

A systematic review and meta-analysis of naproxen for prevention heterotopic ossification after hip surgery

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Abstract

Background: The aim of this study was to assess the efficacy of naproxen in preventing heterotopic ossification (HO) after hip surgery (total hip arthroplasty [THA] and hip arthroscopy).

Methods: Using databases (PubMed, EMBASE, and Web of Science), we conducted an electronic, systematic search of randomized controlled trials (RCTs) comparing naproxen versus placebo on HO after hip surgery. The risk ratio (RR) of the dichotomous data, weighted mean difference (WMD) of continuous data, and 95% confidence intervals (CIs) were calculated to assess the effects of naproxen in patients with hip surgery.

Results: A total of 4 studies including 269 patients were analyzed. Risk of bias was relatively high in allocation concealment and blinding. Compared with control group, administration naproxen was associated with a significantly reduction of the occurrence of HO at final follow-up after hip surgery ($P < .05$). What's more, naproxen was associated with a reduction of the Brooker I and II HO ($P < .05$). However, there was no significant difference between the Brooker III HO between naproxen and control groups ($P > .05$). Furthermore, there was no significant difference between the complications ($P > .05$) between naproxen and control groups.

Conclusion: Naproxen has a beneficial role in reducing the total occurrence of HO, Brooker I and II HO after hip surgery. However, conclusions are limited due to the lack of high-quality studies. More high quality studies may help in a more reliable therapy for HO.

Abbreviations: BMP = bone morphogenic protein, CI = confidence interval, HO = heterotopic ossification, NSAIDs = nonsteroidal anti-inflammatory drugs, RCTs = randomized controlled trials, ROM = range of motion, RR = risk ratio, SD = standard deviation, WMD = weighted mean differences.

Keywords: heterotopic ossification, hip surgery, meta-analysis, naproxen

1. Introduction

Heterotopic ossification (HO) is a common complication of hip surgeries.^[1,2] It is reported that the incidence of HO varied from 0% to 73% following hip surgeries. HO is characterized by abnormal ossification of soft tissues, resulting in the formation of ectopic lamellar bone.^[3,4] HO can occur after injuries to muscle, bone, and brain as well as postoperatively.^[5] For most patients, the extent of HO is mild to moderate, but about 9% of cases are severe, with a Brooker grade greater than III.

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Current prophylaxis strategies for the prevention of HO after hip surgery including drug therapy by nonsteroidal anti-inflammatory drugs (NSAIDs) and corticoids and radiotherapeutic methods.^[6,7] HO usually develops gradually, against which preventive measures are possible to avoid osteoid matrix formation in early phase. Prophylactic treatment of heterotopic ossification now plays a crucial role in the management of heterotopic ossification. A range of drugs have been tried for HO prophylaxis and NSAIDs have been the mainstay of pharmacological therapy.^[7] Naproxen belongs to the non-selective NSAIDs and was used for prophylaxis for prevention of HO after hip surgery for many years. However, whether naproxen has a definite effect on preventing HO after hip surgery is unknown.

The objective of this meta-analysis of RCTs is to further evaluate the whether administration with naproxen has a beneficial role in reducing the total occurrence of HO, Brooker I, II, and III HO after hip surgery.

2. Method

2.1. Literature search

Both published and unpublished literatures were search by 2 reviewers (AHZ and XC) in following database: PubMed (1950–August 2018), EMBASE (1974–August 2018), the Cochrane Library (August 2018 Issue 3), and the Google database (1950–August 2018). Search strategies were listed in Supplement file 1, <http://links.lww.com/MD/C910>. In addition, further articles were obtained by reviewing references of the selected articles.

No language or date restrictions were applied. No ethic approval was necessary for this article due to this study type was systematic review. This meta-analysis was registered in Research Registry (available: <https://www.researchregistry.com/>; number: reviewregistry625).

2.2. Inclusion and exclusion criteria

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines were followed for the inclusion of studies in this systematic review and associated meta-analyses.^[8] Included studies were considered eligible if they met the PICOS criteria as follows:

Population: Patients with hip surgeries (THA and hip arthroscopy).

Intervention: administration naproxen for prophylaxis of HO (any dose).

Comparator: placebo or nothing.

Outcomes: outcomes including incidence of HO at final follow-up, incidence of Brooker I, II, and III HO after surgery and the potential complications.

Study design: RCTs with prospective collected data.

Only published clinical studies were included. There was no restriction on the language of the included studies.

2.3. Data collection and outcome measures

A standard data extraction form was used to collect the relevant data from included studies. Two researchers independently extracted the following data from each study that met the criteria for inclusion: first authors, year of publication, country, participants demographic characteristics, treatment regime for each groups. Discrepancies were resolved by discussion. We identify total incidence of HO at final follow-up as primary outcome. Secondary outcomes including Brooker I, II, and III HO after hip surgery. If there was a discrepancy could not be resolved by consensus, we tried to obtain and confirm data from investigators.

2.4. Quality assessment

We used Cochrane collaboration's tool for assessing the quality of the included studies.^[9,10] Quality assessment included details of random sequence generation, allocation concealment, blinding of participants and personnel, blind outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Each item was scored as high, low, or unclear risk of bias. Any divergences between reviewers were solved by discussion.

