No. (%)	45 (98)	39 (89)
Lower and upper limb involved, No. (%)	1 (2)	0
Fever, No. (%)	8 (17)	2 (5)
Presence of tophus, No. (%)	2 (4)	5 (11)
Mobility, unable to bear weight, No. (%)	25 (54)	29 (66)
Admission to observation ward, No. (%)	3 (7)	8 (18)
Median length of stay in observation ward, h	23.6	23.4

gastrointestinal bleeding (11%;  $P<.05$ ). Their ages ranged from 62 to 84 years. Four were admitted to the hospital, and the fifth was referred to an outpatient clinic. In each case, study medication was stopped, and upper gastrointestinal endoscopy was performed; 3 patients had acute gastric ulcers, of whom 2 received adrenaline injection for active bleeding; 2 patients had gastroduodenal ulcers. No patient developed cardiovascular shock, and all ulcers healed after treatment.

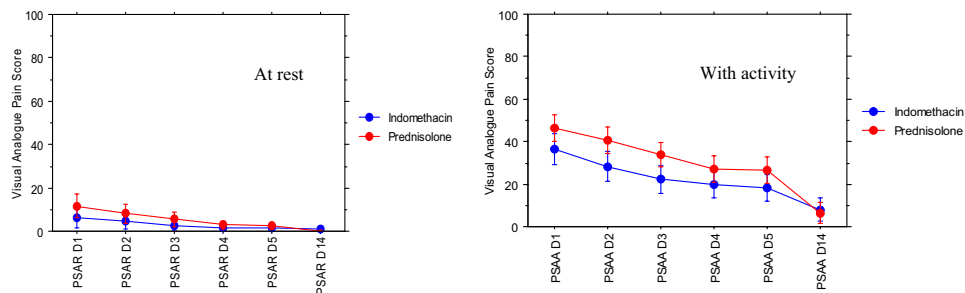
All patients in the 2 groups consumed acetaminophen during the 14 days. The mean total dose of acetaminophen consumed by the prednisolone group was significantly more than that consumed by the indomethacin group (mean 10.3 g, range 1 to 21 g versus mean 6.4 g, range 1 to 21 g;  $P=.008$ ). Overall, within 14 days there were 8 patients in the indomethacin group who relapsed and reattended for further treatment compared with 5 patients in the prednisolone group ( $P$ =nonsignificant). Fifteen patients in the prednisolone group required alternative medication for pain relief compared with 17 patients in the indomethacin group ( $P$ =nonsignificant).

## LIMITATIONS

The diagnosis was made on clinical impression, and joint aspiration was not performed on most patients. However, in routine clinical practice the majority of patients presenting with goutlike arthritis are treated clinically and without joint aspiration, unless there is a high index of suspicion of septic arthritis or atypical features. The relatively small sample size may not have allowed us to detect small differences in pain scores. The sample size was based on our estimation of a clinically significant difference. The safety aspects were not a primary aspect of the study, and as such it was not powered to evaluate safety. It is possible that with larger numbers of



**Figure 3.** Visual analog pain score at rest and with activity during the ED phase. Pain was assessed at rest, at time (T) 0, and at 30 min, 60 min, 90 min, and 120 min. Data are presented as means (95% CIs). There were no statistically or clinically significant differences between the groups either at rest ( $P=.12$ ) or with activity ( $P=.63$ ).



**Figure 4.** Visual analog pain score at rest and with activity during the follow-up phase. Pain was assessed at rest for days (D) 1 to 5 and 14. Data are presented as means (95% CIs). There were no statistically or clinically significant differences between the groups at any point either at rest ( $P=.60$ ) or with activity ( $P=.0026$ ) (see text).

**Table 2.** Adverse effects reported by patients treated with indomethacin or prednisolone for the acute goutlike arthritis.\*

Adverse Effects	Indomethacin (N=46)	Prednisolone (N=44)	P Value
Any adverse event, No. (%)	29 (63)	12 (27)	.0007
Epigastric pain, of No. (%)	14 (30)	0 (0)	<.0001
Other abdominal pain, No. (%)	3 (7)	0 (0)	.09
Rash, No. (%)	1 (2)	3 (7)	.25
Dizziness, No. (%)	9 (19)	2 (5)	.03
Drowsiness, No. (%)	9 (19)	7 (16)	.79
Dry mouth, No. (%)	11 (24)	9 (20)	.83
Indigestion, No. (%)	14 (30)	4 (9)	.02
Nausea, No. (%)	12 (26)	3 (9)	.02
Vomiting, No. (%)	4 (9)	0	.05
Diarrhea, No. (%)	3 (7)	0	.09
Serious adverse effects requiring admission, No. (%)	7 (15)	0	.007
Gastrointestinal hemorrhage, No. (%)	5 (11)	0	<.05
Shortness of breath, No. (%)	1 (2)	0	.98
Chest pain, No. (%)	1 (2)	0	.98

\*Percentages may not sum to 100, because of rounding.

patients, the prednisolone group would also have had some significant adverse events. Finally, the use of placebo injections is artificial and not standard practice. The use of placebo was important to ensure complete blinding but introduces the problem of artificiality. To what extent this limits application to clinical practice is not clear.

