Systemic corticosteroids for acute gout (Review)

Janssens HJ, Lucassen PLBJ, Van de Laar FA, Janssen M, Van de Lisdonk EH

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[Intervention Review]

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Hein J Janssens[1], Peter LBJ Lucassen[2], Floris A Van de Laar[3], Matthijs Janssen[4], Eloy H Van de Lisdonk[5]

[1]Lobith, Netherlands. [2]Department of General Practice and Family Medicine, Radboud University Medical Centre, Nijmegen, Netherlands. [3]Department of General Practice, 117 HAG, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands. [4]Rheumatology, Rijnstate Hospital Arnhem, Arnhem, Netherlands. [5]Department of General Practice and Family Medicine, 117 HAG, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands

Contact address: Hein J Janssens, Transeedijk 62, Lobith, 6915 XZ, Netherlands. h.janssens2@chello.nl.

A B S T R A C T

Background

Gout is one of the most frequently occurring rheumatic diseases, worldwide. Given the well-known drawbacks of the regular treatments for acute gout (non-steroidal anti-inflammatory drugs (NSAIDs), colchicine), systemic corticosteroids might be safe alternatives.

Objectives

To assess the efficacy and safety of systemic corticosteroids in the treatment of acute gout in comparison with placebo, NSAIDs, colchicine, other active drugs, other therapies, or no therapy.

Search methods

Searches were done in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007); MEDLINE (1966 to 2007) through PubMed; EMBASE (1974 to 2007); Web of Science (1975 to 2007); LILACS (1986 to 2007); and databases of ongoing trials (up to April 2007).

Selection criteria

Randomized controlled trials and controlled clinical trials investigating the use of systemic corticosteroids in the treatment of acute gout were included.

Data collection and analysis

Two review authors decided independently which trials to include. The same review authors also collected the data in a standardised form and assessed the methodological quality of the trial using validated criteria. When possible, continuous and dichotomous data were summarised statistically.

Main results

Three head to head trials involving 148 patients (74 systemic corticosteroids; 74 comparator drugs) were included. Placebo-controlled trials were not found. In the studies, different kinds of systemic corticosteroids and different kinds of control drugs were used, both administered in different routes. Intramuscular triamcinolone acetonide was compared respectively to oral indomethacine, and intramuscular adrenocorticotropic hormone (ACTH); oral prednisolone (together with a single intramuscular diclophenac injection) was compared to oral indomethacine (together with a single placebo injection). Outcome measurements varied: average number of

days until total relief of signs, mean decrease of pain per unit of time in mm on a visual analogue scale (VAS) - during rest and activity. In the triamcinolone-indomethacine trial the clinical joint status was used as an additional outcome. Clinically relevant differences between the studied systemic corticosteroids and the comparator drugs were not found; important safety problems attributable to the used corticosteroids were not reported. The quality of the three studies was graded as very low to moderate. Statistical pooling of results was not possible.

Authors' conclusions

There is inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids in the treatment of acute gout. Patients with gout did not report serious adverse effects from systemic corticosteroids, when used short term.

PLAIN LANGUAGE SUMMARY

Systemic corticosteroids for acute gout

This summary of a Cochrane review presents what we know from research about the effect of systemic corticosteroids for acute gout. The review shows that in people with gout:

- systemic corticosteroids may slightly improve patients' assessment of pain and disability. However, this could have occurred by chance;

- there is no precise information about side effects and complications. Only a minority of the patients treated with the steroid oral prednisolone reported minor side effects.

What is gout, and what are systemic corticosteroids?

Gout is a sudden, very painful joint inflammation (arthritis). It usually affects the big toe. The inflammation, which is caused by urate crystals, leads to swelling and redness of the joint, and makes it painful to move or even to touch.

Systemic corticosteroids are drugs that imitate the corticosteroids that are naturally produced by your own body and may help reduce swelling, redness and pain in joints. Systemic corticosteroids come in a pill form or as an injection given by your doctor.

BACKGROUND

Gout is a frequently occurring form of arthritis, mostly localized in the first metatarsophalangeal joint, with the tendency to recur easily. It is an extremely painful acute inflammatory arthritis with a sudden and dramatic onset, often beginning at night (Schumacher 1996; Schlesinger 2004). The arthritis wanes over days to weeks, with or without treatment (Bellamy 1987; Arnold 1988). The severe and painful inflammation is caused by the deposition of monosodium urate (MSU) crystals in the affected joint. The identification of these MSU crystals in the synovial fluid after joint aspiration and microscopic investigation comprises the gold standard for diagnosis. It is thought that the MSU crystal deposition in the joint is a consequence of high serum urate levels, caused by metabolic overproduction or renal undersecretion, or both (Bieber 2004). Uric acid is an end product of purine nucleotide catabolism and is excreted largely by the kidneys. Gout affects at least 1% of adult men in their lifetime, in Western countries (Terkeltaub 2003; Bieber 2004). The estimated incidence of gout in these countries is 0.6 to 2.1 per 1000 per year (Arromdee 2002; Van de Lisdonk 2003; Schlesinger 2004; Van der Linden 2004), with a prevalence of 3 to 7.5 per 1000 per year (Van de Lisdonk 2003; Schlesinger 2004; Van der Linden 2004).

In current practice, non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are the most commonly used agents for the treatment of acute gout (Kim 2003; Terkeltaub 2003; Schlesinger 2004).