2.5. Statistical analysis

The meta-analysis was undertaken by using Stata software, version 13.0 (Stata Corp., College Station, TX). For dichotomous variables, risk ratio (RR) with the corresponding 95% confidence interval (CI) was calculated, and correspondingly weighted mean difference (WMD) was used to estimate numerical variables. Where no heterogeneity was found in the included studies, the data were pooled using a fixed-effect model. Statistical heterogeneity was assessed by I^2 index ($I^2 < 50\%$, no heterogeneity, $I^2 > 50\%$, large heterogeneity).^[11] Publication bias was evaluated by Egger test.^[12] Statistical significance was considered when the P value was $< .05$.

3. Results

3.1. Characteristics of the trials

We identified a total of 441 citations as potential relevant studies. Four RCTs^[13–16] containing 269 patients finally met the predetermined inclusion criteria as Fig. 1. General characteristics of the included studies were presented in Table 1. Two studies were originated from Denmark, 1 from France, and the rest were from America. Sample size ranged from 23 to 54. One study included hip arthroscopy patients and the rest studies only included THA patients. The dose of naproxen ranged from 250 to 500mg.

3.2. Quality assessment of the included studies

The methodological quality of the included trials is summarized in Figs. 2 and 3. All articles^[13–16] included were described as randomized controlled trials. Random sequence generation was reported appropriately in only one study.^[13] Only one study^[16] did not reported allocation concealment. Blinding of outcome assessment was with low risk of bias in 2 studies.^[13,16] Other biases, selective reporting were all with low risk of bias in all of the included studies.

3.3. Total incidence of HO at final follow-up

Four studies^[13–16] totaling 266 patients reported total incidence of HO at final follow-up after hip surgery. There was no heterogeneity between the included studies ($I^2 = 0.0\%$, $P = .578$). And the pooled results indicated that administration of naproxen was associated with reduced the occurrence of HO at 12 months after surgery (RR=0.21, 95% CI 0.11, 0.76, $P = .000$, Fig. 4).

3.4. Incidence of Brooker I HO

Comparison of Brooker I HO between naproxen and control groups was conducted between the 4 included studies, which enrolled 266 patients (135 patients receiving naproxen and 131 patients receiving control), as shown in Fig. 5. Heterogeneity testing showed that there was no heterogeneity between the studies ($P = .939$, $I^2 = 0.0\%$), so the fixed-effect model was used to pool the data for the 2 groups. The overall estimate showed that the naproxen was associated with a reduction of the incidence of Brooker I HO (RR=0.22, 95% CI=0.11–0.45, $P = .000$, Fig. 5).

3.5. Incidence of Brooker II HO

Four included studies consisting of 266 patients (135 patients receiving naproxen and 131 patients receiving control) investigated incidence of Brooker II HO. None heterogeneity among studies ($P = .852$, $I^2 = 0\%$) was found, so we used the fixed-effect model to pool the data. The overall estimate indicated that the pooled MD was 0.34 (95% CI=0.14–0.83, $P = .018$, Fig. 6), suggesting that naproxen has a beneficial role in reducing the incidence of Brooker II HO.

3.6. Incidence of Brooker III HO

Four included studies consisting of 266 patients investigated the incidence of Brooker III HO between naproxen and control groups. None heterogeneity among studies ($P = .970$, $I^2 = 0\%$)

