Systemic corticosteroids versus non-steroidal anti-inflammatory drugs for acute gout: a systematic review

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

to compare pain reduction and adverse events between systemic corticosteroids and NSAIDs in patients with acute gout.

METHODS

Four reviewers systematically and independently searched and evaluated from 4 databases including PubMed, the Cochrane Library, Trip database and Scopus. We included all relevant randomized controlled trials (RCTs) comparing efficacy regarding pain reduction and adverse events of systemic corticosteroids and NSAIDs in patients with acute gout by robust inclusion and exclusion criteria. We assessed the methodological quality using validated tools. Then, continuous and dichotomous data were statistically analysed.

RESULTS

We include 5 RCTs, involving 834 participants with acute gout in this systematic review. Three RCTs with 624 patients indicated that systemic corticosteroids and NSAIDs were similar efficacy in term of pain reduction at rest using a 100 mm-visual analogue scale (VAS) in the first 6 hours (mean difference [MD] 0.64; 95% confidence interval [CI] -2.26 to 3.54, I^2=50%, random-effect model). Two RCTs with 506 participants, systemic corticosteroids were not significantly different from NSAIDs for efficacy in term of pain reduction at activity using a 100 mm-VAS in the first 6 hours (MD -0.28; 95% CI -2.09 to 1.53, I^2=0%, fixed-effect model). Three minor adverse events including nausea, vomiting and indigestion were found significantly higher in those using NSAIDs, (relative risk [RR] 0.23; 95% CI 0.11 to 0.51; RR 0.1; 95% CI 0.02 to 0.54 and RR 0.49; 95% CI 0.28 to 0.84, respectively) while rash was more common in those using systemic corticosteroids (RR 4.61; 95% CI 1.34 to 15.81).

CONCLUSION

Our study found robust evidence that systemic corticosteroids and NSAIDs have similar efficacy for pain reduction but have lesser adverse events in systemic corticosteroids users. Thus, short-term systemic corticosteroids treatment should be considered as first-line alternative to NSAIDs in patients with acute gout.

INTRODUCTION

Global prevalence of gout was 0.8 per 1,000 people in 2010[1] and incidence of acute gout in the United Stated was nearly 180,000 patients in 2008.[2] Those with the attack were commonly treated with non-steroidal anti-inflammatory drugs (NSAIDs) followed by colchicine for relieving symptoms of pain, swelling and redness.[3-7] NSAIDs user often present with gastroduodenal adverse effects such as dyspepsia, nausea, vomiting, abdominal pain, bleeding and heartburn as well as increasing cardiovascular and renal complication[8-12] while gastrointestinal intolerance including nausea, vomiting and diarrhea are also found in those using colchicine.[13,14] Systemic corticosteroid is an alternative treatment for those who cannot tolerate with the adverse effects of NSAIDs or colchicine.[15-17]

A previous systematic review in 2008 with 148 participants stated that adverse events were found less common in those using systemic corticosteroids than that of NSAIDs, however, their comparative efficacies were inconclusive without combined effect sizes of the treatments.[18] There were at least four additional trials since 2008 reported that systemic corticosteroids and NSAIDs had similar efficacy on pain reduction, but they still had limitation regarding small sample size.[19-22] The aim of this systematic review is to compare efficacies and adverse events between systemic corticosteroid and NSAIDs in acute gout.

METHODS

This study is a systematic review to compare pain reduction and adverse events between systemic corticosteroids and NSAIDs in patients with acute gout. It is conducted according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[23] and followed Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) checklist.[24]

SEARCH STRATEGIES

Four independent reviewers systematically searched for articles through PubMed, the Cochrane Library, Trip Database and Scopus. Searching in Pubmed and Cochrane library were undertaken using MeSH terms; "gout" OR "gouty arthritis" AND "steroids" OR "corticosteroids" AND "NSAIDs" OR "anti-inflammatory agents, non-steroidal". We used PICO search in Trip Database and various combinations of following keywords in Scopus; "gout", "acute gout", "acute gout attack", "acute gouty arthritis", "steroid", "corticosteroids" and "NSAIDs".

INCLUSION CRITERIA

STUDY DESIGN

Randomized controlled trials (RCTs).

PARTICIPANTS

Patients with acute gout.

INTERVENTIONS

Systemic corticosteroids.

CONTROLS

NSAIDs.

OUTCOMES

Pain reduction and the adverse events after using the interventions and controls.

Table 1. Characteristics of the included studies.