In the past decades several studies have shown effectiveness of NSAIDs in patients with acute gouty arthritis in reducing pain, swelling, disability, redness and temperature (Sturge 1977; Altman 1988; Maccagno 1991; Shrestha 1995; Schumacher 2002; Rubin 2004; Sutaria 2006). Despite the fact that a recent systematic review located only one placebo-controlled NSAID study, NSAIDs are widely accepted as the drugs of first choice (Sutaria 2006). Gastrointestinal complications like gastritis, ulceration, bleeding, and perforation are the most frequent adverse effects of NSAIDs.

These adverse effects can emerge even within a short period of use (Lewis 2002). Other less frequent side effects of NSAIDs are allergic symptoms, headache, dizziness, and sleepiness. Furthermore, decreased renal function in patients with chronic gout has been attributed to the use of NSAIDs (Perez-Ruiz 2000). Finally, NSAIDs have drawbacks secondary to age and cardiovascular risks, in particular myocardial infarction, loss of renal function, fluid retention, and concurrent use of anticoagulants (Lewis 2002; Kim 2003; Schlesinger 2004; Kearney 2006, Sutaria 2006, Underwood 2006). These drawbacks can be expected in gout patients as they are generally older and often have pre-existing co-morbidities, like renal and cardiovascular disease (Abbott 1988; Conaghan 1994; Fam 1998; Janssens 2003; Bieber 2004; Janssens 2006; Krishnan 2006).

Colchicine has a longstanding history in the treatment of acute gout, even before NSAIDs were available. It is considered a first alternative when NSAIDs are contraindicated. It has a narrow therapeutic window with hazardous side effects, even when patients are treated according to accepted guidelines (Morris 2003). The evidence for its therapeutic use in acute gout is based on one placebo-controlled trial (Ahern 1987). This was the conclusion of a recent Cochrane systematic review (Schlesinger 2006). High doses are advised until relief of pain is obtained, or vomiting or diarrhoea occurs (Conaghan 1994; Morris 2003). The plasma half-life of colchicine is longer when renal function is impaired, a condition which is often seen in gout patients (Wise 1996; Petersel 2007). Other infrequent but serious side effects are bone marrow suppression, myopathy, and neuropathy (Conaghan 1994).

There are arguments to re-appraise the routine status of NSAIDs and colchicine in the treatment of acute gout because of their contraindications and adverse effects (Sutaria 2006). Alternatives with a better risk benefit profile are needed because it can be expected that many gout patients are at risk on routine treatment with NSAIDs and colchicine. Corticosteroids are often mentioned to be such an alternative, particularly in elderly people, as they have potentially effective anti-inflammatory capacity and may have fewer adverse effects when used short term (Groff 1990; Fam 1998; Rowe 2001; Kim 2003; Terkeltaub 2003; Schlesinger 2004; Gotzsche 2005; Sutaria 2006; Underwood 2006). We were aware of a few studies investigating short-term treatments of gout with systemic corticosteroids, which demonstrated treatment effects (Groff 1990, Alloway 1993, Siegel 1994, Werlen 1996). However, these studies had only small numbers of patients, they investigated different types of corticosteroids, and showed considerable methodological differences. We were not able to find systematic reviews on this topic, systemic corticosteroids for acute gout. The reviews that we did find were predominantly narrative, without a predefined systematic method, or without a focus on corticosteroids (Groff 1990; Schumacher 1996; Wise 1996; Terkeltaub 2003; Schlesinger 2004; Sutaria 2006).

OBJECTIVES

To assess the efficacy and safety of systemic corticosteroids in the treatment of acute gout in comparison with placebo, NSAIDs, colchicine, other active drugs, other therapies, or no therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and controlled clinical trials investigating the use of systemic corticosteroids in the treatment of acute gout were eligible for inclusion.

Types of participants

Patients of any age with an acute gouty arthritis diagnosed after identification of MSU crystals were considered for this review. Because of the expected limited number of trials adhering to this criterion, we also considered trials involving patients with a gout diagnosis according to the preliminary criteria of the American College of Rheumatology, the ACR criteria (Wallace 1977), or based on other clinical grounds.

Types of interventions

Only studies that evaluated the benefit or safety of a mono-therapy with systemic corticosteroids were eligible for inclusion. We searched for all studies that compared this therapy with placebo, NSAIDs, colchicine, other active drugs, other therapies, or no therapy.

Types of outcome measures

Primary outcomes were based on patients' assessment of pain and disability, investigators' assessment of clinical symptoms (swelling, erythema, tenderness), and adverse events. If eligible, secondary outcomes such as cost-effectiveness were also considered.

Search methods for identification of studies

See: Cochrane Musculoskeletal Group methods used in reviews. Searching was performed as outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The following electronic databases were used for the identification of the trials.
* The Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL) (up to 2007).
* PubMed (including MEDLINE) (1966 to 2007).

