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Comparison of Prednisolone, Etoricoxib, and Indomethacin in Treatment of Acute Gouty Arthritis: An Open-Label, Randomized, Controlled Trial

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Background: At present there are several kinds of medicine for treating acute gout arthritis (AGA). This study compared the efficacy and safety of prednisolone, etoricoxib, and indomethacin in the treatment of AGA.

Material/Methods: This was an open-label, randomized, active-comparator study in patients with AGA. Patients were randomized to 4 days of prednisolone 35 mg qd, etoricoxib 120 mg qd, or indomethacin 50 mg tid. The primary efficacy endpoint was the reduction of self-assessed pain in the index joint from baseline. Secondary endpoints included changes in physician's assessment of tenderness, erythema, swelling, and joint activity; patient assessment of response to therapy; and safety.

Results: We analyzed 113 patients. Baseline demographics were comparable among treatment groups. Oral prednisolone, etoricoxib, and indomethacin were similarly effective in improving pain, tenderness, and joint activity over 4 days. For inflammation, oral prednisolone, etoricoxib, and indomethacin were similarly effective in reducing erythema, but prednisolone might be more effective in reducing swelling than indomethacin. The patient response to therapy was similar in the 3 groups. There were more total adverse events with indomethacin compared with the other 2 drugs.

Conclusions: Efficacy was comparable among prednisolone, etoricoxib, and indomethacin for the treatment of AGA. Prednisolone might be more effective in reducing inflammation and it had a better safety profile.

MeSH Keywords: Arthritis • Arthritis, Gouty • Indomethacin • Inflammation • Prednisolone

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Background

Gouty arthritis is the most common inflammatory joint disease in men aged >40 years [1], with an overall global age-standardized prevalence of 0.08%, or 0.13% in men and 0.03% in women [2]. Gouty arthritis is a joint disease caused by deposition of monosodium urate, associated with purine metabolic disorder [3–5]. The progress of gout generally consists of 3 stages: hyperuricemia without symptoms, gout attacks with intermittent periods without symptoms, and long-term chronic gout without remission [6]. Gout itself may be disabling [7], as hyperuricemia may lead to renal failure [3]. Although pain may be the first complaint of patients with gout, an effective treatment should take into account both pain and potential inflammation [8,9]. The specific mechanisms leading to the inflammatory response of gouty arthritis are not fully understood. A study [10] found that the environmental toxin 4-Nonylphenol may promote an inflammatory response in inflammatory bowel disease, but whether it plays a role in the inflammatory response of the gout arthritis is not clear.

At present, non-steroidal anti-inflammatory drugs (NSAIDs) are the main treatment for gout, and these drugs are not only used for analgesia, but also for inhibiting inflammation [3,11]. The effect of indomethacin in the treatment of AGA is generally accepted, and its common dosage is 50 mg 3 times a day [12]. Although the tolerance of indomethacin is not good, it is still the criterion standard drug for the treatment of AGA [3]. However, many clinical studies found that indomethacin has various adverse effects (AEs) [13–16], and the gastrointestinal (GI) tract AEs are particularly significant [17].

Selective cyclooxygenase (COX)-2 inhibitors were developed in response to the demand for NSAIDs with less AEs. These agents mainly inhibited COX-2 enzyme, which catalyzes the synthesis of prostaglandin and participates in inflammatory reaction [18], while COX-1 was preserved to protect the integrity of the GI mucosa [18]. Selective COX-2 inhibitors have similar effects on analgesia and anti-inflammatory effects as do non-selective NSAIDS, but the GI tract adverse effects are greatly reduced [17,19]. Etoricoxib is a very effective selective COX-2 inhibitor for treating acute gout [14–16].

On the other hand, some authors suggested that systemic corticosteroids might be a safe alternative, particularly in elderly people [9,11]. A trial has shown that oral prednisolone 35 mg qd for 5 days was well tolerated, and had the same efficacy as naproxen 500 mg bid for the management of acute gout [20]. This finding was consistent with the results of another randomized double-blind study [13] showing that prednisolone plus paracetamol was as effective as indomethacin plus paracetamol in patients with gout.

So far, previous studies compared the effects of prednisolone with indomethacin and etoricoxib with indomethacin, but there is no study comparing these three drugs for treating AGA. Therefore, the aim of the present randomized, open-label, active-comparator, controlled trial was to compare the analgesic efficacy, anti-inflammatory efficacy, and tolerability of prednisolone 35 mg qd, indomethacin 50 mg tid, and etoricoxib 120 mg qd for the treatment of AGA.

