Comparison of intramuscular compound betamethasone and oral diclofenac sodium in the treatment of acute attacks of gout

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SUMMARY

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of acute gouty arthritis but have the risk of gastrointestinal bleeding and cardiovascular toxicity. Glucocorticoid was as effective as oral NSAIDs in the initial treatment of gout arthritis of patients intolerant of NSAIDs. However, whether glucocorticoid has the same or preferable effect as oral NSAIDs on patients with acute gouty arthritis irrespective of gastrointestinal and cardiovascular risks factor remains unknown. This study was to compare the efficacy, safety and tolerance of compound betamethasone (diprospan) 7 mg intramuscular injection (i.m.) once for all during the study with diclofenac sodium 75 mg twice a day in the treatment of acute gouty arthritis. Methods: Sixty patients with acute gouty arthritis were randomised (1 : 1) to receive compound betamethasone 7 mg i.m. once for all during the study or diclofenac sodium 75 mg twice a day for 7 days in this open-label study. Pain intensity, tenderness, swelling and global assessment of response to therapy were collected as end-points for the treatment. Results: The mean change in pain intensity from baseline to Day 3 and Day 7 in both treatment groups demonstrated that compound betamethasone had preferable efficacy over diclofenac sodium on Day 3 and comparable efficacy on Day 7. The compound betamethasone group had fewer adverse effects (AEs) than diclofenac sodium group. No statistically significant differences were observed about serum uric acid levels at different pain intensity at baseline. Conclusions: A single dose of compound betamethasone may be better than diclofenac sodium for the treatment of acute gouty arthritis.

Introduction

Gout is a disorder of purine metabolism and results from deposition of monosodium urate crystal in and around the joints caused by hyperuricaemia. Acute attack of gout can cause severe pain and non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs for its treatment (1).

However, NSAIDs can cause gastrointestinal bleeding and cardiovascular toxicity (2,3), and in some conditions they are not as effective as expected. Latest studies demonstrated that oral prednisolone was as effective as oral NSAIDs in the initial treatment of gout arthritis of patients intolerant of NSAIDs (4,5). However, whether glucocorticoid has the same or preferable effect as oral NSAIDs on patients with acute gouty arthritis irrespective of gastrointestinal and cardiovascular risks remains unknown.

Compound betamethasone (diprospan) is a combination of quick-acting betamethasone sodium phosphate and long-acting betamethasone dipropionate which can reduce the production of inflammatory mediator. Whether intramuscular administration of this kind of corticosteroid has a preferable effect than oral NSAIDs remains unknown. The aim of this study was to evaluate the efficacy and safety of intramuscular injection (i.m.) with compound betamethasone 7 mg once for all during the study vs. oral administration with diclofenac sodium 75 mg twice a day in the treatment of acute gouty arthritis, and to compare the toleration of patients in the two kinds of treatment.
Methods
Study design and patients
We undertook an open-label parallel-group randomised trial at Qilu Hospital of Shandong University between July 2009 and July 2012. Diagnosis of gout was based on the American College of Rheumatology criteria for primary gout (6). After screened, eligible patients were recruited into the study and randomised (1 : 1) to receive compound betamethasone (diprospan) 7 mg i.m. only once during the study, or diclofenac sodium 75 mg oral administration twice a day for 7 days. Informed, written consent had been obtained from all patients. The study was performed according to the Declaration of Helsinki, and the procedures had been approved by ethics committee of Qilu Hospital of Shandong University.

Inclusion criteria: The patients who had an acute attack of gout within 24 h were enrolled into the study and the pain intensity of the involved joints was at least moderate (2 on a 5-point Likert scale) in the target joint at baseline. Pain intensity at baseline was assessed in the absence of analgesia. All the patients were in the stage of non-chronic gouty arthritis and the regular treatment preventing the flare of gout is unnecessary. All the patients were followed up by the same physician who observed and studied them during the 7 days and all the patients in both the groups were inpatients hospitalised for other diseases such as fracture, osteoarthritis, rheumatoid arthritis, diabetes mellitus and cerebrovascular disease.

Exclusion criteria: patients were excluded if they had ischaemic heart disease, heart failure, gastrointestinal haemorrhage or active gastrroduodenal ulceration less than 90 days before being screened, inflammatory bowel disease, gastric surgery, erosive oesophagitis, gastric-outlet obstruction, or active malignant diseases. Other conditions included allergy to diclofenac sodium and compound betamethasone, serum alanine transaminase or aspartate transaminase concentrations more than twice and serum creatinine concentration more than the upper limit of normal (according to the central laboratory definition).

