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Review

Optimal strategies for the prevention of heterotopic ossification after total hip arthroplasty: A network meta-analysis

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ABSTRACT

Background: Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), selective NSAIDs, and radiation are widely used for the prevention of heterotopic ossification (HO) after total hip arthroplasty (THA). Previous studies have suggested that nonselective NSAIDs, selective NSAIDs and radiation can prevent HO after THA, though the results are conflicting. In this network meta-analysis, we aimed to comprehensively analyze the efficacy and safety of three strategies for preventing HO after THA compared to a placebo.

Patients and methods: Relevant studies about nonselective NSAIDs, selective NSAIDs, radiation and controls that were used to prevent HO after THA were collected. Data were extracted independently by two reviewers. Network meta-analysis was applied to assess treatment efficacy and safety. The surface under the cumulative ranking curve (SUCRA) method was used to assess which treatment was ranked the highest. The node-splitting method was used to calculate inconsistency.

Results: Radiation was found to be the most efficient option for preventing overall incidence of HO and Brooker IV, I, II and III HO after THA. Selective NSAIDs were the safest option, and radiation was ranked second for preventing HO after THA, as the treatments were ranked taking discontinuation caused by nongastrointestinal side effects (DNGSE) and the incidence of complications into consideration.

Conclusions: A network meta-analysis concluded that radiation is the most efficacious method for preventing HO after THA.

1. Introduction

Total hip arthroplasty (THA) is one of the most common and effective options for end-stage hip osteoarthritis or femoral head necrosis [6,36]. Heterotopic ossification (HO) following THA is a common complication and can result in impingement. The incidence of HO ranges from 5% to 90% in open reduction and internal fixation patients and from 16% to 53% in THA patients [3,10]. When HO reaches higher degrees of ossification (a Brooker classification of IV), patients can experience pain and a decreased range of motion. Therefore, it is necessary to prevent the occurrence of HO in patients undergoing THA.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and radiation, two distinct treatment options, are the two most commonly used options for preventing HO. There are two common types of NSAIDs, selective NSAIDs and nonselective NSAIDs. The literature on the efficacy and safety of both selective and nonselective NSAIDs in preventing HO after THA is inconclusive. There is also controversy around whether using NSAIDs or radiation is best for preventing HO after THA. For example, according to Vavken et al., NSAIDs and radiation have comparable effects on postoperative occurrence of HO [39]. Although in a separate meta-analysis by Vavken et al., pooled results indicated that NSAIDs were more cost-effective than radiation in preventing HO after THA [40]. However, the previous meta-analyses have the following disadvantages: (1) they did not distinguish between selective and nonselective NSAIDs; and (2) they did not make direct comparisons between selective NSAIDs and radiation.

In this network meta-analysis, we aimed to explore the most efficacious treatment option among selective NSAIDs, nonselective NSAIDs and radiation for preventing HO after THA.

2. Material and methods

This meta-analysis was reported with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines.