Material and Methods

Study design

This was an open-label, randomized, controlled, parallel-group trial in patients with AGA to compare the efficacy and safety of prednisolone, etoricoxib, and indomethacin in the treatment of AGA. The study was carried out at the Department of Endocrinology of Nanfang Hospital affiliated to Southern Medical University between April 2015 and August 2015. The study was on the approval of the ethical committee of the Nanfang Hospital affiliated to Southern Medical University. All the patients signed the informed consent. The study was registered at the Chinese Clinical Trials Register (#ChiCTR-IPR-15006269)

Patients

One hundred and fifty inpatients aged ≥18 years with AGA within 72 h of onset were consecutively screened. These patients were diagnosed with gout according to the clinical criteria of the 1977 American College of Rheumatology classification criteria [21].

Inclusion criteria were: 1) gout attacks within 72 h of screening; 2) The degree of pain in the index joint was at least moderate (2 on a 5-point Likert scale) at baseline; and 3) the index joint was defined as the joint that was the most painful at the time of randomization. Exclusion criteria were: 1) chronic gouty arthritis stage; 2) clinical suspicion of joint infection or other joint disease; 3) polyarticular gout involving more than four joints; 4) coronary heart disease, heart failure, gastrointestinal hemorrhage, or a history of peptic ulcer; 5) the digestive tract operation history, inflammatory bowel disease, or malignant tumor; 6) using NSAIDs or corticosteroids within 72 h before the baseline assessments; 7) allergic to any of the study drugs; 8) abnormal liver function with transaminase levels higher than 2 times the upper limit of normal; or 9) renal insufficiency with serum creatinine levels greater than 200 μmol/L.

One hundred-thirty-two patients were randomly assigned (using computer-generated tables and sequential sealed envelopes prepared by a statistician independent to the trial) to receive

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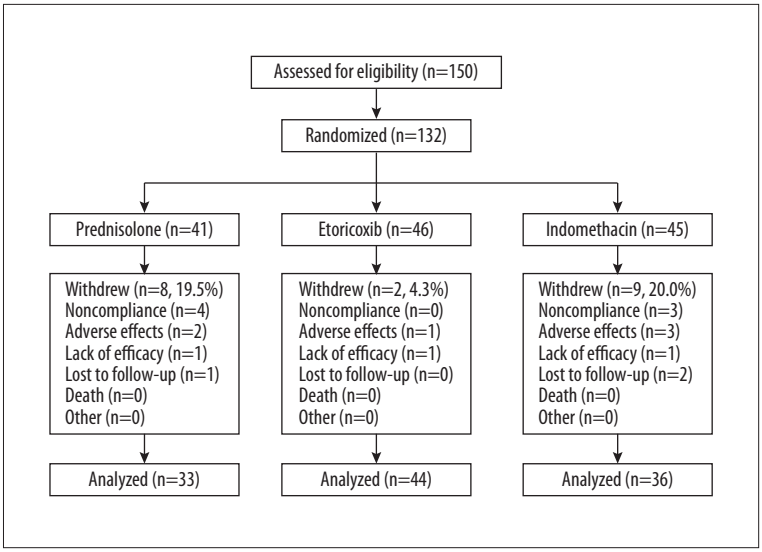

Figure 1. Patient flowchart.

either prednisolone (35 mg qd, Tianjin Lisheng Pharmaceutical Co., Ltd., Shenzhen, China; n=41), etoricoxib (120 mg qd, Merck Frost, Montreal, Canada; n=46), or indomethacin (50 mg tid, Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China; n=45).

Because AGA is self-limiting, only the first 4 days of treatment was analyzed for drug efficacy. Assessment of pain intensity at baseline was performed without the use of analgesic therapy. All patients were followed up by the same physician who observed and studied them during the 4 days. This study allowed patients to continue (without dose change) low-dose aspirin (≤100 mg daily) and if patients had used allopurinol for at least 4 weeks, they were allowed to continue its use.

Endpoints

The primary endpoint was the reduction of pain in the index joint as experienced by the patient. Secondary endpoints included the changes of physician's assessment of tenderness, erythema, swelling and joint activity from baseline, and also included the patients' global assessment of response to therapy. Safety was assessed by observing AEs.