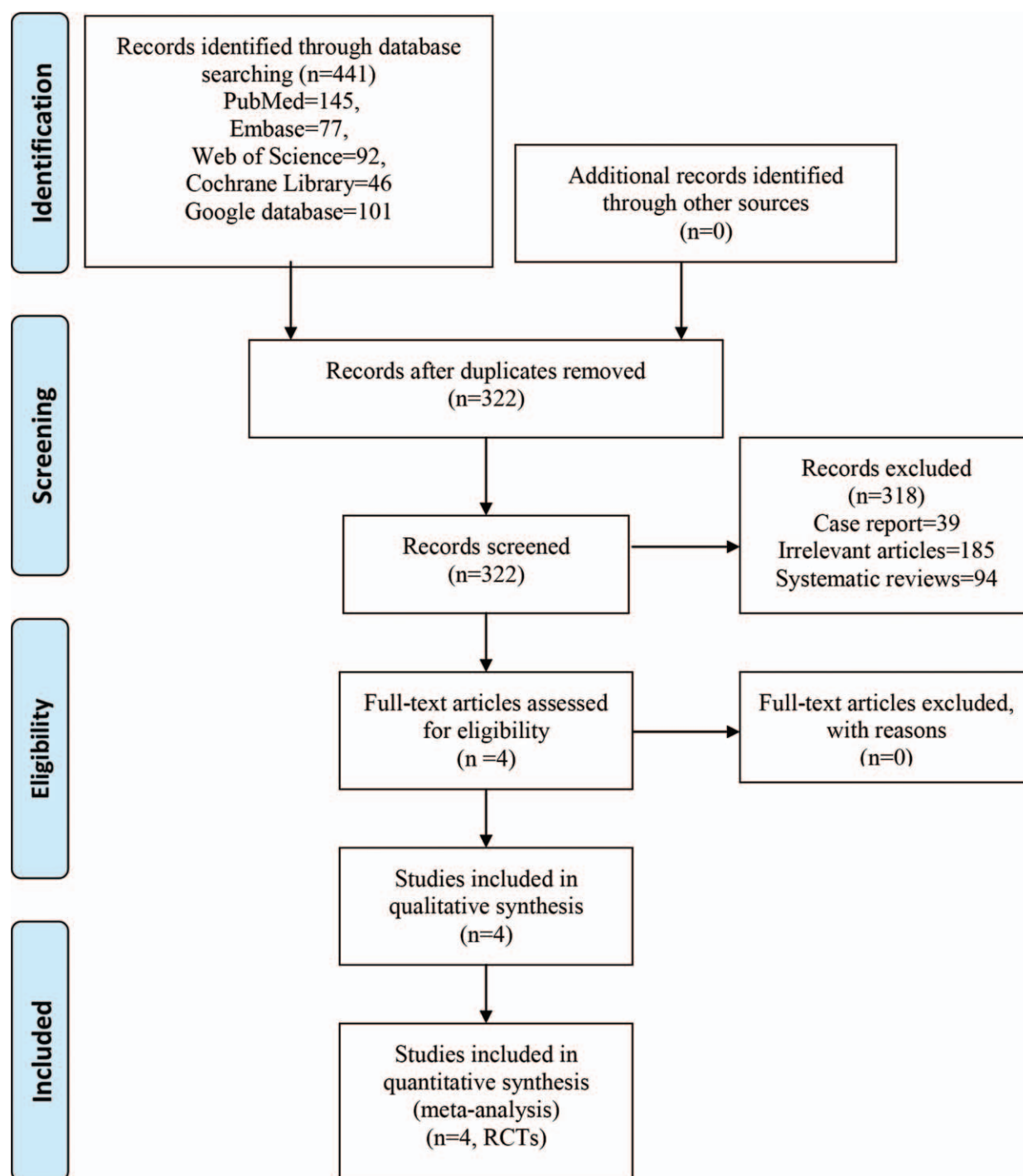


Figure 1. PRISMA flowchart for the included studies. PRISMA=preferred reporting items for systematic reviews and meta-analysis.

Table 1

The general characteristic of the included studies.

Author	Country	Sample (I/C)	Age (I/C)	Surgery	Intervention	Control	Outcomes	Follow-up	Study
Beckmann 2015	American	54/54	35.1/35.1	Hip arthroscopy	Naproxen (500 mg, twice daily, total 3 weeks)	Placebo	1,2,3,4,5	3 weeks	RCTs
Vielpeau 1999	France	28/28	66/62.8	THA	Naproxen (250 mg, 3 times daily, total 6 weeks)	Placebo	1,2,3,5	6 weeks	RCTs
Gebuhr 1991	Denmark	28/27	75/70	THA	Naproxen (500 mg twice on operation day, 250 mg, 3 times daily, total 4 weeks)	Placebo	2,3,5	4 weeks	RCTs
Gebuhr 1995	Denmark	27/23	72/73	THA	Naproxen (500 mg twice daily for 7 days from operation day on)	Placebo	1,2,3,4	12 weeks	RCTs

C = control group; I = intervention group; THA = total hip arthroplasty. 1, the occurrence of HO at 1.5 months after surgery; 2, the occurrence of HO at 3 months after surgery; 3, the occurrence of HO at 6 months after surgery; 4, the occurrence of HO at 12 months after surgery; 5, the occurrence of complications.