Study assessment parameters and efficacy end-points
Pain intensity of the affected joints [using a 5-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme)] was recorded by patients in a diary at baseline [before start of treatment on Day 1 (h 0)], and 4 h (h 4) after treatment with the first dose of medication each day during the study. Patients’ global assessment of response to therapy was also recorded by each patient on a 5-point Likert scale (0 = very good, 1 = good, 2 = fair, 3 = poor, 4 = very poor) 4 h after the first dose of medication each day.

In this study, the physician assessed: joint tender-ness on palpation or passive movement of the affected joints (4-point Likert scale: 0 = no pain, 1 = patient states ‘there is pain’, 2 = patient states ‘there is pain’ and winces, 3 = patient states ‘there is pain’ and winces and withdraws), joint swelling (4-point Likert scale: 0 = no swelling, 1 = palpable, 2 = visible, 3 = bulging beyond the joint margins) as well as the global response to treatment on a 5-point Likert scale (0 = very good, 1 = good, 2 = fair, 3 = poor, 4 = very poor).

The end of study visit occurred on Day 7 when patients completed the study or at the early termination visit if patients discontinued the treatment. The efficacy end-points included the mean changes in pain intensity, patients’ global assessment of response to therapy, physician’s assessment of tenderness, swelling and the global assessment of response to therapy from baseline to Day 3 and Day 7 or termination visit of the study.

Adverse effects
All adverse events (AEs) and serious AEs (SAEs) were recorded. AEs mainly included gastrointestinal reaction and cardiovascular toxicity related to NSAIDs and hyperglycaemia related to glucocorticoid.

Statistical analysis
SPPS 13.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. Data were expressed as mean ± SD when normally distributed and median ± IQR when non-normally distributed. All the data were analysed with the homogeneity test. The differences between compound betamethasone group and diclofenac sodium group were compared by two independent sample t-tests or non-parametric tests. The comparison of serum uric acid (SUA) levels at different pain intensity of the affected joints at baseline was performed by one-way analysis of variance. A probability value, p < 0.05 was considered statistically significant.

Results
A total of 60 patients were randomised to receive treatment with compound betamethasone 7 mg i.m. once for all during the study (n = 30), or diclofenac sodium 75 mg oral administration twice a day for 7 days (n = 30). All the patients completed the study without discontinuing treatment. At baseline, there was no significant difference in terms of demographic and disease characteristics between two
groups (Table 1). The statistic of pain intensity was shown in Figure 1.

The mean change in pain intensity from baseline to Day 3 in both treatment groups, demonstrated that compound betamethasone 7 mg i.m. only once had preferable efficacy over diclofenac sodium 75 mg oral administration twice a day (Table 2) from Day 1 to Day 3 (p < 0.05) and comparable efficacy from Day 4 to Day 7 (p > 0.05) (Figure 2). The percentage of patients who reported severe or extreme pain at baseline (compound betamethasone, 90.0%; diclofenac sodium, 93.3%) was reduced to 56.7% at the first assessment (4 h after start of treatment) in compound betamethasone group and 73.3% in diclofenac sodium group, respectively. The patients’ global assessment of response to therapy revealed that compound betamethasone was more effective than diclofenac sodium on Day 3 (p = 0.013). Significant differences in the physician’s assessments of global response to therapy, joint swelling and tenderness on Day 3 were also observed between treatments (p < 0.05). No significant differences were observed between the treatments for all the five assessment indexes on Day 7 (p > 0.05).

The compound betamethasone group had fewer AEs than the diclofenac sodium group. Hyperglycaemia and sleep disorder mainly occurred to a few patients treated with compound betamethasone and gastrointestinal discomforts were more frequent in patients with diclofenac sodium (Table 3). There was no SAE reported during the study in the two groups.

The average SUA level was 450.0 ± 211.6, 498.8 ± 139.7 and 526.0 ± 135.2 μmol/l, respectively, and the corresponding pain intensity of the affected joints was 2, 3 and 4 at baseline in patients with gout. No significant differences in SUA levels at different pain intensity of the affected joints at baseline (p = 0.501) were observed (Figure 3).

Discussion

Both European League Against Rheumatism guidelines and American College of Rheumatology recommend that oral NSAIDs are the first line agents for systemic treatment of acute gout. In the absence of contraindications, an NSAID is a convenient and well-accepted option (7,8). In our present study, we selected diclofenac sodium, a non-selective COX-2 inhibitor as control for acute attack of gout. Diclofenac sodium acts locally and systemically as an anti-inflammatory agent and has convincing effect of relieving acute pain (9).