The degree of pain in the index joint was represented by a 5-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe, 4=extreme) recorded by the patients in a diary at baseline [before start of treatment on Day 1 (h 0)], and probably 4 h after the first dose of drugs on days 2 to 4. The physician evaluated the following indicators: joint tenderness on palpation or passive movement of the index joint (3-point Likert scale: 0=no pain, 1=patient states 'there is pain', 2=patient states 'there is pain' and withdraws his affected limbs), joint erythema (3-point Likert scale: 0=absent, 1=not assessable, 3=present), joint swelling (4-point Likert scale: 0=no swelling, 1=palpable, 2=visible, 3=bulging beyond the joint margins) and joint activity (4-point Likert scale: 0=no restriction, 1=moderately restricted, 2=significantly restricted, not engaging in general activities, 3=unbearable, cannot take care of themselves) at baseline and at follow-up visits. The physician also assessed patients' global response to treatment on a 5-point Likert scale (0=very good, 1 =good, 2=fair, 3= poor, 4= very poor) at the end of the study on Day 4.

Adverse effects

AEs during treatment were recorded. AEs mainly included gastric or abdominal pain, dizziness, edema, fatigue or drowsiness, and dry mouth.

The recurrence of gouty arthritis was diagnosed according to the 1977 American College of Rheumatology classification criteria [21]. The degree of pain in the index joint had to be at least mild (2 on a 5-point Likert scale).

Statistical analysis

SPSS 20.0 for Windows (IBM, Armonk, NY, USA) was used for analysis. For baseline characteristic data in the three groups, normally distributed data are presented as the mean ± standard deviation (SD) and were tested using one-way ANOVA. Non-normally distributed data are presented as median (range) and were analyzed using the Kruskall-Wallis test. The chi-square test was used for frequencies analysis. For repeated measure data (pain, tenderness, erythema, swelling, and activity), a general linear model was chosen to observe each of the outcome variables (pain, tenderness, erythema, swelling, and activity) across changing time points to determine the treatment effects within and between groups. Significance was defined as a $P<0.05$.

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Table 1. Characteristics of the patients.

Variable	Prednisolone	Etoricoxib	Indomethacin	P
Age (years, mean±SD)	44.03±15.37	44.43±15.08	43.81±12.29	0.981
Men, n (%)	100%	100%	97.2%	0.343
History of gout (years, median (range))	2.00 (0–8)	2.00 (0–8)	2.00 (0–17)	0.892
BMI (kg/m^2, mean ±SD)	25.02±2.98	25.00±3.37	26.40±2.88	0.132
Uric acid (pre-treatment) (μmol/L, mean ±SD)	550.41±122.57	528.71±135.44	523.58±118.15	0.642
Number of attacks in past year (median (range))	2.00 (0.2–48)	1.00 (0.5–48)	1.00 (0–48)	0.814
Onset time, n (%)				0.279
≤24 h	8 (24.2%)	6 (13.6%)	6 (16.7%)	
≤48 h	19 (57.6%)	25 (56.8%)	24 (66.7%)	
≤72 h	6 (18.2%)	13 (29.5%)	6 (16.7%)	
Index joint				0.839
Metatasophalangeal joint 1	13 (39.4%)	16 (36.4%)	15 (41.7%)	
Other foot joints, ankle, or knee	19 (57.6%)	27 (61.4%)	21 (58.3%)	
Elbow, wrist, or hand	1 (3.0%)	1 (2.3%)	0	
Patients' assessment of pain on baseline, n (%)				0.625
None	0	0	0	
Mild	0	0	0	
Moderate	7 (21.2%)	17 (38.6%)	13 (36.1%)	
Severe	19 (57.6%)	16 (36.4%)	15 (41.7%)	
Extreme	7 (21.2%)	11 (25.0%)	8 (22.2%)	
Tenderness, n (%)				0.602
No pain	1 (3.0%)	3 (6.8%)	2 (5.6%)	
Patient states 'there is pain'	14 (42.4%)	21 (47.7%)	18 (50.0%)	
Patient states 'there is pain' and withdraws	18 (54.6%)	20 (45.5%)	16 (44.4%)	
Erythema, n (%)				0.972
Absent	2 (6.1%)	2 (4.5%)	4 (11.1%)	
Not assessable	13 (39.4%)	17 (38.6%)	11 (30.6%)	
Present	18 (54.5%)	25 (56.8%)	21 (58.3%)	
Joint swelling, n (%)				0.029
No swelling	0	1 (2.3%)	0	
Palpable	7 (21.2%)	15 (34.1%)	13 (36.1%)	
Visible	7 (21.2%)	13 (29.5%)	15 (41.7%)	
Bulging beyond joint margins	19 (57.6%)	15 (34.1%)	8 (22.2%)	
Activity, n (%)				0.266
No restricted	0	0	0	
Moderate restricted	6 (18.2%)	11 (25.0%)	12 (33.3%)	
Significantly restricted	12 (36.4%)	19 (43.2%)	12 (33.3%)	
Unbearable, cannot take care of themselves	15 (45.4%)	14 (31.8%)	12 (33.3%)	