Author (year), country	Methods	Participants	Interventions	Control	Outcomes
Man (2007), Hong Kong, China	Controlled randomized trial; double blinded	90 patients	44 patients (male 35) received oral prednisolone 30 mg od 5 days with oral paracetamol 1000 mg prn q. 4 hours	46 (male 39) patients received oral indomethacin 50 mg tid for 2 days and 25 mg tid for 3 days after 1 initial intramuscular injection with 75 mg diclofenac -paracetamol 1000 mg prn q. 4 hours	Primary outcomes: pain reduction at rest and activity (using a 100 mm-VAS); secondary outcome: adverse events
Janssens (2008), the Netherlands	Controlled randomized trial; double blinded	120 patients	60 patients received oral prednisolone 35 mg od and oral placebo naproxen bid	60 patients received oral naproxen 500 mg bid and oral placebo prednisolone od	Primary outcomes: pain reduction at res t (using a 100 mm-VAS); secondary outcomes: adverse events, general disability, walking disability
Zhang (2014), China	Parallel-group randomized trial	60 patients	30 patients received oral compound betamethasone (diprospan) 7mg i.m. only once during the study	30 patients received oral diclofenac sodium 75 mg bid for 7 days	Primary outcomes: pain reduction (using a 5 point Likert scale); secondary outcomes: adverse events, joint tenderness/swelling (using a 5 point Likert scale)
Timothy (2016), Hong Kong, China	Two recent double-blind, randomized, controlled trials	416 patients	208 patients received oral prednisolone 10 mg 3 tabs od and placebo 2 tabs tid for 2 days followed by oral prednisolone 10 mg 3 tabs od and placebo 1 tab tid for 3 days with oral paracetamol 1 gm prn q. 6 hr.	208 patients received oral indomethacin 25 mg 2 tabs tid and placebo 6 tabs od for 2 days, followed by oral indomethacin 25 mg 1 tab tid and placebo 6 tabs once a day for 3 days with oral paracetamol 1 gm prn q. 6 hr.	Primary outcomes: pain reduction at rest and activity (using a 100 mm-VAS); secondary outcomes: adverse events, joint swelling, joint redness, uses of paracetamol, return visits
Lingling (2016), China	Opened-label, randomized, controlled, parallel-group trial	150 patients	41 patients received oral prednisolone 35 mg qid	45 patients received oral indomethacin 50 mg tid	Primary outcomes: pain reduction (using a 5 point Likert scale); secondary outcomes: adverse events, joint tenderness, erythema, swelling and joint activity