2.1. Search strategy

Potential randomized controlled trials (RCTs) were identified from

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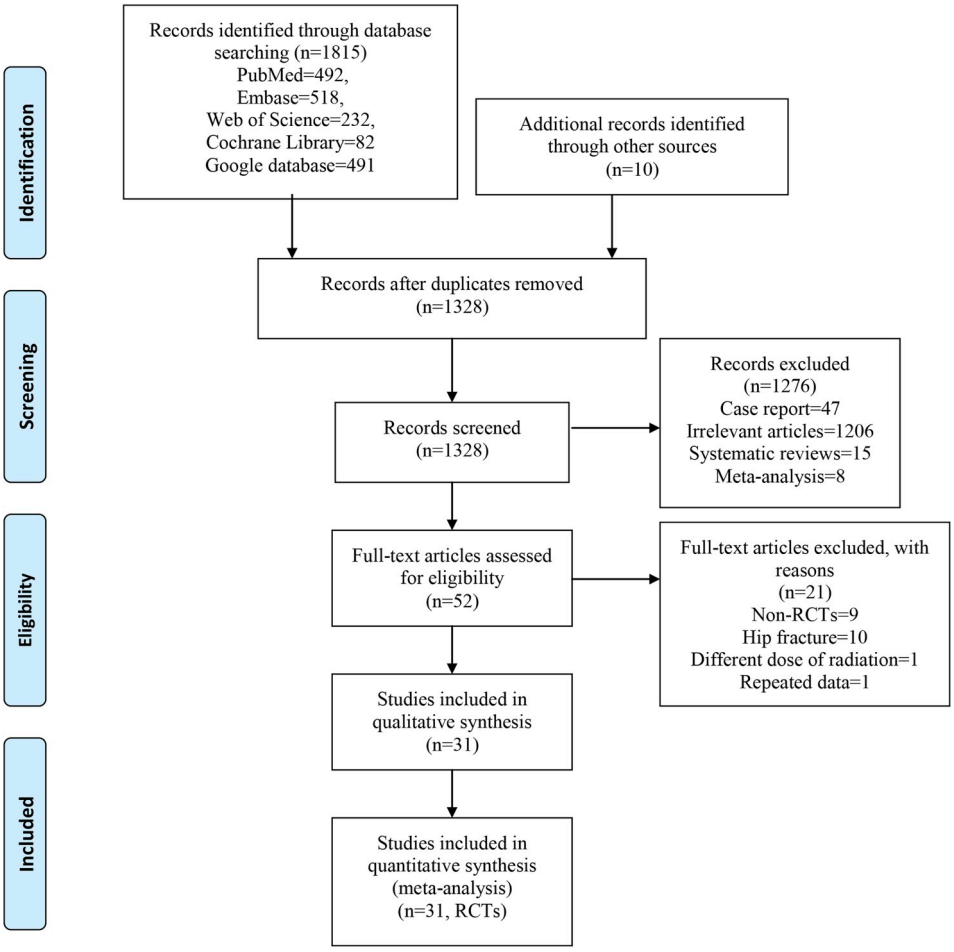

Fig. 1. Flow chart of study selection.

inception of the databases (PubMed, Embase, Web of Science, Cochrane Library and Google database) through December 2017. Keywords and mesh terms were as follows: "Arthroplasty OR Replacement OR Hip" OR "arthropl? OR pros? OR surg? OR replac? [tiab]" OR "hip prosthesis OR joint prosthesis") AND "heterotopic ossification" OR ("radiation [mesh]" OR "radiation" "radiotherapy?"). The reference lists from retrieved articles and other potential data sources were manually reviewed to identify any studies that were initially omitted.

2.2. Inclusion and exclusion criteria

Inclusion criteria for this network meta-analysis were as follows. (1) The study used a randomized controlled trial (RCT) or quasi RCT design. (2) Subjects enrolled in the study were adult patients preparing for THA. (3) The study made a comparison between at least two of the four prophylaxis HO intervention methods included in the present analysis, i.e., nonselective NSAIDs, selective NSAIDs, radiation and controls. (4) Clinical outcomes of the enrolled study included a Brooker IV HO classification, overall incidence of HO, incidence of Brooker I, II and III HO classifications, DNGSE, DGSE and the incidence of complications.

The exclusion criteria were as follows: (1) studies that were combined with other strategies to prevent HO after THA; (2) non-RCTs; (3) studies of patients who had hip fractures but did not receive THA; and (4) studies that lacked sufficient data to synthesize outcomes.

2.3. Data extraction and quality assessment

Data extraction was conducted by two reviewers (). All of the data were collected in a pregenerated standard Microsoft® Excel (Microsoft Corporation, Redmond, Washington, USA) file. If there were discrepancies between the two reviewers, discussion was used until an agreement was reached. If there were insufficient data to pool, we attempted to contact the original author to obtain the additional data.

The general characteristics extracted from the included studies included author's name, publication year, country, treatment and comparison protocols, duration of the treatment, clinical outcomes (incidence of Brooker IV HO; overall incidence of HO; incidence of Brooker I, II and III HO; DNGSE; DGSE; and the incidence of complications) and follow-up duration. The quality of eligible RCTs was evaluated according to the Cochrane Collaboration Handbook (www.cochrane.de). A total of 7 domains were used to assess the overall quality: random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each domain was measured as low, unclear or high bias.