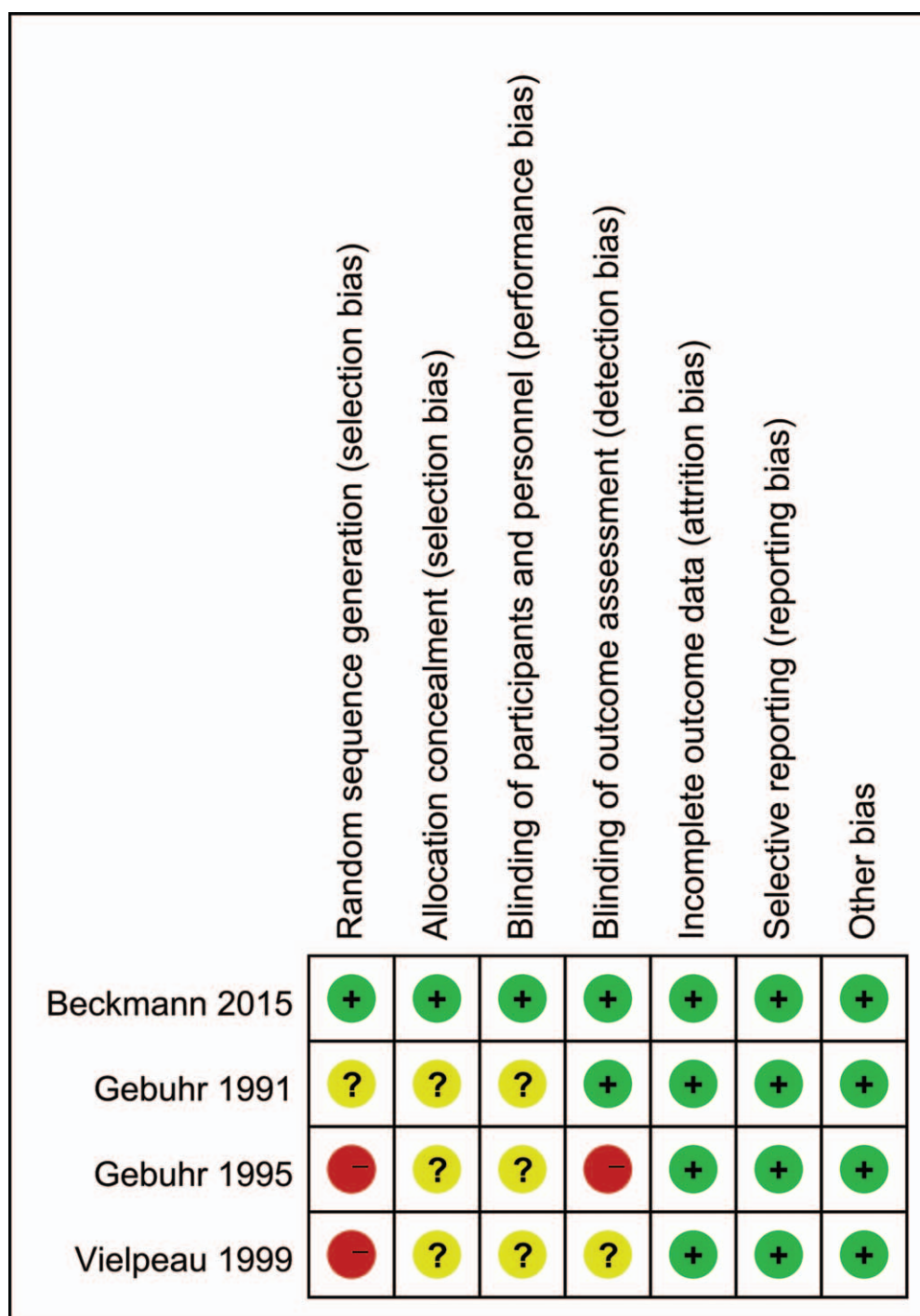


Figure 2. The risk of bias summary for the included studies.

was found, so we used the fixed-effect model to pool the data. Pooled results shown that, compared with control group, naproxen has no effects on the reduction of the incidence of Brooker III HO (RR=0.23, 95%CI=0.04–1.32, $P=.100$, Fig. 7).

4. Complication

A total of 2 studies reported complications between naproxen and control groups with no heterogeneity ($I^2=0.0\%$, $P=.719$). Final results shown that there was no significant difference

between the occurrence of complications (RR=1.26, 95% CI 0.83, 1.93, $P=.282$, Fig. 8). All of the complications of the included studies were listed in Table 2

4.1. Publication bias

For the meta-analysis of naproxen on total incidence of HO at final follow-up, there was no evidence of publication bias by inspection of the funnel plot (Fig. 9) and formal statistical tests (Egger test, $P=.72$; Begg test, $P=.65$).

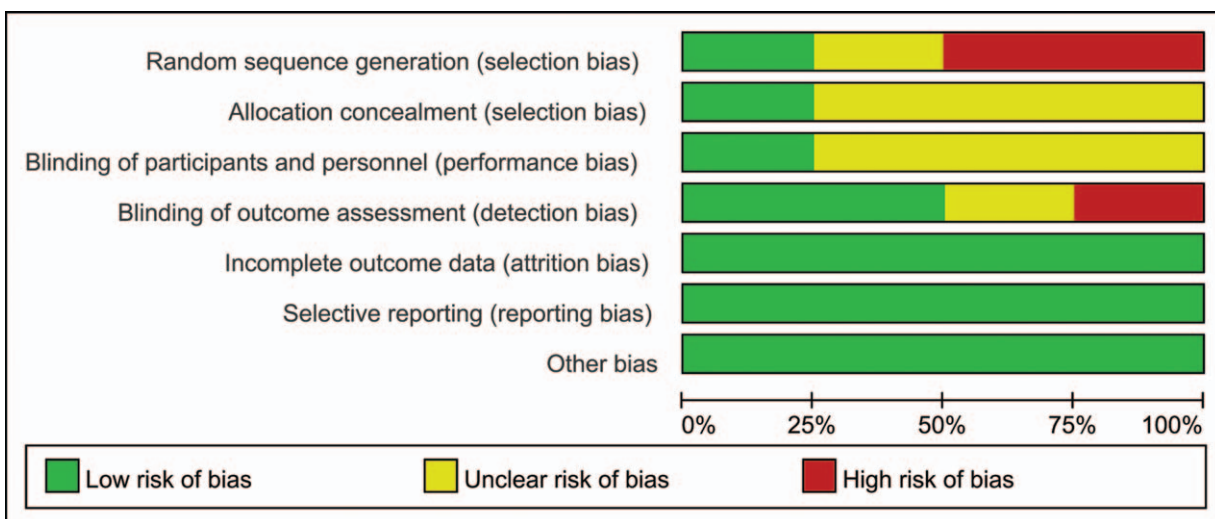


Figure 3. The risk of bias graph for the included studies.

5. Discussion

5.1. Main findings

This is the first meta-analysis that comparing naproxen for preventing the occurrence of HO after hip surgery (hip fracture and THA). Our meta-analysis found that naproxen compared with placebo significantly reduced the occurrence of HO at final follow-up for hip surgery patients; naproxen has no benefit on the complications after hip surgery.

5.2. Compared with other meta-analysis

Only one relevant meta-analyses on the topic have been published.^[17] Although the main finding of our meta-analysis was consistent with previous meta-analyses, differences between ours and the previous ones should be noted. First, previous meta-analysis only comparing total incidence of HO after hip surgery. In comparison, our current meta-analysis comparing the occurrence of HO according to Brooker criteria. Second, we used Grade evidence to summary the grade