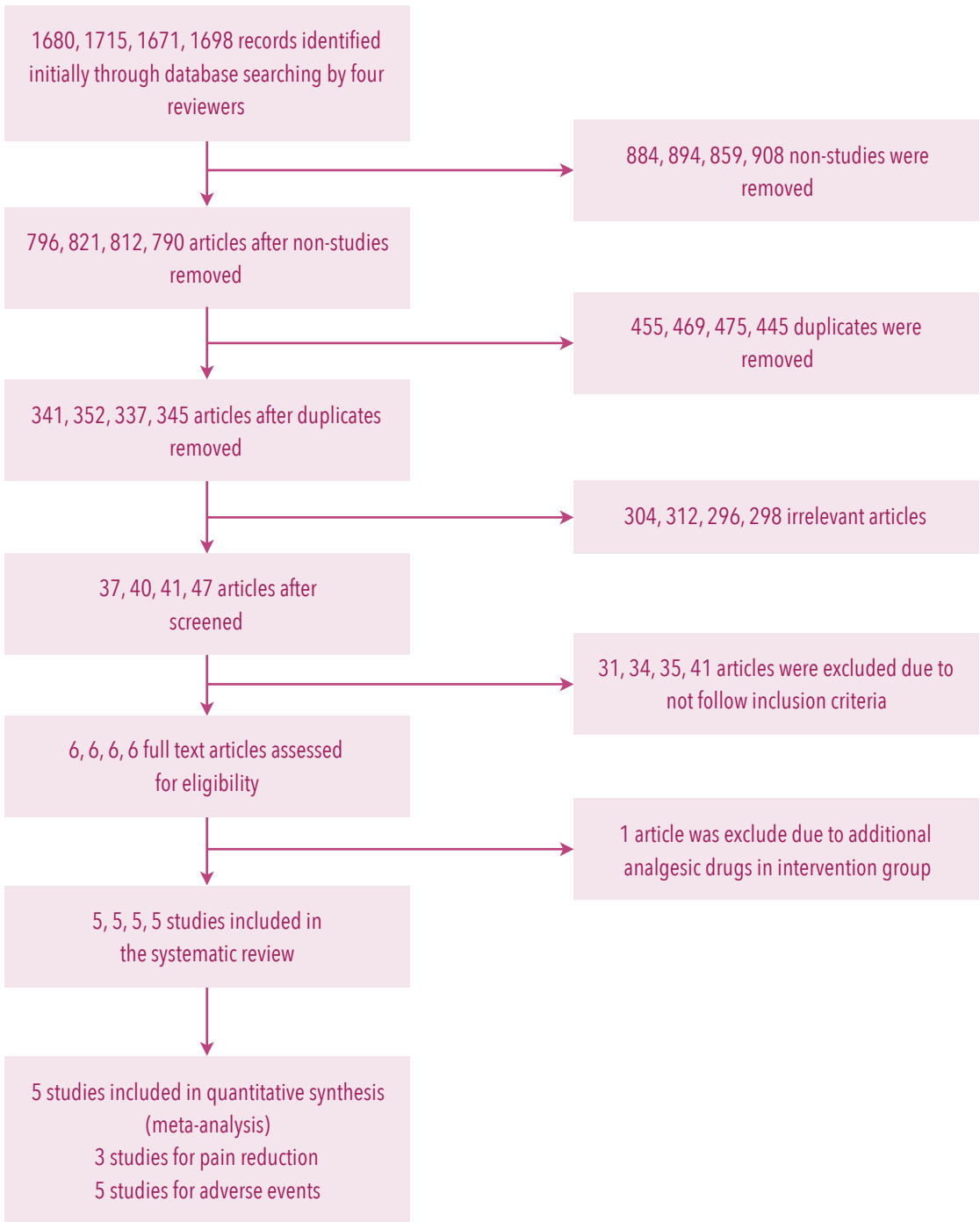

Figure 1. Study flow diagram

Table 2. Quality assessment of the included study based on Jadad score

Item	Man (2007), Hong Kong	Janssens (2008), The	Zhang (2014), China	Timothy (2016), China	Lingling (2016), China
Was the study described as randomized?	1	1	1	1	1
Was the method used to generate the sequence of randomization described and appropriate?	1	1	1	1	1
Was the study described as double blind?	1	1	0	1	0
Was the method of double blind described and was it appropriate?	1	1	0	1	0
Was there a describe of withdrawals and dropouts?	1	1	1	1	1
Score	5	5	3	5	3

Table 3. Summary of results comparing pain reduction of acute gout patients between systemic corticosteroids and NSAIDs

Outcomes	Number of studies	Participants	Number of patients		Mean difference	95%CI
			steroids	NSAIDs		
Primary outcome: pain reduction at rest in the first 6 hours using a VAS 100 mm	3	624	311	313	0.64	-2.26 to 3.45
pain reduction with activity at 2 hours using a VAS scale 100 mm	2	506	252	254	-0.28	-2.09 to 1.53
pain reduction at rest using a 5-Likert scale	1 [Lingling Xu (2016)]	86	41	45	0.11	-0.16 to 0.39
	1 [Zhang (2014)]	60	Number of patients had severe or extreme pain in each group (%)		Difference of number of patients on severe or extreme pain reduction between the two groups: preferable systemic corticosteroids (no statistical data reporting)	
		-baseline	27 (90.0%)	28 (93.3%)		
		-4 hours	17 (56.7%)	22 (73.3%)		

Table 4. Adverse events between systemic corticosteroids and NSAIDs at the end of studies.

Adverse events	Man(2007), Hong Kong		Janssens (2008), The Netherlands		Zhang (2014), China		Timothy (2016), China		Lingling (2016), China		RR (95%CI)
	Steroids (N=46)	NSAIDs (N=44)	Steroids (N=60)	NSAIDs (N=60)	Steroids (N=30)	NSAIDs (N=30)	Steroids (N=208)	NSAIDs (N=208)	Steroids (N=33)	NSAIDs (N=36)	
Major adverse events											
Require hospitalization	0	7	-	-	-	-	-	-	-	-	0.06 (0.00,1.09)
Minor adverse events											
Abdominal pain	0	17	9	9	0	3	12	23	2	3	0.47 (0.19, 1.18)
Dizziness	2	9	4	4	0	1	24	31	0	4	0.61 (0.34, 1.10)
Nausea	3	12	-	-	0	4	4	15	-	-	0.24 (0.11, 0.52)
Dry mouth	9	11	-	-	-	-	35	22	0	1	1.16 (0.64, 2.11)
Drowsiness or fatigue	7	9	-	-	-	-	26	27	0	2	0.88 (0.57, 1.36)
Indigestion or flatulence	4	14	-	-	0	2	13	19	-	-	0.47 (0.23, 0.94)
Vomiting	0	4	-	-	-	-	1	10	-	-	0.10 (0.02, 0.54)
Dyspnea	0	1	3	3	-	-	-	-	-	-	0.80 (0.20, 3.25)
Rash	3	1	-	-	-	-	11	2	-	-	4.49 (1.30, 15.53)