2.4. Statistical analyses

Network meta-analysis concerning multiple treatments was performed with a random-effect model within a Bayesian framework [22]. The pooled estimates of the odds ratios (OR) and 95% credible intervals (CrIs) were used to evaluate the eight outcomes (incidence of Brooker IV HO; overall incidence of HO; incidence of Brooker I, II and III HO; DNGSE; DGSE; and the incidence of complications). All of the outcomes were calculated by the R (V.3.2.2) GEMTC package (version.0.6) [26]. Furthermore, we examined comparisons made with direct and indirect evidence. The P value was greater than 0.05, which indicated that there was little consistency between the studies [7]. We also sorted the four different strategies (nonselective NSAIDs, selective NSAIDs, radiation and controls)

by rank probabilities. The rank probabilities were assessed for each strategy by the surface under the cumulative ranking curve (SUCRA). A lower SUCRA value indicates a better rank for the intervention [32]. The publication bias of this network meta-analysis was assessed by Deek's funnel plot asymmetry test. P values less than 0.05 were considered to be statistically significant for differences between studies.

3. Result

3.1. Study characteristics

Fig. 1 demonstrates the flow of studies in the review process. A total of 1815 references (PubMed = 492, Embase = 518, Web of Science = 232, Cochrane Library = 82, Google database = 491) were identified using the search strategies. After removing 497 duplicates, 1328 studies were selected through title and abstract screening, and full texts were obtained for further evaluation. After prescreening, 1276 studies were excluded for not meeting the inclusion criteria. A total of 31 studies [1,2,4,5,8,9,11–14,16–21,23,25,28–31,33–35,37,38,41–43,45] containing 7769 patients were found to fulfil the inclusion criteria and were reviewed in the present network meta-analysis.

The general characteristics of the included studies is shown in Table 1. Included studies were published between 1991 and 2016. A total of 8 nonselective NSAIDs (ibuprofen, indomethacin, naproxen, flurbiprofen, aspirin, ketorolac, diclofenac and ketoprofen) and 5 selective NSAIDs (meloxicam, tenoxicam, rofecoxib, celecoxib and etoricoxib) were examined in the included studies. The age of patients in the included studies ranged from 56 to 73 years. Follow-up duration ranged from 1.5 months to 24 months. There were two types of radiation included: preoperative and postoperative. The daily dose of radiotherapy ranged from 3 Gy to 8 Gy.

3.2. Quality assessment

The risk of summary and risk of bias graphs are shown in Fig. 2A and B, respectively. The percent of studies with a low risk of bias for random sequence generation and allocation concealment was 25%. The remaining 75% of studies had an unclear risk of bias. The percent of studies with a low risk of bias for blinding of participants and personnel was 30%, while 55% of studies were at a low risk of bias for outcome assessment. The percent of studies having low risks of bias for incomplete outcomes, selective reporting and other biases were 90%, 95% and 62%, respectively. Fig. 3 shows the network plots of eligible comparisons for the overall incidence of HO; the incidences of Brooker I, II, III or IV HO; DNGSE; DGSE; and the incidence of complications after THA.

4. Results from network meta-analysis

4.1. Incidence of Brooker IV HO

A network pairwise meta-analysis was performed examining the impact of the different strategies in preventing the primary outcome of Brooker IV HO. As shown in the results, both nonselective NSAIDs and radiation were associated with a reduction in the incidence of Brooker IV HO (OR = 0.19, 95% CrI 0.028–0.69; OR = 8.8e-10, 95% CrI 9.4e-14–0.053, Fig. 4).

Table 1
Main characteristics of included studies. 1; overall incidence of HO; 2; incidence of Brooker I HO, 3, incidence of Brooker II HO, 4, incidence of Brooker III or IV HO, 5, DNGSE, 6, the incidence of complications.