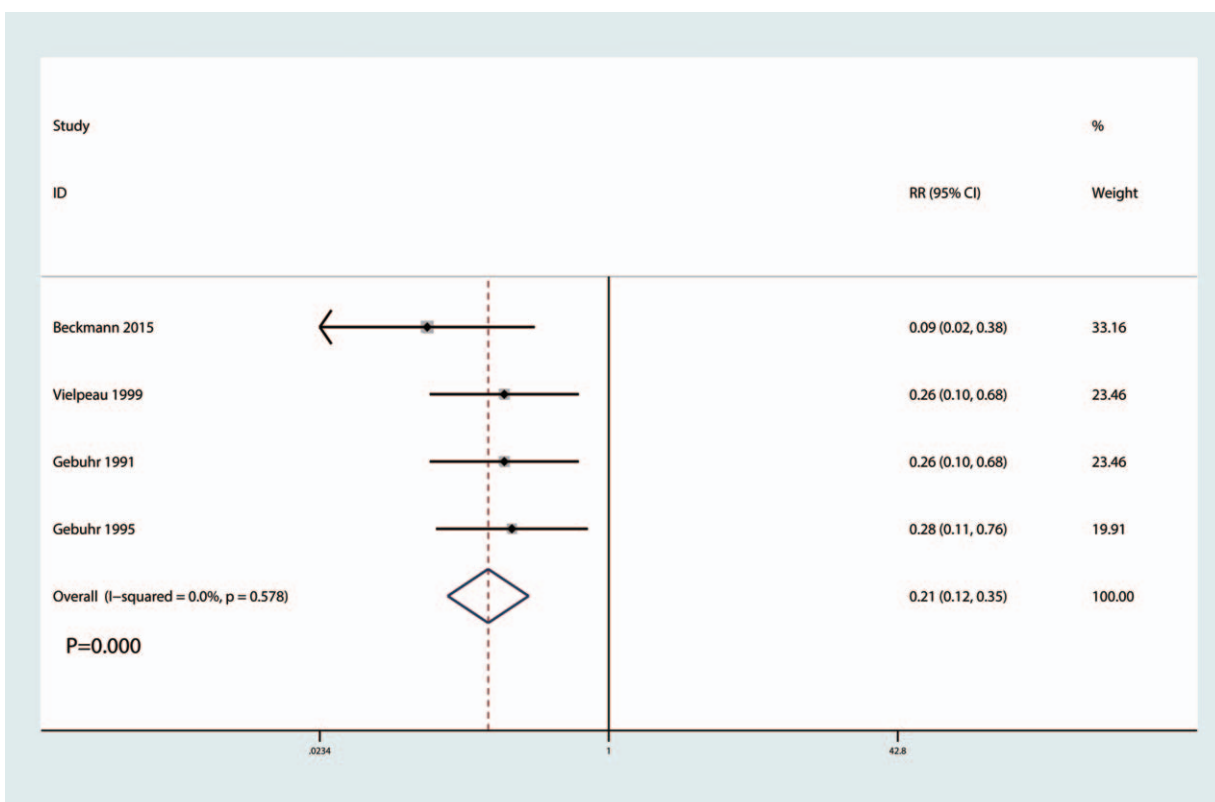


Figure 4. Forest plot comparing the occurrence of HO at final follow-up after hip surgery between the 2 groups. HO=heterotopic ossification.