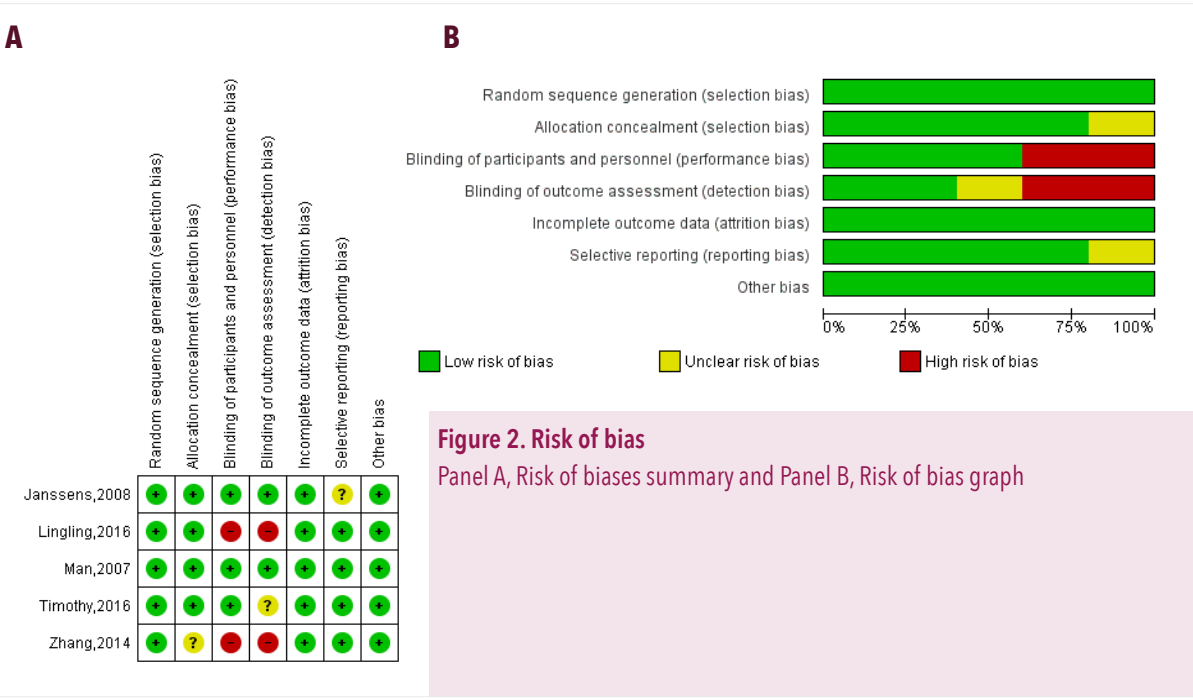

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

EXCLUSION CRITERIA

We excluded articles that used additionally paracetamol or codeine in only intervention or control group and inadequate therapeutic dosage of systemic corticosteroids or NSAIDs.

QUALITY OF REPORTING AND RISK OF BIAS

We evaluated quality and risk of bias of the included studies using Jadad score[25] and the Cochrane Collaboration's tool, recommended by Cochrane Handbook for Systematic Reviews of interventions. The Cochrane Collaboration's tool classifies the study's biases into three groups (low risk, high risk and unclear risk) and regards the following evaluation: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases.

DATA EXTRACTION

We extracted data regarding the first author's name, year of publication, country where the study was conducted, method of study, a number of participants, interventions as systemic corticosteroids as well as NSAIDs and outcomes in term of pain reduction and adverse events. Disagreeable data were determined by discussion between the four reviewers.

DATA ANALYSES

We identified different type of outcome data which pain reduction is continuous data and adverse events are dichotomous data. We calculated mean difference (MD) and 95% confidence interval (CI) for pain reduction at rest and activity while calculated relative risk (RR) and 95%CI for adverse events between systemic corticosteroids and NSAIDs in the patients with acute gout. All data were analysed by Review Manager 5.3 statistical software (RevMan 5.3) and shown the result in

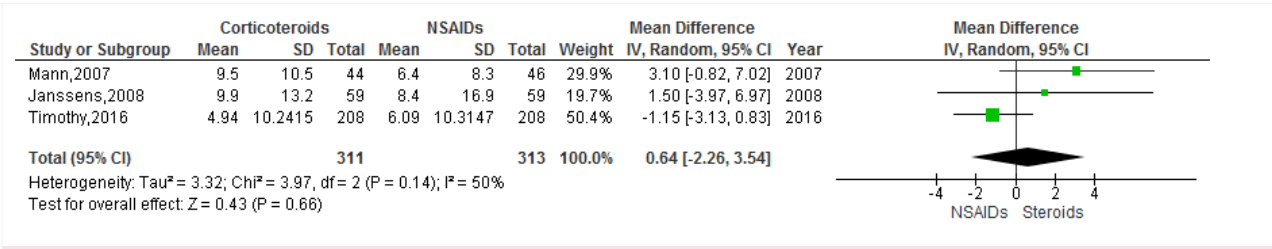

Figure 3. Forest plot of comparison: systemic corticosteroids versus NSAIDs, outcome: 1.1 pain reduction at rest in the first 6