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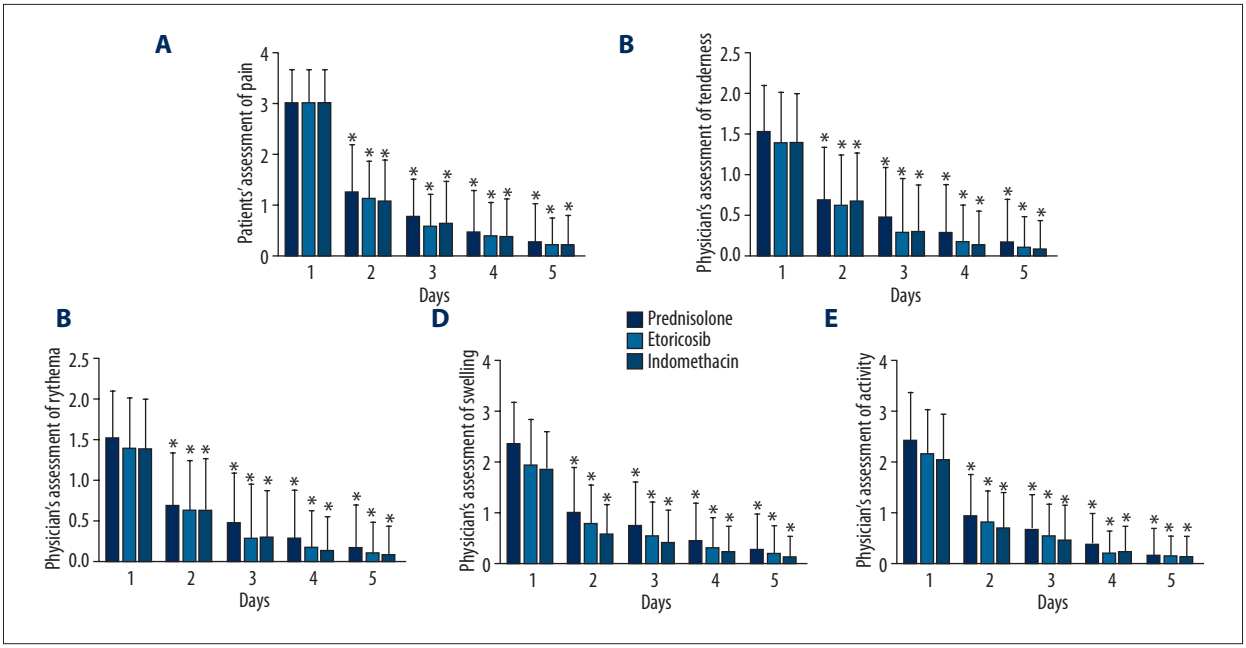

Figure 2. (**A**) Mean change in pain of the index joint from baseline (primary endpoint). * P<0.001 *vs.* baseline of the same group. (**B**) Mean change in tenderness of the index joint from baseline. * P<0.001 *vs.* baseline of the same group. (**C**) Mean change in erythema of the index joint from baseline. * P<0.001 *vs.* baseline of the same group. (**D**) Mean change in swelling of the index joint from baseline. The decrease in the swelling index was better with prednisolone than with indomethacin (P=0.01). * P<0.001 *vs.* baseline of the same group. (**E**) Mean change in activity of the index joint from baseline. * P<0.001 *vs.* baseline of the same group.

Results

Characteristics of the patients

Figure 1 presents the patients' flowchart: 132 patients were randomized, and 113 patients were finally analyzed. The baseline demographic and clinical characteristics were similar in the 3 groups, except for joint swelling (Table 1).