Compared with NSAID, glucocorticoid showed a preferable or comparable effect. Man et al. reported

| Table 1 | Demographic and disease characteristics of patients in two groups at baseline |
|---------|---------------------------|----------------------------|-----------------|
| Item                              | Compound betamethasone (n = 30) | Diclofenac sodium (n = 30) | p-value |
| Age (years), mean ± SD            | 52.3 ± 13.5                   | 54.2 ± 15.1                 | 0.32    |
| Men, n (%)                        | 29 (96.7%)                    | 29 (96.7%)                  |         |
| Joint swelling, n (%)             |                                |                            |         |
| No swelling                       | 0                             | 0                           |         |
| Palpable                          | 8 (26.7%)                     | 6 (20.0%)                   |         |
| Visible                           | 13 (43.3%)                    | 16 (53.3%)                  |         |
| Bulging beyond joint margins      | 9 (30.0%)                     | 8 (26.7%)                   |         |
| Erythema, n (%)                   |                                |                            |         |
| Present                           | 29 (96.7%)                    | 29 (96.7%)                  |         |
| Absent                            | 1 (3.33%)                     | 1 (3.33%)                   |         |
| Pain intensity assessment, n (%)  |                                |                            |         |
| None                              | 0                             | 0                           |         |
| Mild                              | 0                             | 0                           |         |
| Moderate                          | 3 (10.0%)                     | 2 (6.7%)                    |         |
| Severe                            | 13 (43.3%)                    | 11 (36.7%)                  |         |
| Extreme                           | 14 (46.7%)                    | 17 (56.7%)                  |         |
| Distribution of affected joints, n (%) |                          |                            |         |
| First metatarsophalangeal joint   | 18 (60.0%)                    | 19 (63.3%)                  |         |
| Insteps                           | 6 (20.0%)                     | 7 (23.3%)                   |         |
| Ankles                            | 3 (10.0%)                     | 3 (10.0%)                   |         |
| Heels                             | 1 (3.33%)                     | 0                           |         |
| Knees                             | 2 (6.7%)                      | 1 (3.33%)                   |         |
| Uric acid (μmol/l), mean ± SD     | 499.5 ± 153.2                 | 518.1 ± 133.8               | 0.619   |
| Normal uric acid, n (%)           | 10 (33.3%)                    | 9 (30.0%)                   |         |
that oral prednisolone/acetaminophen combination was as effective as oral indomethacin/acetaminophen combination in relieving pain of acute gouty arthritis but was associated with fewer adverse effects (4). Another double-blind, randomised equivalence trial showed oral prednisolone and naproxen were equally effective in the initial treatment of gout arthritis over 4 days (5). As for glucocorticoid injections, two small sample studies showed that it was as safe and effective as NSAID in the treatment of acute gout, and was particularly useful to patients with contraindications to therapy with NSAIDs (10,11).

Glucocorticoid is widely recognised as an antagonistic regulator of inflammation induced by cytokines, and existing researches suggest that it would antagonise the majority of pro-inflammatory molecules throughout the genome. Compound betamethasone (diprospan) is an anti-inflammatory corticosteroid used for joint injections, gouty arthritis and many other problems that are responsive to corticosteroids. Quick-acting betamethasone sodium phosphate can quickly alleviate pain by promoting the production of anti-inflammatory cytokines and inhibiting the production of pro-inflammatory cytokines and long-acting betamethasone dipropionate can maintain such effect for about a week. In our present study, compound betamethasone 7 mg i.m. only once showed a comparable and more rapid effectiveness than diclofenac sodium 75 mg oral administration twice a day for 7 days. Though the two treatments resulted in a similar end-point on Day 7, compound betamethasone functioned more rapidly than diclofenac sodium. This means the patients treated with compound betamethasone endured shorter pain than those with diclofenac sodium. At the same time, compared with oral NSAID or glucocorticoid every day and intra-articular corticosteroids, compound betamethasone 7 mg i.m. once for all during the study is more convenient.

One even more important consideration is about the drug safety besides effectiveness. The NSAIDs use
was limited to some patients because of its gastrointestinal adverse effect (2) and cardiovascular risks (3). Therefore, alternative treatment options that are efficacious but better tolerated are desirable. Our present study demonstrated that compound betamethasone was well tolerated, resulting in fewer AEs than diclofenac sodium for the treatment of acute gout. Thus, compound betamethasone 7 mg i.m. once for all was safer than diclofenac sodium 75 mg oral administration twice a day for 7 days against acute attack of gout.