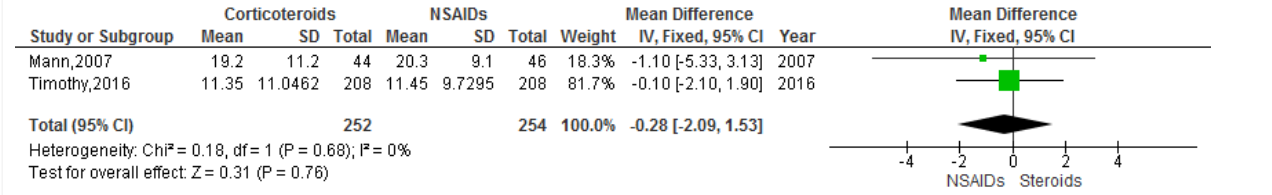

Figure 4. Forest plot of comparison: systemic corticosteroids versus NSAIDs, outcome: 1.2 Pain reduction at activity at 2 hours.

form of forest plots. Publication bias was shown in form of funnel plot. Statistical significance was described as $P<0.05$. If I^2 more than 40%, heterogeneity will be observed and we will use random-effects model for the meta-analysis. If I^2 less than 40%, we will use fixed-effects model.

RESULTS

STUDY CHARACTERISTIC

We initially identified 1680, 1715, 1671 and 1698 records by four reviewers, respectively, 884, 894, 859 and 908 records were removed due to non-studies, out of which 341, 352, 337 and 345 remaining after removed their duplicates. After screening for relevant studies, there were 37, 40, 41 and 47 articles remaining. Then, 31, 34, 35 and 41 articles were excluded mainly because of no acute gout patients and no systemic corticosteroids or NSAIDs using. We retrieved full-text studies for assessment which we included 6 studies and a study was excluded due to adding paracetamol or codeine in the only intervention group. The remaining 5 studies[19-22,26] with 834 participants were included in the analysis (Table 1). Three of them with 624 participants and two of them with 506 participants were included in the meta-analysis for pain reduction at rest and activity, respectively, and all trials were included in the meta-analysis for estimate adverse events (Figure 1).

ASSESSING RISK OF BIAS

The five studies were assessed using Jadad score and the Cochrane Collaboration's tool for assessing risks of bias. Three studies scored 5 points from Jadad score while two studies scored 3 points (Table 2). Risks of bias using the Cochrane Collaboration's tool is shown in Figure 2.

RANDOM SEQUENCE GENERATION

All studies reported the methods of random sequence.

ALLOCATION CONCEALMENT

All studies reported the methods of random sequence excepts the study by Zhang et al did not report details on concealing patient allocation.

Figure 5. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.3 nausea.

Figure 6. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.4 vomiting.

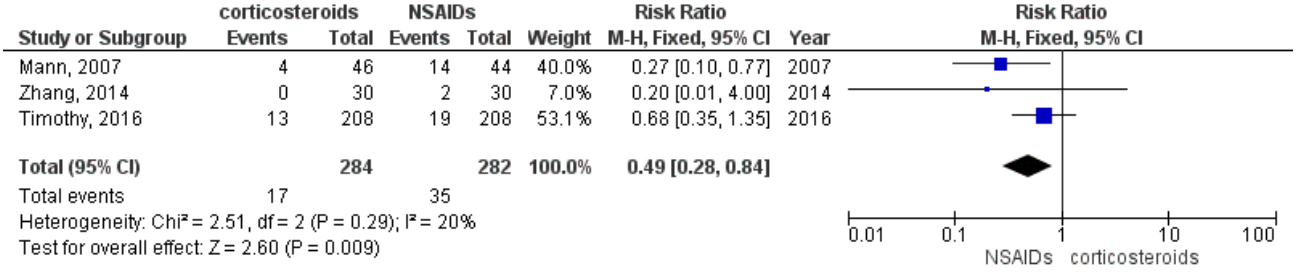

Figure 7. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.5 indigestion.