Treatment efficacy

Figure 2 show that all 3 drugs significantly decreased the symptoms of acute gout attack in time—patients' assessment of pain (P<0.05, Figure 2A), physician's assessment of tenderness (P<0.05, Figure 2B), erythema (P<0.05, Figure 2C), swelling (P<0.05, Figure 2D), and activity (P<0.05, Figure 2E).

Results showed that oral prednisolone, etoricoxib, and indomethacin were similar in the efficacy of reducing pain (P>0.05, Table 2) and tenderness (P>0.05, Table 2) in AGA over 4 days. In terms of relieving inflammation, oral prednisolone, etoricoxib, and indomethacin were similar in the efficacy of reducing erythema (P>0.05, Table 2). However, prednisolone might be more effective to reduce swelling compared with indomethacin (P<0.05, Table 2). The 3 drugs were equally effective in improvement of joint activity (P>0.05, Table 2). The patients' global response to therapy were similar among the 3 groups (P>0.05, Table 3).

Recurrence and adverse effects

There was no significant difference in the recurrence rate 1 month later among the 3 treatment groups (P>0.05, Table 4). Total AEs in the indomethacin group were significantly more frequent compared with the other 2 groups (P<0.05, Table 4).

Discussion

The purpose of the present study was to compare the efficacy and safety of prednisolone, etoricoxib, and indomethacin in the treatment of pain and inflammation in AGA. Results showed that oral prednisolone, etoricoxib, and indomethacin were similar in the efficacy of improving pain, tenderness, and joint activity in AGA over 4 days. For inflammation, oral prednisolone, etoricoxib, and indomethacin were similar in the efficacy of relieving erythema, but prednisolone might be more effective to reduce swelling compared with indomethacin. The patients' evaluation of response to treatment efficacy was similar in the 3 groups. There were more AEs with indomethacin compared with the 2 other drugs. These results suggest that each treatment was as effective as the others,

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Table 2. Comparison of the mean changes of patients' assessment of pain, physician's assessment of tenderness, erythema, swelling, and activity in the three groups.

Group	Assessment contents	LS mean difference (SE)	95% CI	P
Prednisolone *vs.* Etoricoxib	Pain	0.12 (0.131)	–0.15 to 0.38	0.383
	Tenderness	0.11 (0.097)	–0.08 to 0.31	0.246
	Erythema	0.06 (0.111)	–0.16 to 0.28	0.586
	Swelling	0.21 (0.125)	–0.04 to 0.46	0.092
	Activity	0.15 (0.108)	–0.06 to 0.36	0.170
Prednisolone *vs.* Indomethacin	Pain	0.11 (0.138)	–0.16 to 0.39	0.415
	Tenderness	0.13 (0.102)	–0.08 to 0.33	0.222
	Erythema	0.11 (0.116)	–0.12 to 0.34	0.343
	Swelling	0.33 (0.131)	0.07 to 0.58	0.014
	Activity	0.19 (0.113)	–0.03 to 0.42	0.088
Etoricoxib *vs.* Indomethacin	Pain	0.00 (0.128)	–0.26 to 0.25	0.984
	Tenderness	0.01 (0.095)	–0.18 to 0.20	0.903
	Erythema	0.05 (0.108)	–0.16 to 0.26	0.645
	Swelling	0.11 (0.122)	–0.13 to 0.35	0.353
	Activity	0.04 (0.105)	–0.16 to 0.25	0.669

SE – standard error; CI – confidence interval.

Table 3. Patients' response to treatment.

Patients' response to treatment, n (%)	Prednisolone	Etoricoxib	Indomethacin	P
Very good	16 (48.5%)	23 (52.3%)	16 (44.4%)	0.743
Good	11 (33.3%)	15 (34.1%)	14 (38.9%)	
Fair	2 (6.1%)	5 (11.4%)	3 (8.3%)	
Poor	2 (6.1%)	0	2 (5.6%)	
Very poor	2 (6.1%)	1 (2.3%)	1 (2.8%)	

and that the choice of a treatment should be made based on each patient's condition and comorbidities.

The 2012 ACR guidelines [11] propose the single use of NSAIDs, systemic corticosteroids, and oral colchicine, but without priority of 1 drug over the others, and recommend that physicians choose the drug based on patient preference, previous treatment reaction, and complications. However, since the therapeutic and toxic doses are very similar, colchicine easily leads to AEs [9]. Therefore, in the present study, colchicine was not selected as a study drug.