* EMBASE (1974 to 2007).
* Web of Science (1975 to 2007).
* LILACS (www.bireme.br/bvs/I/ibd.htm) (1986 to 2007).
* Databases of ongoing trials (up to April 2007).
Ongoing trial databases included: Current Controlled Trials (http://www.controlled-trials.com, with links to other databases of ongoing trials); UK National Research Register (http://www.update-software.com/National/nrr-frame.html); USA Center Watch Clinical Trials Listing Service (http://www.CenterWatch.com/); USA National Institutes of Health (http://clinicalstudies.info.nih.gov/).
We performed a search combining search procedures for clinical trials, gout, and systemic corticosteroids (see below). We combined these procedures with the Boolean operator AND. In the strategy for clinical trials we used a sensitive and valid procedure (Robinson 2002); in the search strategy for gout and corticosteroids we developed a strategy using keywords (MeSH headings) and text words. We tested our procedures extensively by running the searches and subsequently checking whether known articles on the topic of gout or corticosteroids were missing.
The search strategy for PubMed is given below (see Appendix 1 as well).
#1 Gout
"gout" [mh] OR gout* [tw] OR "Hyperuricemia"[mh] OR toph* [tw] OR arthritis uric* [tw] OR artritis uric* [tw] OR uric acid dis* [tw]
#2 Corticosteroids
"Glucocorticoids"[mh] OR "Adrenal Cortex Hormones"[mh] OR "Steroids"[mh] OR glucocortic* [tw] OR adrenal Cortex Horm* [tw] OR prednison* [tw] OR prednisol* [tw] OR cortison* [tw] OR hydrocort* [tw] OR methylprednis* [tw] OR triamcinol* [tw] OR dexamethas* [tw] OR betamethas* [tw] OR beclomethas* [tw] OR paramethas* [tw] OR dexametas* [tw] OR betametas* [tw] OR beclometas* [tw] OR parametas* [tw]
#3 Controlled trials
(Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (clinical trial [tw]) OR ((singl*[tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (latin square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])
Whole search
#1 AND #2 AND #3
Abbreviations: mh: exploded medical subject heading (Medline medical index term); mh:noexp: non-exploded medical subject heading (MEDLINE medical index term); tw = text word; pt = publication type. The asterisk (*) stands for any character(s).
For EMBASE and Current Contents, this strategy was adapted because these databases have different interfaces. The necessary changes in the search string were done so that the search became more sensitive (that is yielded a higher number of 'hits').

Data collection and analysis

Study selection

To select studies for further assessment, two review authors (HJ and PL) independently reviewed the titles and abstracts of every record retrieved. Articles were selected if this information indicated that the study: (1) included patients with crystal-proven gout or patients with a gout diagnosis based on the preliminary criteria of the ACR, or with a diagnosis on other clinical grounds; (2) compared systemic corticosteroid treatment with placebo or other interventions; (3) assessed one or more of the required outcome measures; (4) used random allocation [or for controlled clinical trials, an allocation under the control of the investigator] to the comparison groups. If there was any doubt regarding the information from the title and abstract, the full article was retrieved for clarification. In a case of disagreement about including a study, a third review author (EvdL) was consulted for a definitive decision. Inter-observer agreement for study selection was measured using the kappa statistic (Cohen 1960).

Quality assessment of the selected studies

Two review authors (HJ and PL) assessed the quality of each retrieved trial independently using the following quality characteristics.
1. Selection bias. A) Method of randomization: the randomization procedure was scored as adequate when the resulting sequences were unpredictable (i.e., computer generated schemes, tables of random numbers, coin tossing). B) Allocation concealment: scored as adequate when participating patients and investigators could not foresee assignment (i.e., by central randomization remote from trial site, sequentially numbered and sealed radio-opaque envelopes).
2. Performance bias. Methods of (double) blinding, if applicable: blinding was considered adequate when the interventions were similar in size, colour, and shape; or when a double dummy method was applied. If trials reported blinding we also investigated whether the blinding was checked.
3. Attrition bias. A) Description of withdrawals and drop-outs: handling of drop-outs was considered adequate when studies gave a complete description of all patients failing to participate until the end of the trial and when the data were analysed on an intention-to-treat (ITT) basis. B) Number of drop-outs: overall drop-out rate < 15% was considered adequate. C) Selective drop-out: a difference in drop-out rate between the groups < 10% was considered adequate.

4. Detection bias. Method of blinding outcome assessment: this blinding was considered adequate if the researchers assessing the outcomes were completely blinded for the intervention.

In a case of disagreement regarding the assessment of the quality characteristics, one of the other review authors (FvdL) was invited to make the final decision.

In addition to these criteria, studies were broadly subdivided into the following three quality scores, as recommended in the Cochrane Handbook for Systematic reviews of Interventions (Higgins 2005).

A - All quality criteria met: 1. adequate randomization and allocation concealment, 2. adequate blinding, 3. adequate ITT analysis or drop-out rate less than 15% and selective drop-out less than 10%, or both; low risk of bias.

B - One or more quality criteria only partially met: 1. adequate randomization or adequate allocation concealment, 2. mentioning of blinding but exact method unclear, 3. inadequate or unclear ITT analysis but drop-outs less than 15% or selective drop-out less than 10%); moderate risk of bias.

C - One or more quality criteria not met: 1. inadequate randomisation and allocation concealment, 2. inadequate or no blinding, 3. inadequate ITT and drop-out rate equal to or greater than 15% and selective drop-out equal to or greater than 10%; high risk of bias.

Data extraction

Two review authors (HJ and PL) independently extracted the data concerning characteristics of the selected studies by using a standard form. This form included the following items.

1. General aspects: title, authors, source, contact address; language of publication; year of publication; duplicate publication; sponsoring.

2. Trial characteristics: design and setting; randomization (and method); allocation concealment (and method); blinding (patients, people administering treatment, outcome assessors) and check of successful blinding.

3. Intervention details: placebo or comparison interventions, or both (dose, route, timing); co-medication or other accompanying treatment (dose, route, timing).

4. Participant details: sampling (random or convenience); exclusion criteria; total number and numbers in the comparison groups; age, sex, and other baseline characteristics; diagnostic criteria; only new or all cases; assessment of compliance; withdrawals and losses to follow up (reasons, description).