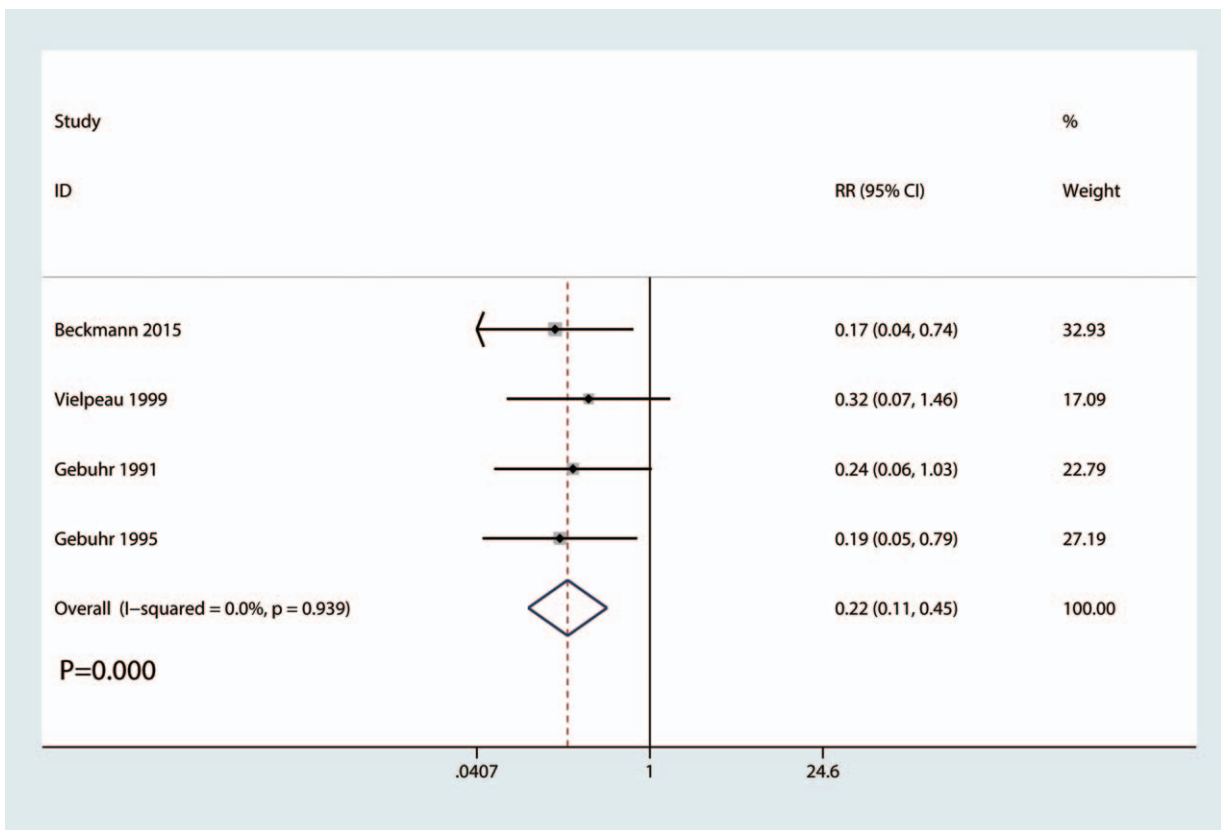


Figure 5. Forest plot comparing the incidence of Brooker I HO after surgery between the 2 groups. HO=heterotopic ossification.

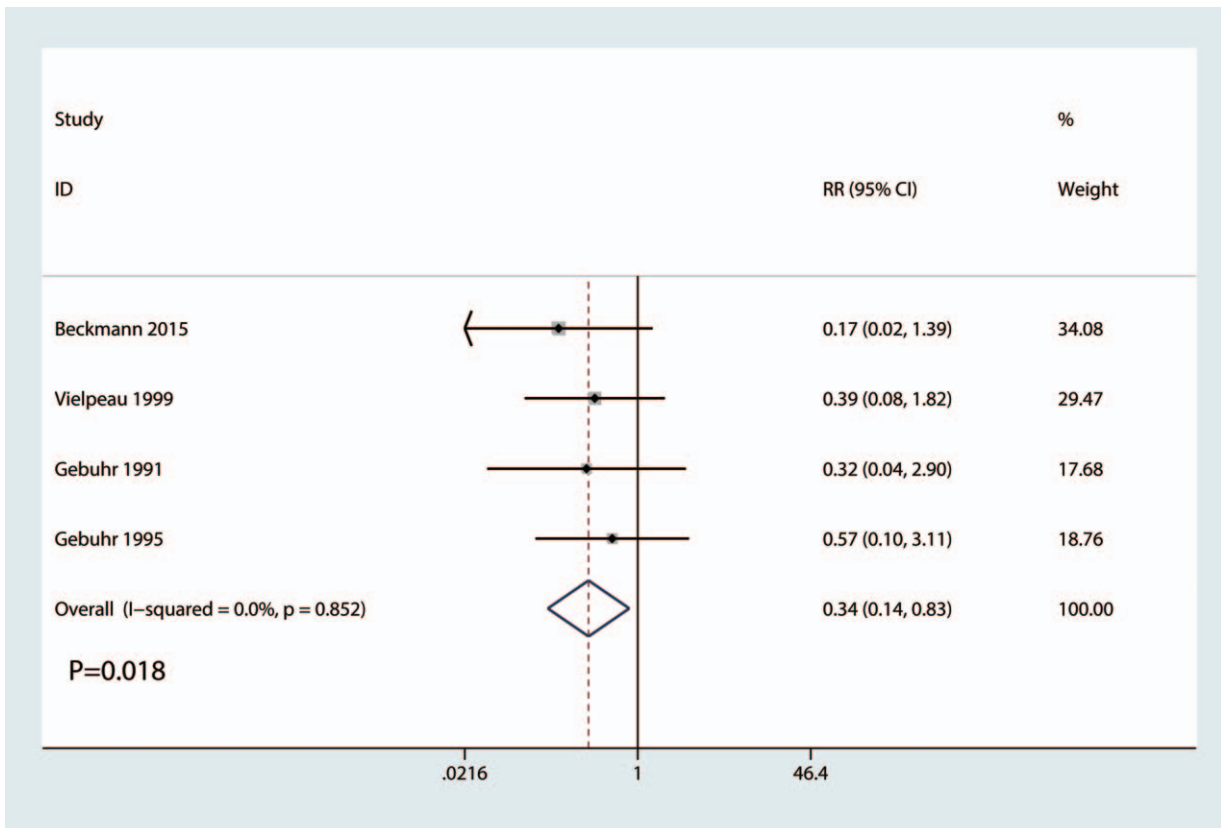


Figure 6. Forest plot comparing the incidence of Brooker II HO after surgery between the 2 groups. HO=heterotopic ossification.