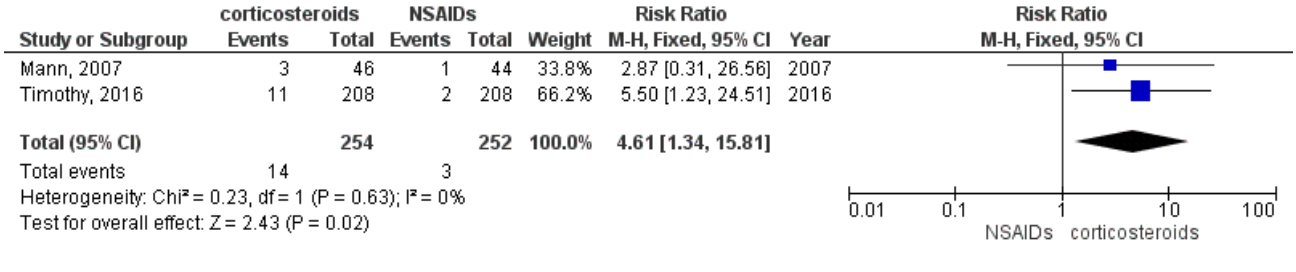

Figure 8. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.6 rash.

BLINDING OF PARTICIPANTS AND PERSONNEL

All studies reported that participants were blinded excepts the study by Zhang et al and Lingling et al were not blinded.

BLINDING OF OUTCOME ASSESSMENT

Two studies by Zhang et al and Lingling et al did not blind of outcome assessors and a study by Timothy et al did not describe on blinding of outcome assessors.

INCOMPLETE OUTCOME DATA

All studies were at low risk of bias in this category.

SELECTIVE REPORTING

All studies reported properly describe except the study by Janssens et al did not report adverse effects clearly.

OTHER BIAS

All studies had no potential conflict of interest.

PRIMARY OUTCOMES

PAIN REDUCTION AT REST

Pain reduction at rest was not significantly different between those using systemic corticosteroids and that of NSAIDs, measured by 100 mm-visual analog scale (VAS) in the first 6 hours (MD 0.64; 95% CI -2.26 to 3.54, I^2=50%, random-effect model) (Figure 3).

PAIN REDUCTION AT ACTIVITY

Pain reduction at activity was not significantly different between those using systemic corticosteroids and that of NSAIDs, measured by 100 mm-VAS in the first 2 hours (MD, -0.28; 95% CI, 2.09 to 1.53; I^2=0%, fixed-effect model) (Figure 4).

ADVERSE EVENTS

Adverse events rate were concluded from five studies. Major adverse events including death, life-threatening condition, hospitalization, disability or permanent damage, congenital anomaly and required intervention[27] were reported in the study by Man et al that those using systemic corticosteroids had lesser hospitalization requirement than that of NSAIDs (RR 0.06; 95% CI 0.00 to 1.09) while minor adverse events were reported in all included studies. Comparing systemic corticosteroids to NSAIDs, minor adverse events including nausea, vomiting and indigestion were found significant lower in those using systemic corticosteroids, (RR 0.23; 95% CI 0.11 to 0.51; RR 0.1; 95% CI, 0.02 to 0.54 and RR 0.49; 95% CI, 0.28 to 0.84, respectively) while rash was more common in those using systemic corticosteroids (RR 4.61; 95% CI 1.34 to 15.81) (Figure 5-8). Others adverse events including drowsiness, abdominal pain, dizziness, dyspnea and dry mouth were not significantly different between using systemic corticosteroids and NSAIDs (RR 0.86; 95% CI 0.56 to 1.33; RR 0.47; 95% CI 0.19 to 1.18; RR 0.62; 95% CI 0.41 to 0.95; RR 0.77; 95% CI 0.20 to 3.01; RR 1.28; 95% CI 0.85 to 1.92, respectively) (Table 4) (Figure 9-13).

PUBLICATION BIAS

We present funnel plots of the outcomes (Figure 14). However, we did not interpret due to small number of studies.

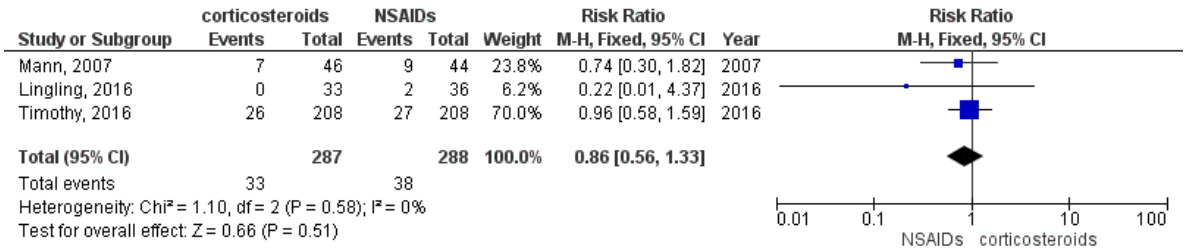

Figure 9. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.7 drowsiness or fatigue.