5. Outcome measures and methods of assessing outcomes: continuous scales (e.g., visual analogue scales); dichotomous outcomes (e.g., presence or absence of pain); categorical scales (e.g., none, mild, moderate, severe, extreme); validated questionnaires; or other reported methods (e.g., amount of days required for total resolution of all symptoms); and length of follow up.

Data analysis

We planned to summarize the data statistically, if available and sufficiently homogeneous.

We expected dichotomous, ordinal, and continuous data. If possible, dichotomous data were expressed as relative risks (RR). Peto odds ratio (Peto OR) were used when incidence rates were small. We expressed continuous data as weighted mean differences (WMD) when outcomes were measured in a similar way. In all other cases, standardized mean differences (SMD) were used.

We intended to calculate the overall results based on the random-effects model; to test the heterogeneity using the Z-score and the Chi-square statistic (significance level $P < 0.10$); and to quantify the effect of heterogeneity by means of the I^2 statistic, ranging from 0 to 100% including its 95% confidence interval. I^2 demonstrates the percentage of total variation across studies due to heterogeneity, and it could be used to judge the consistency of the evidence (Higgins 2002). A value greater than 50% may be considered as substantial heterogeneity. Possible sources of heterogeneity were assessed by sensitivity and subgroup analyses. Publication bias was tested using a funnel plot.

The analyses were performed with the most recent version of RevMan Analyses in Review Manager.

Sensitivity and subgroup analyses

We preplanned sensitivity analyses to evaluate the influence on the effect size of the following.

1. Published versus unpublished studies, if any.

2. Studies with or without certain quality characteristics: adequate randomization; adequate allocation concealment; adequate method of blinding; adequate ITT analyses; adequate blinding for outcome assessment; adequate method of blinding of analyses; an overall drop-out rate less than 15%; difference of drop-out rates between the main treatment groups less than 10%; a quality score A or B, as recommended in the Cochrane Handbook for Systematic reviews of Interventions (compared to studies with score of C)(Higgins 2005).

3. Small versus large studies.

4. English language versus other than English language.

5. Sponsored by industry versus other or no industry funding.

6. Gout diagnosis based on identification of MSU crystals versus no crystal identification.

We also preplanned subgroup analyses to explore the influence on effect sizes of the following variables.

1. Age.

2. Gender.

3. The route of administration (oral, rectal, intramuscular).

4. Type of steroid.

5. Dose (low, medium, high; based on data).

6. Duration of intervention.

7. Diagnosis criteria (crystal proven, according to ACR, other).

8. Race.

9. Blood level of uric acid.

Finally, for the exploration of the robustness of the results, we

planned to repeat the analysis using different measures of effect size (relative risk, risk difference) and different statistical models (fixed-effect and random-effects models).

Clinical relevance tables

When data were appropriate, we planned to compile clinical relevance tables to improve the readability of the review. For dichotomous outcomes, we planned to calculate the number needed to treat from the relative risk, using the Visual Rx NNT Calculator (Cates 2003). For continuous outcomes and when possible, the absolute benefit as the difference between the improvement in the intervention group and the improvement in the control group was assessed in the units as given in the original publication. Moreover, we intended to calculate the relative difference in improvement as the difference of the percentage change in the intervention group and the percentage change in the control group.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
We identified 2083 study titles and abstracts from the predefined databases. Eight of 2083 were independently selected by the two review authors (HJ and PL) to retrieve the full article with the aim of evaluating the definite eligibility for inclusion in the review. The inter-observer agreement of this selection procedure, expressed as kappa, was 0.93 (95%CI 0.80 to 1.00; standard error 0.067).
After reading the full publication, both authors independently concluded that four of the eight studies did not meet the inclusion criteria (Axelrod 1988; Groff 1990; Conaghan 1994; Werlen 1996). One study was retrieved from trial registers (ISRCTN14648181). This study is being conducted by our own group, and to date the data are not analysed or published. Finally, we selected three studies for inclusion (Alloway 1993; Siegel 1994; Man 2007).
In the first included study, intramuscular injections with triamcinolone acetonide were compared with oral indomethacine (Alloway 1993). In this study the diagnosis of gout in the 27 participants (all male) was confirmed by identification of MSU crystals. Afflicted joints were not described. The mean number of involved joints per patient was more than two. Exclusion criteria were: any infectious process, anticoagulant therapy, uncontrolled diabetes mellitus. Patients currently taking colchicine, allopurinol, or an uricosuric agent were allowed to continue this medication during the study. Triamcinolone acetonide-treated patients were given paracetamol with codeine for analgesia. Fourteen patients (mean age 61.2 years) were injected once with 60 mg triamcinolone acetonide and, if necessary, an additional injection. Patients were eligible to receive a second injection if they had less than 50% improvement at the first follow up. Three patients received a second injection two days after entry in the study. Thirteen patients (mean age 62.8 years) received indomethacine tablets, 50 mg three times a day, with permission to taper their medication after at least two days in response to symptomatic improvement. An important difference between the two treatment groups at baseline was that five patients in the triamcinolone acetonide group versus one patient in the indomethacine group used colchicine. Seven patients were lost to follow up (four in the triamcinolone acetonide group, three in the indomethacine group). Patients were evaluated by an unblinded observer at 1 to 2, 3 to 4, 10 to 14, and 30 days for symptomatic improvement (using a 5-point-scale: total resolution, improvement of > 50%, improvement of <50%, no change, worsening of symptoms or involvement of previously uninvolved joints), for the number of active joints, the presence of toxicity to therapy, and the presence of rebound arthropathy. The final efficacy outcomes were the number of days required for total resolution of all symptoms, and the clinical joint status at 3 follow-up moments.
In the second study, intramuscular injections with triamcinolone acetonide were compared with intramuscular injections of adreno-corticotropic hormone (ACTH) (Siegel 1994). All 31 patients (all male) had their diagnosis of acute gout confirmed by joint aspiration of MSU crystals. Afflicted joints were not described. The mean number of involved joints was more than 2.5 for each patient. Patients with a history of uncontrolled diabetes, congestive heart failure, infection, or severe coronary artery disease were excluded. Patients currently taking colchicine, allopurinol, or an uricosuric agent were allowed to continue this medication during the study. Sixteen patients (mean age 62.4 years) were injected with 60 mg triamcinolone acetonide and, if necessary, one or more additional injections. Fifteen patients (mean age 69.6 years) were given 40 IU ACTH intramuscularly and, if necessary, one or more additional injections. One patient allocated to ACTH treatment was lost to follow up for unknown reasons. Patients were eligible for a repeat injection if they had < 50% improvement at each subsequent follow-up visit. Two patients in the ACTH group did not reach a 50% improvement after three injections and were treated with triamcinolone acetonide, but were not analysed. The time interval between re-injections was not reported. There were no statistical differences between the two treatment groups at baseline, except for a higher erythrocyte sedimentation rate (ESR) in the triamcinolone acetonide group: 45.57 versus 40.25 (P-value 0.003). The researchers did not consider this difference clinically relevant. Patients were evaluated by unblinded (different) observers at 1 to 2, 3 to 4, 10 to 14, and 30 days for symptomatic improvement (using a 5-point-scale: total resolution, improvement of > 50%, improvement of <50%, no change, worsening of symptoms or involvement of previously uninvolved joints), for the number of active joints, for the clinical joint status, for side effects, and for rebound arthropathy. The final efficacy outcome was the number of days to 100% resolution of the symptoms.