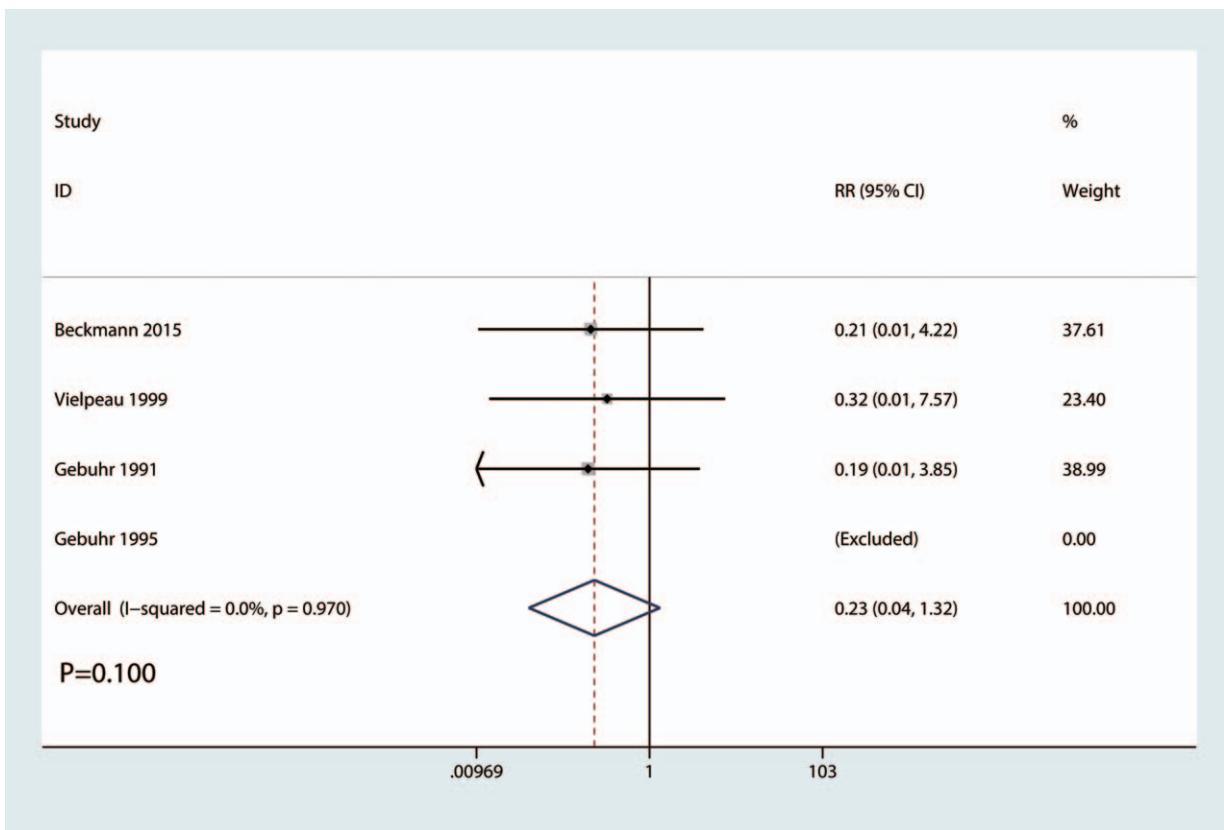


Figure 7. Forest plot comparing the incidence of Brooker III HO after surgery between the 2 groups. HO=heterotopic ossification.

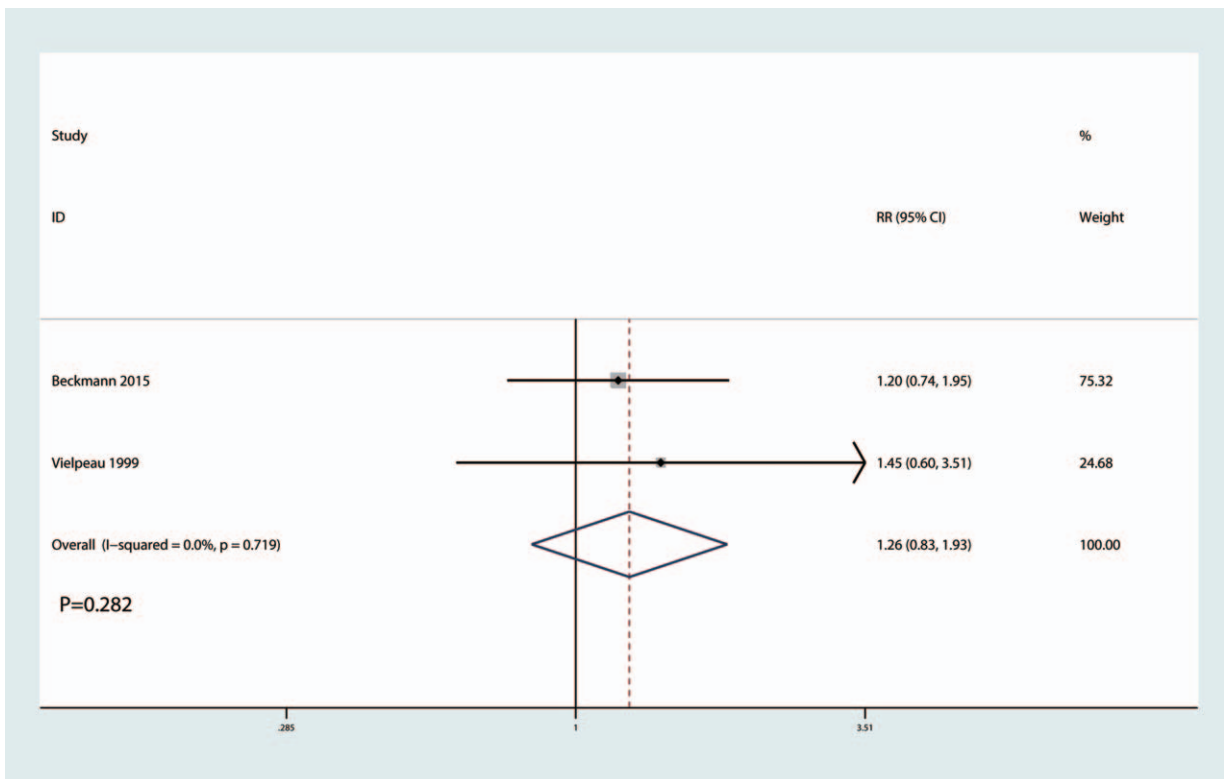


Figure 8. Forest plot comparing the occurrence of complications after surgery between the 2 groups.