Instead, we selected 2 NSAIDs as the study drugs. One was etoricoxib, which has been confirmed with excellent efficacy in the acute phase of gout [14–16], and the other is the criterion standard drug, indomethacin. Oral administration of high doses of NSAIDs is recommended as the first-line therapy for AGA [11]. Results showed that etoricoxib had an equal efficacy with indomethacin, indicating that a selective, potent, and rapid COX-2 inhibitor is effective enough to treat AGA, which has been confirmed in several previous studies [14–16].

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Table 4. Recurrence and adverse effects.

	Prednisolone	Etoricoxib	Indomethacin	P
Recurrence	17 (52.2%)	26 (58.1%)	20 (54.2%)	0.621
Total adverse effects	2/33 (6.1%)	3/44 (6.8%)	11/36 (30.6%)	0.003
Gastric or abdominal pain	2/33 (6.1%)	0	3/36 (8.3%)	0.170
Dizziness	0	2/44 (4.5%)	4/36 (11.1%)	0.116
Edema	0	1/44 (2.3%)	1/36 (2.8%)	0.648
Fatigue or drowsiness	0	0	2/36 (5.6%)	0.113
Dry mouth	0	0	1/36 (2.8%)	0.340

The drawbacks of NSAIDs are especially important in patients with gout because these patients are already at high risk of GI tract adverse effects [22]. Indeed, most of them are middle-aged or elderly [23], and many have comorbidities, such as renal and cardiovascular diseases [24,25]. In the indomethacin group, 30.6% of patients experienced AEs, but in the etoricoxib group only 6.8% of patients experienced AEs, showing that although both drugs are NSAIDS, the safety of etoricoxib is significantly better than that of indomethacin.

The efficacy of prednisolone in reducing pain was comparable to indomethacin after 4 days of treatment. In terms of reducing joint swelling, the effect of prednisolone was significantly better than that of indomethacin, which implies that prednisolone may be better at reducing inflammation than indomethacin. Corticosteroids have a significant non-specific inhibition role on the inflammation caused by various factors and in various stages. Some studies [13,20] have confirmed that the early use of prednisolone can quickly relieve the symptoms and signs of acute attacks, and that it is a safe, effective, and inexpensive method of treatment. In a study [13], the prednisolone group patients used slightly more acetaminophen as an adjunct for reducing pain, showing that prednisolone alone may lack enough efficacy to relieve pain in AGA. However, in the present study, the effects on pain relief were similar between the 2 drugs.

Generally, physicians have reservations about the use of prednisone, for several reasons. Usually, physicians with more experience use NSAIDs to treat AGA. In addition, the long-term use of corticosteroids may cause many AEs, such as Cushing syndrome, diabetes mellitus, hypertension, and osteoporosis. Corticosteroids can only cause severe AEs when used long-term at high doses; if they are taken in low to moderate doses for short periods, few AEs occur. The GI tract AEs of prednisone also appear to be less severe than those of NSAIDs [26]. Long-term AEs, such as diabetes mellitus and osteoporosis, are not related to AGA treatment, due to the very short treatment time. In the present study, the AE incidence rate in the prednisolone group (6.1%) was significantly lower than in the indomethacin group (30.6%), consistent with a previous study [13].

The present study is not without limitations. First, the sample size was small and from a single center. Second, the diagnosis was mainly made based on clinical symptoms, and in most patients, joint aspiration or ultrasound examination was not performed. In routine clinical practice, however, most patients presenting with gout-like arthritis are treated according to clinical symptoms but not joint aspiration, unless there is a high suspicion of infectious arthritis or in cases with atypical features. Third, we only observed the first 4 days of drug treatment. Because AGA is self-limited, this design focused the efficacy of drugs on the initial days of the attack, and avoided the impact of spontaneous remission, which could interfere with the efficacy analysis. Finally, we selected patients within 72 h of onset, and most within 48 h. However, the 2012 ACR guidelines [11] recommend that AGA should be treated within 24 h after onset. However, patients' reluctance to go to the hospital and to pay medical fees may play a role in patients presenting more than 24 h after symptom onset, as well as patients living far from the hospital.

Conclusions

In conclusion, efficacy was comparable among prednisolone, etoricoxib, and indomethacin in treating AGA. Prednisolone might be more effective in reducing inflammation and was better tolerated.

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Conflict of interest

All authors declare that they have no conflict of interest.

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