In the third included trial, oral prednisolone was compared to intramuscular diclophenac combined with oral indomethacine (Man 2007). Diagnosis of all 90 patients in this study was based on clinical judgement, without predefined criteria. Afflicted joints were not described. In more than 90% of the patients a single joint was involved, most of the time in the lower limb. Exclusion criteria were: clinical suspicion of sepsis or other joint disease; lack of transport or telephone after diagnosis; significant co-morbidity that would interfere with assessment; dementia or confusion; active gastrointestinal symptoms; serum creatine level greater than 200 mmol/l; bleeding disorder; allergy to a study drug; joint aspiration that excluded the diagnosis of gout. Patients were instructed to use paracetamol (1 gram every 4 hours) as required. All patients in the diclophenac plus indomethacine group (N = 46, mean age 66 years) received an intramuscular injection of 75 mg diclophenac at the start of the trial, and 50 mg indomethacine three times a day for two days then 25 mg indomethacine three times a day for three days. Patients in the predisolone group (N = 44, mean age 64 years) received an initial placebo injection and 30 mg prednisolone daily for five days. There were no important differences between the treatment groups at baseline. The mean rate of decrease in pain at rest and with activity during the first two hours and at five-day follow ups were the primary outcomes, assessed with a 100 mm visual analogue scale. Medication was stopped In seven patients of the diclophenac plus indomethacine group after serious gastrointestinal adverse effects.

Risk of bias in included studies

We summarized the quality of the included trials in Table 1. With respect to selection bias, only one study had both adequate randomization and adequate allocation concealment (Man 2007). The risk of attrition bias (degree of drop-out and selective drop-out) was low in one study (Siegel 1994). An adequate intention-to-treat analysis was only performed in one study (Man 2007). Blinding (performance bias) was adequate in one study (Man 2007). The other studies were not blinded. Outcome assessment in all studies was not blinded or no information was provided. The overall quality scored according to the three-point scale recommended in the Cochrane Handbook for Systematic Reviews of Interventions was B (moderate risk of bias) for one study (Man 2007) and C (high risk of bias) for the two other studies.

Effects of interventions

Efficacy

The efficacy of the three included studies (involving 148 patients) are summarised in Table 2. From the included studies we extracted six different outcome measures which represented treatment efficacy, and provided enough data to analyze them. It should be noted that if systemic corticosteroids are more effective than the comparative drugs the presented mean difference is positive.

The average number of days until complete resolution of symptoms

The mean differences in the average number of days until complete resolution of symptoms, between triamcinolone acetonide and indomethacine, and triamcinolone acetonide and ACTH were 0.9, and 0.3 days respectively (P-values 0.66, and 0.89; measures of uncertainty, for example 95% CI, were not reported).

Clinical joint status at three follow-up moments

On comparing triamcinolone acetonide and indomethacine, the differences between the mean clinical joint scores after 1 to 2, 3 to 4, and 10 to 14 days respectively, as assessed by an unblinded investigator, were 0.5, 0.03, and -0.3 on a 5-point categorical scale (P-values 0.24, 0.94, and 0.25 respectively; measures of uncertainty, for example 95% CI, were not reported).

Reduction of the pain at rest per hour during the first two hours

Regarding pain reduction during the first two hours after the start of the treatment, as assessed by the patient on a VAS of 100 mm, the mean difference between prednisolone and diclophenac plus indomethacine was 3.2 mm per hour for pain at rest (95% CI -0.78 to 7.14).