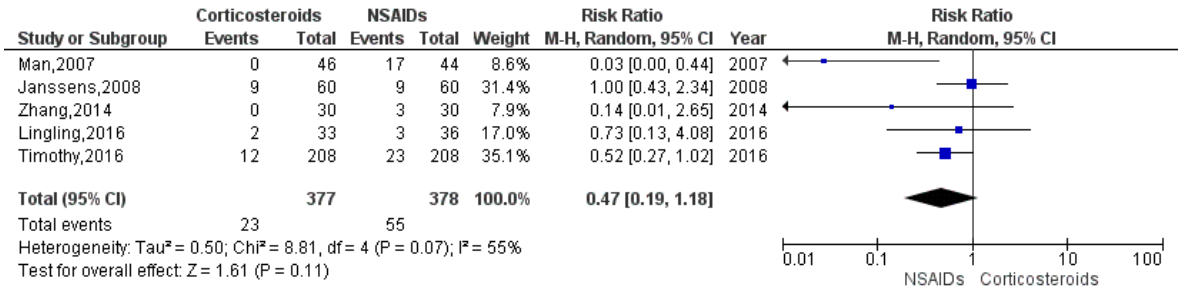

Figure 10. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.8 abdominal pain.

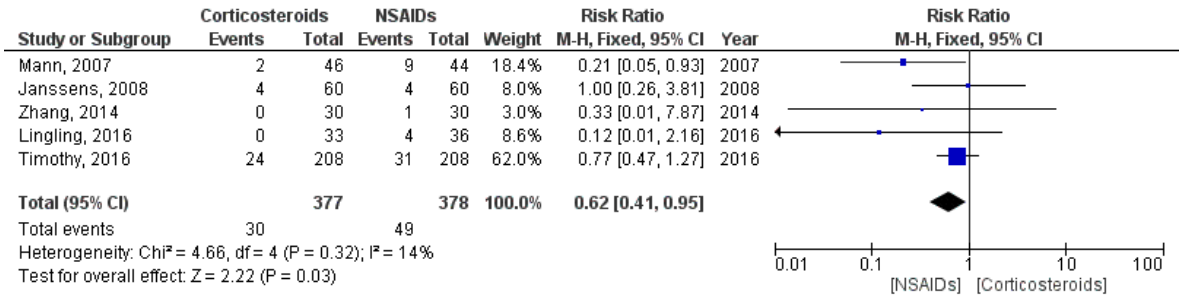

Figure 11. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.9 dizziness.

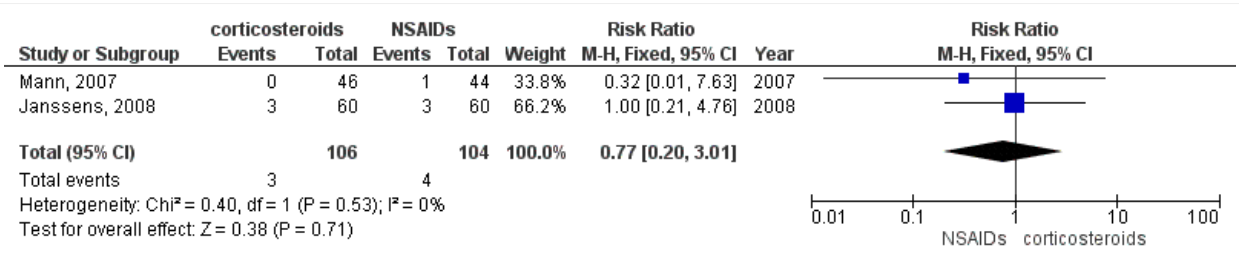

Figure 12. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.10 dyspnea.

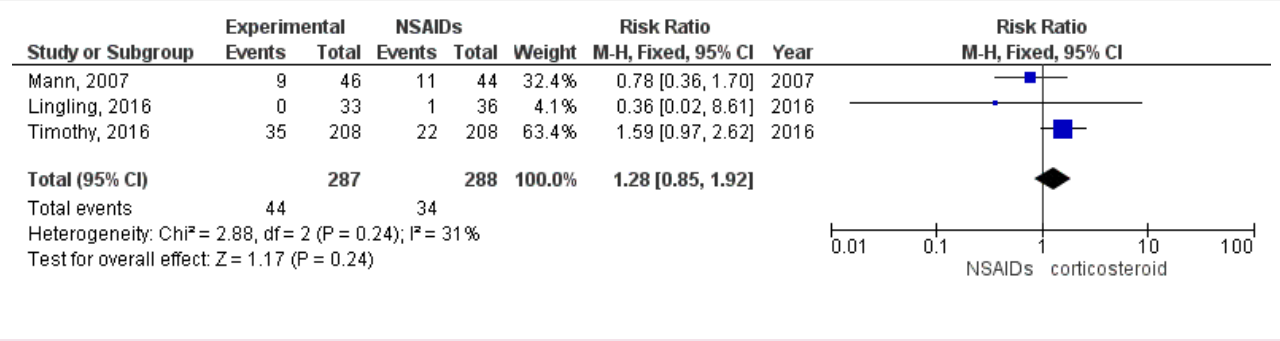

Figure 13. Forest plot: comparison systemic corticosteroids versus NSAIDs, outcome: 1.11 dry mouth.