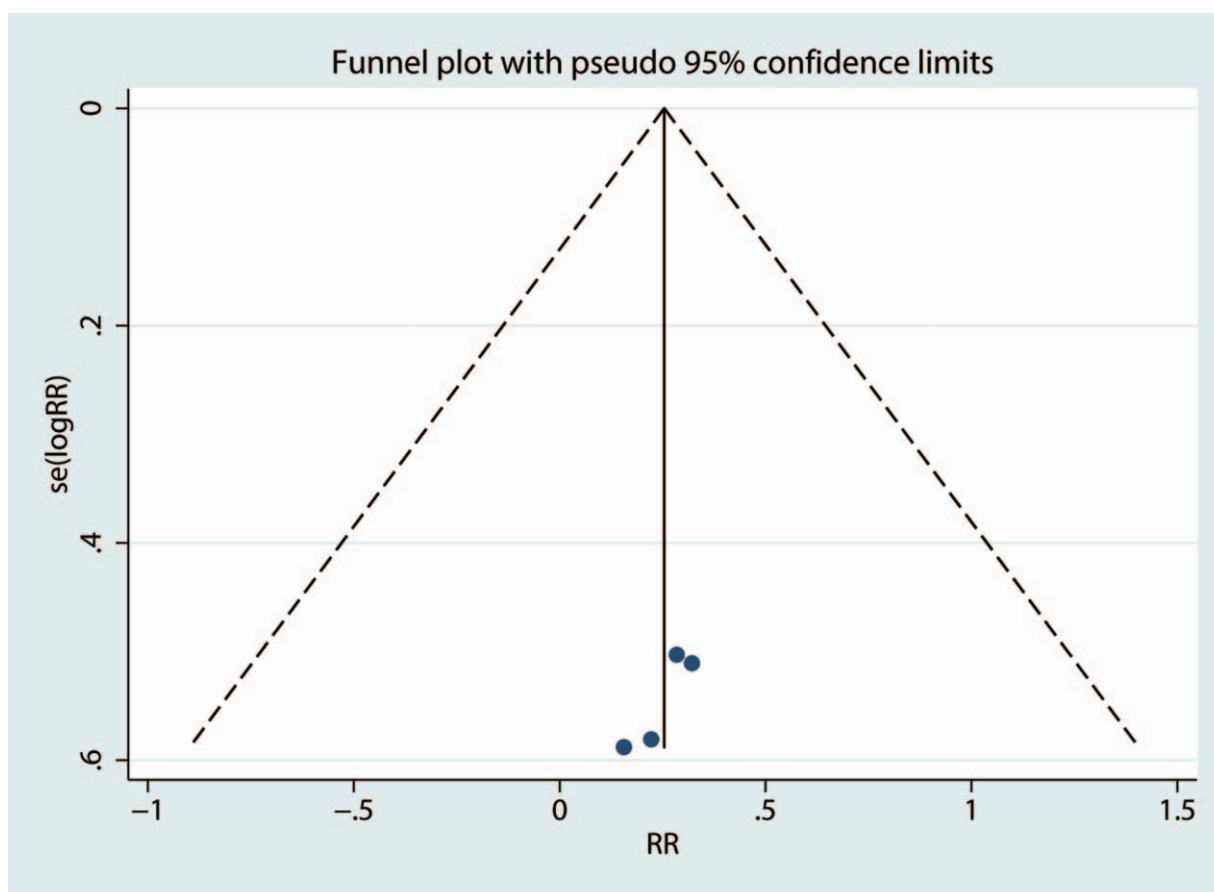


Figure 9. Funnel plot of the occurrence of HO at final follow-up. HO=heterotopic ossification.

evidence of the outcomes. Third, we performed subgroup analysis and sensitivity analysis to further increase the robust of our results.

5.3. Implications for clinical practice

Our meta-analysis showed that the benefit existed only naproxen but not placebo in preventing HO after hip surgery. Beckmann et al^[13] found that prophylaxis with naproxen was effective in reducing the prevalence of HO following hip arthroscopy. Therefore, naproxen might be the optimal drug for hip surgery. Yeung et al^[18] revealed that the incidence of postoperative HO may be decreased with the use of NSAID prophylaxis in hip arthroscopy. For current meta-analysis, it is difficult to clarify which dose of naproxen is more efficient since the current evidence is limited and further trials are warranted.

5.4. Limitations

This meta-analysis has limitations. First, there were some methodological limitations in the included RCTs. Second, the possibility of publication bias was not measured since the number of the included studies was <10. Third, one study focused on the arthroscopy patients and may cause large heterogeneity for the final outcomes. Given these limitations, the results of this meta-analysis should be interpreted cautiously.

5.5. Implications for further studies

We performed subgroup analysis for the outcomes, trials should pay attention to the methodological design, and double-blinded and clearly reported randomized controlled trials are required. What's more, different dose of naproxen (from 250 to 500 mg) was administration and further studies should be compared for different dose of naproxen for preventing HO after hip surgery.

6. Conclusions

In conclusion, naproxen is efficacious in HO prophylaxis and can be used routinely after hip surgery. There is no difference in the incidence of complications between naproxen and control groups.

Author contributions

Conceptualization: Ke-Lai Wang.

Data curation: Xiang Chen, Ke-Lai Wang.

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Software: Xiang Chen, Qing-Xia Zhao.

Supervision: Qing-Xia Zhao.

Validation: Qing-Xia Zhao.

Writing – original draft: Ai-Hua Zhang.

Writing – review & editing: Ai-Hua Zhang.

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