Reduction of the pain with activity per hour during the first two hours

The mean difference between prednisolone and diclophenac plus indomethacine was -1.1 mm for the reduction of pain during activity (95% CI -5.34 to 3.24).

Reduction of the pain at rest per day after two weeks

Regarding the decrease of the pain at rest during the first two weeks, the mean difference was 0.5 mm per day (95% CI 0.03 to 0.89) comparing prednisolone and diclophenac plus indomethacine.

Reduction of the pain with activity per day after two weeks

For the reduction of the pain with activity after two weeks, the mean difference was 1.2 mm (95% CI 0.44 to 2.00) comparing prednisolone and diclophenac plus indomethacine.

We did not perform clinical relevance tables for pain or any other major outcome as the two triamcinolone acetonide studies did not provide adequate data for this, and the difference in the pain outcome at the end of the follow up in the third study was statistically not significant.

Adverse events

No adverse effects were reported in the triamcinolone acetonide-treated patients or in the ACTH-treated patients (Alloway 1993; Siegel 1994). In the indomethacine group of the first trial, 20% of the patients noted dyspepsia (Alloway 1993). In the third study, statistically significant differences were found in adverse events between the prednisolone-treated patients and the diclophenac plus indomethacine-treated patients: 27% versus 63% for any adverse event; and 0% versus 15% for serious adverse effects requiring hospital admission (11% gastrointestinal bleeding) (Man 2007). Adverse effects in the diclophenac plus indomethacine group were: epigastric pain (30%), other abdominal pain (7%), rash (2%), dizziness (19%), drowsiness (19%), dry mouth (24%), indigestion (30%), nausea (26 %), vomiting (9%), diarrhoea (7%), gastroin-

testinal haemorrhage (11%), shortness of breath (2%), and chest pain (2%); and in the prednisolone group: rash (7%), dizziness (5%), drowsiness (16%), dry mouth (20%), indigestion (9%), and nausea (9%) (Man 2007).

As there were no clinically important adverse events related to the studied systemic corticosteroids, we had no reason to compile a clinical relevance table.

Sensitivity analyses

We did not perform any sensitivity analyses as the number of studies included in our review was too small.

DISCUSSION

In this systematic review we retrieved three studies, including 74 patients with acute gout , that involved treatment with systemic corticosteroids. There were no placebo-controlled studies. All were active comparator-controlled trials. None of the studies reported clinically relevant differences between the systemic corticosteroids and the comparator drugs. No important safety problems attributable to the corticosteroids were found. Most adverse events were related to the comparator drugs, in particular to the NSAIDs.

Conclusions from the present review about the efficacy, effectiveness, and safety of systemic corticosteroids in the treatment of acute gout must be interpreted cautiously, for the following reasons.

1. The use of comparator drugs in controlled trials presupposes efficacy of the comparator drug. However, there is hardly any evidence for the efficacy of the comparator drugs that were used. Although the efficacy of NSAIDs is generally accepted, we were aware of only one placebo-controlled study showing efficacy of NSAIDs (Sutaria 2006). We were not aware of evidence for the efficacy of ACTH and, regarding its effectiveness, we located only one comparator-controlled study (Axelrod 1988).

2. None of the studies were designed to show equivalence. Therefore, if study outcomes do not show statistical differences (P > 0.05) this does not designate the existence of equal effectiveness of the studied drugs regarding these outcomes (Jones 1996).

3. The methodological quality of the included studies is very low; according to the Cochrane Handbook for Systematic reviews of Interventions two of the three studies were scored C, indicating very low quality (Alloway 1993; Siegel 1994). The third study was scored B (Man 2007), indicating moderate quality.

4. There was a substantial heterogeneity between the included studies. Different kinds of systemic corticosteroids (triamcinolone acetonide and prednisolone) administered in different ways (intramuscular and oral) were compared with different kinds of comparator drugs (indometacine and ACTH). Studies used different inclusion criteria (for example, diagnosis with and without identification of MSU crystals) and different outcome measurements (for example, days until complete resolution, change on a VAS in mm).

5. Two of the three studies had no predesigned method for how to register and analyse adverse effects, and the number of patients was too small to provide a more definitive conclusion about safety. However, safety problems from systemic corticosteroids in a short course of treatment are very unlikely in other medical situations (Rowe 2001; Gotzsche 2005).

The strength of our review is that we searched all available databases, included publications without language restriction, and used independent researchers for inclusion and exclusion (with good kappa values), as well as for data extraction. A limitation was that we did not request additional data from the authors of the excluded or included studies, nor did we request gout experts or pharmaceutical companies to provide unpublished trials.

In conclusion, the efficacy of systemic corticosteroids in acute gout and their effectiveness, equivalent to the regularly used drugs (in particular NSAIDs), require more evidence. Derived from this review, the evidence can be graded as a maximum of Silver according to the four-point scale grading system (Platinum, Gold, Silver, and Bronze) described in the book *Evidence-based Rheumatology* (Tugwell 2004), and as recommended by the Cochrane Musculoskeletal Review Group.

AUTHORS' CONCLUSIONS

Implications for practice

Based on this review, we were not able to define evidence-based implications for medical practice although we expect that systemic corticosteroids could have the potential to become a safe treatment alternative in the management of acute gout.