## DISCUSSION

This is the first double-blind randomized placebo-controlled study comparing commonly used, inexpensive, and easily available indomethacin and prednisolone in the treatment of acute goutlike arthritis. Our results indicate that the treatment of acute goutlike arthritis with commonly prescribed doses and frequencies of prednisolone and indomethacin produces similar pain relief. However, patients in the prednisolone group took significantly more acetaminophen than the indomethacin group as an adjunct for pain relief. Prednisolone supplemented with acetaminophen may be as effective as indomethacin in relieving pain. Patients taking prednisolone experienced far fewer serious or other adverse effects compared with patients taking indomethacin.

Although NSAIDs have been recommended as the first-line therapy for acute gouty arthritis,<sup>25</sup> there have been some studies on the role of steroid in the treatment of the condition. In a small preliminary study, it was suggested that a short course of oral corticosteroid therapy could be used effectively for acute gout when NSAIDs are contraindicated.<sup>16</sup> Subsequently, in another small study of 27 patients, single intramuscular injections of betamethasone, intravenous methylprednisolone, or oral diclofenac resulted in prompt and equal improvement.<sup>26</sup> Glucocorticoid therapy was well tolerated. The sample size was small, adverse effects were not reported, and oral corticosteroids were not used. In another small study (27 patients), the safety and effectiveness of intramuscular triamcinolone in the treatment of acute gout were also noted.<sup>27</sup>

A review article by Kim et al<sup>1</sup> reported that therapies available for managing acute gout, which included corticotropin, corticosteroids, colchicines, and NSAIDs, were associated with significant adverse events. However, in our study, we found that there were no cases of upper gastrointestinal bleeding in the group treated with prednisolone, whereas 5 (11%) patients in the indomethacin group developed upper gastrointestinal bleeding. Although none of the patients died because of the adverse effects, the occurrence of upper gastrointestinal bleeding, especially in the elderly, is a cause of significant morbidity.<sup>9-12</sup>

The pain score at rest and during activity followed a similar pattern and trend of improvement in both the prednisolone and indomethacin groups. However, patients in the prednisolone group used slightly more acetaminophen, suggesting that prednisolone alone may not be enough to relieve the pain associated with the disease. Studies that compared cyclooxygenase-2 (COX-2) inhibitors with NSAIDs found that the former had a similar comparable efficacy but better tolerability.<sup>28-30</sup> However, COX-2 inhibitors are expensive and are less accessible to the general population. Even more important is the concern about the cardiovascular safety of COX-2 inhibitors.<sup>28,31,32</sup> The use of corticosteroids in the treatment of acute gout has also been known to be effective. Corticosteroids have been used clinically in the treatment of a large variety of conditions, ranging from allergic or ectopic diseases, asthma, and connective tissue diseases to other inflammatory conditions.

Analgesic recommendations usually rank corticosteroids as a second line of treatment, whereas the NSAIDs are usually tried first.<sup>4,25</sup> There are several possible reasons for physicians' reluctance to use corticosteroids. Physicians have more experience with NSAIDs in the treatment of gout. In addition, corticosteroids have received bad publicity in terms of their numerous long-term adverse effects such as Cushing syndrome, osteoporosis, diabetes mellitus, and hypertension. The recent report of avascular necrosis after use of high-dose methylprednisolone in the treatment severe acute respiratory syndrome is another vivid example.<sup>33</sup>

Our results are in line with epidemiologic reports that acute gouty arthritis most commonly affects elderly patients and that the risk of serious gastrointestinal toxicity of NSAIDs is higher in this age group.<sup>8</sup> According to the findings in our study, we recommend that moderate doses of oral prednisolone supplemented with oral acetaminophen be considered as first-line therapy in the treatment of acute gout.

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*Supervising editor:* Richard C. Dart, MD, PhD

*Author contributions:* CYM had the idea for the study and has overseen the entire planning, execution, analysis, and preparation of article. PAC obtained approval. He is guarantor of the work. ITFC, PAC, and THR participated in the planning, execution, and analysis. THR prepared the statistical analysis. CYM wrote the first draft of the article, and all authors have

contributed to the final version. CYM takes responsibility for the paper as a whole.

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*Address correspondence:* Chi Yin Man, MD, Accident and Emergency Medicine Academic Unit, Trauma and Emergency Centre, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China; 852-2632-1033, fax 852-2648-1469; E-mail thrainer@cuhk.edu.hk.

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