Table 2

The data of the other end-points except for pain intensity in both groups

|                         | Compound betamethasone 7 mg i.m. once for all | Diclofenac sodium 75 mg oral administration twice a day |
|-------------------------|-----------------------------------------------|--------------------------------------------------------|
|                         | Baseline | Day 3 | Day 7 | Baseline | Day 3 | Day 7 |
| **Physician’s assessments of study joint tenderness, n (%)** |          |       |       |          |       |       |
| 0                       | 0        | 8 (26.7%) | 28 (93.3%) | 0        | 2 (6.7%) | 26 (86.7%) |
| 1                       | 1 (3.3%) | 15 (50.0%) | 2 (6.7%) | 2 (6.7%) | 17 (56.7%) | 3 (10.0%) |
| 2                       | 14 (46.7%) | 6 (20.0%) | 0 | 9 (30.0%) | 10 (33.3%) | 1 (3.3%) |
| 3                       | 15 (50.0%) | 1 (3.3%) | 0 | 19 (63.3%) | 3 (10.0%) | 0 |
| **Physician’s assessments of study joint swelling, n (%)** |          |       |       |          |       |       |
| 0                       | 0        | 7 (23.3%) | 29 (96.7%) | 0        | 2 (6.7%) | 27 (90.0%) |
| 1                       | 8 (26.7%) | 16 (53.3%) | 1 (3.3%) | 6 (20.0%) | 17 (56.7%) | 3 (10.0%) |
| 2                       | 13 (43.3%) | 6 (20.0%) | 0 | 16 (53.3%) | 9 (30.0%) | 0 |
| 3                       | 9 (30.0%) | 1 (3.3%) | 0 | 8 (26.7%) | 2 (6.7%) | 0 |
| **Physician’s global assessment of response to therapy, n (%)** |          |       |       |          |       |       |
| 0                       | 0        | 10 (33.3%) | 28 (93.3%) | 2 (6.7%) | 26 (86.7%) |
| 1                       | 14 (46.7%) | 2 (6.7%) | 0 | 16 (53.3%) | 3 (10.0%) |
| 2                       | 5 (16.7%) | 0 | 0 | 10 (33.3%) | 1 (3.3%) |
| 3                       | 0        | 0 | 0 | 2 (6.7%) | 0 |
| 4                       | 1 (3.3%) | 0 | 0 | 0 | 0 |
| **Patient’s global assessment of response to therapy, n (%)** |          |       |       |          |       |       |
| 0                       | 0        | 10 (%) | 29 (96.7%) | 3 (10.0%) | 26 (86.7%) |
| 1                       | 12 (%) | 1 (3.3%) | 0 | 14 (46.7%) | 2 (6.7%) |
| 2                       | 6 (%) | 0 | 8 (26.7%) | 2 (6.7%) |
| 3                       | 1 (%) | 0 | 1 (3.3%) | 0 |
| 4                       | 1 (%) | 0 | 4 (%) | 0 |

Table 3

Incidence of adverse events, irrespective of relationship with study drug

|                         | Compound betamethasone 7 mg i.m. once (n = 30) | Diclofenac sodium 75 mg b.i.d (n = 30) |
|-------------------------|-----------------------------------------------|----------------------------------------|
| **AEs, n (%)**          | 4 (13.3%) | 8 (26.7%) |
| Related to study drug   | 3 (10.0%) | 6 (20.0%) |
| Discontinuation         | 0 | 0 |
| **SAEs, n (%)**         | 0 | 0 |
| **Most frequent AEs**   | Abdominal pain, n (%) | 0 | 3 (10.0%) |
| Nausea, n (%)           | 0 | 4 (13.3%) |
| Flatulence, n (%)       | 0 | 2 (6.7%) |
| Headache, n (%)         | 1 (3.3%) | 1 (3.3%) |
| Dizziness, n (%)        | 0 | 1 (3.3%) |
| Eyelid oedema, n (%)    | 0 | 2 (6.7%) |
| Hyperglycaemia, n (%)   | 2 (6.7%) | 0 |
| Sleep disorder, n (%)   | 1 (3.3%) | 0 |

AEs, adverse events; SAEs, serious adverse events.
Risk of acute gout increases with elevated urate concentration (12,13); however, many people with high serum urate never develop gout. Meanwhile, many patients with acute gout (11–49%) have normal SUA levels (14). Normal SUA at acute attack of gout resulted from UA either acting as a negative acute-phase reactant or increasing in renal excretion during acute episodes. SUA has limited diagnostic value, especially during an acute attack of gout (15). In our present study, 19 (31.7%) patients had normal SUA. No significant relationship was observed between SUA levels and pain intensity of the affected joints. Though some patients presented with normal SUA levels during the acute attacks of gout, almost all patients had a history of hyperuricaemia.

In conclusion, this study showed that compound betamethasone 7 mg i.m. once for all was more effective and had quicker effects than diclofenac sodium 75 mg oral administration twice a day for 7 days for acute attack of gout within 24 h. Two therapeutic regimens had comparable efficacy on Day 7. Compound betamethasone had better tolerance and fewer AEs compared with diclofenac sodium. SUA levels did not correlate with pain intensity of the affected joints. Based on these findings, this study suggests that a single dose of compound betamethasone may be a better regimen and an alternative option for the treatment of acute attack of gout.

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Author contributions

YK Zhang and H Yang contributed to this study: concept and design of the study, interpretation of results and data analysis/interpretation. LJ Song drafted the article, JY Zhang and YC Fan was responsible for critical revision of article. All authors read and approved the final manuscript.

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