Implications for research

Despite the potential of corticosteroids in relieving inflammation in acute gout without important safety problems, the real efficacy and clinical effectiveness requires more evidence. Therefore, well-designed, high quality trials are necessary. As placebo-controlled studies are hardly feasible because of ethical considerations, we advise randomized double blind equivalence trials with NSAIDs as comparator drugs, given that they have a generally accepted efficacy and effectiveness. Future trialists should be aware of predefined design conditions (for example a power calculation based number of patients, range of equivalence) and the use of comparable outcome measures, for example those recommended by the OMERACT 7 Special Interest group (Schumacher 2005).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alloway 1993

Methods	Active comparator controlled non-randomized trial; non blinded
Participants	27 patients (all men) presenting at a hospital rheumatology department with acute gout, diagnosed after MSU-crystal identification
Interventions	14 patients received a systematic corticosteroid: triamcinolone acetonide (TCA) 60mg by intramuscular injection, and if necessary a number of additional injections; 13 controls received oral indomethacine (IDN) 50mg TID, with the permission to taper their medication after at least 2 days in response to symptomatic improvement (control therapy). TCA treated patients were given additionally paracetamol with codeine for analgesia
Outcomes	The symptomatic improvement on a 5-point scale, the number of active joints, presence of toxicity, and presence of rebound arthropathy. The final efficacy outcome was the number of days required for total resolution of all symptoms, and in addition, the clinical joint status at 3 follow-up moments
Notes	No outcome measurement by the patient. 4 patients in the TCA group and 3 in the IDM group were lost to follow up

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Man 2007

Methods	Active comparator controlled randomized trial; double blinded
Participants	90 patients presenting at a university hospital emergency department with an acute arthritis clinically "suggestive of gout"
Interventions	44 patients (male 35) received a systematic corticosteroid: 30mg oral prednisolone daily for 5 days. 46 (male 39) patients received indomethacine (IDM) 50mg TID for 2 days and 25mg TID for 3 days after 1 initial intramuscular injection with 75mg diclofenac (control therapy). In both treatment arms additional paracetamol 1000mg every 4 hours as required
Outcomes	Pain reduction at rest, as with activity, scored on a visual analogue scale of 10cm
Notes	7 patients, all from the IDM group, had to stop the study medication because of adverse effects

Risk of bias

Man 2007 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Siegel 1994

Methods	Active comparator randomized controlled trial; non blinded.
Participants	31 patients (all men) presenting at a hospital rheumatology department with acute gout, diagnosed after MSU-crystal identification
Interventions	16 patients received a systematic corticosteroid: triamcinolone acetonide 60mg by intramuscular injection. 15 received adrenocorticotropic hormone (ACTH) 40 IU by intramuscular injection (control therapy). If necessary a number of additional injections was given in both treatment arms
Outcomes	Patient's improvement of pain, mobility, and swelling on a 5-point scale, the number of active joints, the joint status, side effects, and presence of rebound arthropathy. The final efficacy outcome was the number of days required for total resolution of all symptoms
Notes	One patient allocated to ACTH treatment was not characterized, and lost to follow up. Two patients of the ACTH group were excluded from the analysis because of insufficient response

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Axelrod 1988	Systematic corticosteroids not studied.
Conaghan 1994	Non-systematic review; no clinical trial.
Groff 1990	Prospective, non-controlled trial.
Werlen 1996	No outcome measurement by the patient. No differentiation between patients with gout and patients with chondrocalcinosis

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN14648181

Trial name or title	Randomized double-blind trial of prednisone and naproxen in treatment of crystal proven acute gout
Methods	
Participants	Primary care gout patients diagnosed after the identification of MSU crystals
Interventions	Five days, by oral administration, either prednisolon 35mg (= 30mg prednisone) once a day or naproxen at a dose of 500 mg twice a day. Patients received blind capsules containing active prednisolon and placebo naproxen, or active naproxen and placebo prednisolon
Outcomes	Primary outcomes: Patient assessment of pain in the study joint, indicated on visual analogical scales two times a day, during 4 days ; Secondary outcomes: 1. Patient's global disability 2. The walking disability, if the study joint was in the leg or foot 3. Safety and tolerability of prednisone versus naproxen.
Starting date	April 1st 2004
Contact information	Dr E van de Lisdonk, Department of General Practice and Family Medicine 229, Radboud University Nijmegen Medical Centre PO Box 9191, Nijmegen, 6500 HB, The Netherlands, Tel +31 (0)24 36
Notes	

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Quality of studies

Study	Randomi-sation	Allocation conceal.	Treatment blinding	ITT analy-sis	Total drop-out	Selective drop-out	Blind out-come-assess	Overall quality
	A=adequate B= unknown or inadequate	A=adequate B= unknown or inadequate	A= adequate B= blinding but method un-clear C=non-blinded, in-adequate, or unknown	A= adequate B= ITT inade-quate C=un-clear or no re-ported data on drop-out or loss to fol-low up	A<15% B>/=15% or unknown	A=differ-ence in drop-out rate in main groups<10% B>/=10% or unknown	A=adequate B=mention-ing of blind-ing but exact method un-clear C=non blinded, in-adequate or unknown	A=all quality criteria met B=one or more quality criteria only partially met C=one or more criteria not met
Alloway 1993	B	B	C	C	B	A	C	C
Man 2007	A	A	B	A	A	B	C	B
Siegel 1994	B	B	C	C	A	A	C	C