DISCUSSION

SUMMARY OF EVIDENCE

We have assessed 5 RCTs involving 834 participants in this systematic review. All of the included articles compared capability in pain reduction and adverse events between systemic corticosteroids and NSAIDs. From three studies with 624 participants, we found that using systemic corticosteroids were not significantly different in pain reduction comparing to NSAIDs with moderate heterogeneity that may be due to difference in dosages of interventions, measurement scales, durations of assessment and methodology quality.

In all of the included studies, we found that there was higher incidence of minor adverse events including nausea, vomiting and indigestion in those using NSAIDs while rash has more events in those using systemic corticosteroids. Major adverse events were reported in one study that NSAIDs users required hospitalization more than systemic corticosteroids user. Thus, systemic corticosteroids was found superior to NSAIDs in pain reduction and adverse events.

STRENGTH AND LIMITATIONS

This review contains the largest number of acute gout patients comparing systemic corticosteroids to NSAIDs in pain reduction and adverse events. We searched through available and reliable databases. Results of this meta-analysis arose from combining data across included studies that were different in methodology quality regarding Jaded score and Cochrane Collaboration's tool. However, most of them were high quality, hence, the combined outcomes were reliable. The methodological limitations of our study are different duration of assessment, pain measurement, poor available data and incomplete reporting of statistical data thus they did not be combined with outcome analysis for pain reduction. We did not receive additional data from the authors of two included studies.[20,22] We did not conduct subgroup analyses for addressing heterogeneity due to data limitation.

COMPARISON TO OTHER STUDIES

Our review based on five trials shows robust evidence that no significant difference in pain reduction between using systemic corticosteroids and NSAIDs in acute gout. This result was

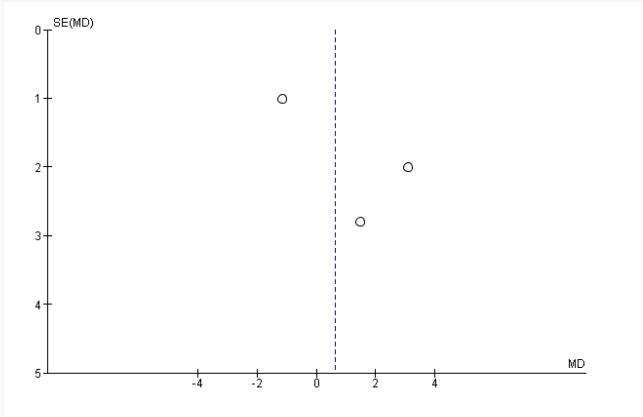

Figure 14. Funnel plot: systemic corticosteroids versus NSAIDs, outcome: 1.1 pain reduction at rest at in the first 6 hours.

supported by previous review which included 2 RCTs overlapping with ours.[28] Another review identifying 3 RCTs stated that the efficacy of systemic corticosteroids in acute gout were inconclusive with no meta-analysis as various types of systemic corticosteroids were used in the primary studies, administered in different routes and different kinds of comparator drugs.[18] However, the current review was able to conclude the treatment outcomes regarding to pain reduction as we included additional four RCTs with larger sample sizes in which NSAIDs were the comparator drugs.

The present review shows that efficacies on pain reduction of systemic corticosteroids and NSAIDs are similar with lower rate of adverse events and there are also two systematic reviews which state that short course of these drugs were safe.[29,30] Moreover, there is a study reported that oral prednisolone is more cost-effective than indomethacin for treatment in patients with acute gout.[31] However, many guidelines for acute gout management recommend that NSAIDs are the first line drugs for pain reduction.[16,32] Those recommendation, nonetheless, based on RCTs without comparing NSAIDS with systemic corticosteroids.

CONCLUSION AND IMPLICATION

Our systematic review including five RCTs showed that efficacy of systemic corticosteroids and NSAIDs in pain reduction was similar in patient with acute gout, but three minor adverse events including nausea, vomiting and indigestion were found more often in those using NSAIDs. Therefore, we prefer short-term systemic corticosteroids to NSAIDs especially in those with contraindications for NSAIDs.

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COMPETING INTERESTS: This study has no competing on interest.
FUNDING:None

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