Table 2. Efficacy results of included studies

Study	n	Outcome	Results	Note
Alloway 1993	I = 14; C = 13	Average number of days until complete resolution	I 7.4 (SD 4.55); C 8.3 (SD4.35); Difference 0.9 p=0.66	3 of 10 patients received a second injection (= I). Lost to follow up: n=7 (I: n=4; C: n=3)
		Mean joint score after 1 to 2, 3 to 4, and 10 to14 days (5-point scale: 0=total res-olution, 1=improvement of > 50%, 2=improvement of <50%, 3=no change, 4= worsening of symptoms)	I: 1.0 (SD 0.72) to 0.62 (SD 0.78) to 0.50 (SD 0 . 16). C: 1.5 (SD 0.85) to 0.65 (SD 0.63) to 0.20 (SD 0. 37); Differences: 0.5 (p=0. 24), 0.03 (p=0.94), and -0. 30 (p=025)	3 of 10 patients received a second injection (=I). 7 pa-tients were lost to follow up (I: n=4; C: n=3)

Table 2. Efficacy results of included studies *(Continued)*

Mann 2007	I = 44; C = 46	Mean decrease (mm on a VAS) per hour of pain at rest within the first 2 hours	I -9.5 (SD 10.5); C -6.4 (SD 8.3); Difference 3.2 (95%CI -0.78 to 7.14), p= 0.12	The difference in mean pain score was at no time more than 13mm, which was unlikely to be clinically relevant according to the authors
		Mean decrease (mm on a VAS) per hour of pain during activity within the first 2 hours	I -19.2 (SD 11.2); C -20.3 (SD 9.1); Difference -1.1 (95%CI: -5.34 to 3.24), p=0.63	The difference in mean pain score was at no time more than 13mm, which was unlikely to be clinically relevant according to the authors
		Mean decrease (mm on a VAS) per day of pain at rest after 2 weeks	I -0.7 (SD 1.2); C -0.3 (SD0.7); Difference 0.5 (95%CI: 0.03 to 0.89), p= 0.04	The difference in mean pain score was at no time more than 13mm, which was unlikely to be clinically relevant according to the authors. Lost to follow up: n=7 (I: n=0; C: n=7*) * had to stop the study after adverse effects
		Mean decrease (mm on a VAS) per day of pain during activity after 2 weeks	I -2.9 (SD 2.0); C -1.7 (SD 1.6); Difference 1.2 (95%CI: 0.44 to 2.00). p= 0.0026	The difference in mean pain score was at no time more than 13mm, which was unlikely to be clinically relevant according to the authors. Lost to follow up: n=7 (I: n=0; C: n=7*) * had to stop the study after adverse effects
Siegel 1994	I = 16; C = 15	Average number of days until complete resolution	I 7.6; 7.9; Difference 0.3 p=0.89	4 of 16 patients required a second I-injection, 9 of 14 a second C-injection. 3 patients required a third C-injection. Lost to follow up: n=3 (I: n=0; C: n=3*) *2 because of <50% improvement after 3 C-injections
	I = Intervention; C = Control		SD = Standard Deviation	

APPENDICES

Appendix 1. MEDLINE search strategy

#1 Gout

"gout" [mh] OR gout* [tw] OR "Hyperuricemia"[mh] OR toph* [tw] OR arthritis uric* [tw] OR artritis uric* [tw] OR uric acid dis* [tw]

#2 Corticosteroids

"Glucocorticoids"[mh] OR "Adrenal Cortex Hormones"[mh] OR "Steroids"[mh] OR glucocortic* [tw] OR adrenal Cortex Horm* [tw] OR prednison* [tw] OR prednisol* [tw] OR cortison* [tw] OR hydrocort* [tw] OR methylprednis* [tw] OR triamcinol* [tw] OR dexamethas* [tw] OR betamethas* [tw] OR beclomethas* [tw] OR paramethas* [tw] OR dexametas* [tw] OR betametas* [tw] OR beclometas* [tw] OR parametas* [tw]

#3 Controlled trials

(Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (clinical trial [tw]) OR ((singl*[tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (latin square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])

Whole search

#1 AND #2 AND #3

Abbreviations: mh: exploded medical subject heading (Medline medical index term); mh:noexp: non-exploded medical subject heading (MEDLINE medical index term); tw = text word; pt = publication type. The asterisk (*) stands for any character(s).

WHAT'S NEW

Last assessed as up-to-date: 7 December 2007.

Date	Event	Description
22 April 2008	Amended	Converted to new review format. CMSG ID: C155-R

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

HEIN JANSSENS: conceived the review; selected the studies and assessed the quality; extracted and analyzed the data; wrote the manuscript of the protocol and the article; edited the protocol and the article.

PETER LUCASSEN: selected the studies and assessed the quality; extracted and analyzed the data; contributed to the writing of the manuscript of the protocol and the article, reviewed the manuscript of the protocol and the article.

FLORIS VAN DE LAAR: contributed to the writing of the manuscript and the article; reviewed the manuscript of the protocol and the article; contributed to the editing of the protocol and the article.

MATTHIJS JANSSEN: contributed to the conception of the review; reviewed the manuscript of the protocol and the article.

ELOY VAN DE LISDONK: contributed to the conception of the review; reviewed the manuscript of the protocol and the article.

DECLARATIONS OF INTEREST

All the authors declared no possible conflict of interest.

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- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adrenal Cortex Hormones [administration & dosage; *therapeutic use]; Adrenocorticotropic Hormone [therapeutic use]; Gout [*drug therapy]; Indomethacin [therapeutic use]; Triamcinolone [therapeutic use]

MeSH check words

Humans