Study	Country	Treatment/Comparison	Duration, days	Outcomes	Follow-up	Age (mean, years)
Ahrengart 1994	Sweden	Ibuprofen (n = 21, 1500 mg)/Placebo (n = 26)	10 days/10 days	1,2,3,4,5	12 months	70
Barthel 2002	German	Meloxicam (n = 123, 7.5mg/n = 26, 15 mg)/Indomethacin (n = 26, 100 mg)	14 days/12 days	1,2,3,4,6	12 months	63
Burssens 1995	Belgium	Tenoxicam (n = 29, 10mg/20 mg)/Placebo (n = 29)	42 days/42 days	1,2,3,4,6	6 months	61
Elmstedt 1985	Sweden and Finland	Ibuprofen (n = 21, 1200)/Placebo (n = 21)	92 days/92 days	1,2,3,4	12 months	70
Fransen 2006	Australia and New Zealand	Ibuprofen (n = 449, 1200 mg)/Placebo(n = 407)	14 days/14 days	1,2,3,4,5,6	12 months	66
Gebuhr 1991	Denmark	Naproxen (n = 28, 750 mg)/Placebo(n = 27)	28 days/28 days	1,2,3,4,5	12 months	73
Gebuhr 1996	Denmark	Tenoxicam (n = 61, 40 mg/20 mg)/Placebo (n = 62)	5 days/5 days	1,2,3,4,5	12 months	72
Grohs 2007	Sweden	Rofecoxib (n = 50, 25 mg)/Indomethacin (n = 25, 100 mg)	7 days/7 days	1,2,3,4,5,6	12 months	60
Hoikka 1990	Finland	Flurbiprofen (n = 34, 200 mg)/Placebo (n = 34)	21 days/21 days	1,2,3,4,5	6 months	49
Kienapfel 1999	Germany	Indomethacin (n = 55, 100 mg)/radiation (n = 50, 600 cGy)/Placebo (n = 49)	42 days/3.5 days/42 days	1,2,3,4,5,6	18 months	65
Kjaersgaard-Andersen 1993	Denmark	Indomethacin (n = 19, 100 mg)/Placebo (n = 22)	14 days/14 days	1,2,3,4,5	3 months	
Neal 2000	New Zealand	Aspirin (n = 1332, 162 mg)/Placebo(n = 1337)	35 days/35 days	1,2,3,4	9 months	71
Persson 1998	Sweden	Ibuprofen (n = 46, 1200 mg)/Placebo (n = 45)	21 days/21 days	1,2,3,4,5	12 months	65
Pritchett 1995	America	Ketorolac (n = 152, 90 mg)/Placebo (n = 151)	2 days/2 days	1,2,3,4	24 months	
Reis 1992	Germany	Diclofenac (n = 80, 150 mg)/Placebo(n = 80)	42 days/42 days	1,2,3,4,5	24 months	70
Saudan 2007	Switzerland	Celecoxib (n = 123, 400 mg)/Ibuprofen (n = 127, 1200 mg)	10 days/10 days	1,2,3,4,5	3 months	59
Schmidt 1988	Denmark	Indomethacin (n = 102, 75 mg)/Placebo (n = 99)	42 days/42 days	1,2,3,4	12 months	70
van der Heide 2007	Netherlands	Rofecoxib (n = 85, 50 mg)/Indomethacin (n = 89, 150 mg)	7 days/7 days	1,2,3,4	12 months	68
Vielpeau 1999	France	Naproxen (n = 28, 750 mg)/Indomethacin (n = 27, 75 mg)/Placebo (n = 27)	42 days/42 days	1,2,3,4	6 months	
Wahlstrom 1991	Sweden	Diclofenac (n = 50, 150 mg)/Placebo (n = 50)	42 days/42 days	1,2,3,4,5	24 months	64
Zhao 2011	China	Celecoxib (n = 25, 200 mg)/Indomethacin (n = 25,75 mg)	42 days/42 days	1,2,3,4,6	1.5 months	71
Vastel 2005	French	Ketoprofen (300 mg)/Celecoxib(2 × 200 mg/d)	5 days/7 days	1,2,3,4	12 months	65
Winkler 2016	Germany	Diclofenac(2 × 75 mg/d)/Etoricoxib(1 × 90 mg/d)	9 days/9 days	1,2,3,4,6	6 months	
Legenstein 2003	Austria	Indomethacin (2 × 50 mg/d)/Meloxicam(1 × 7.5 mg/d)	12 days/12days	1,2,3,4,6	6 months	
Romano 2004	Italia	Indomethacin (2 × 50 mg/d)/Celecoxib(2 × 200 mg/d)	20 days/20 days	1,2,3,4,5,6	12 months	59
Kolbl 1997	Germany	Indomethacin(n = 31, 50 mg)/radiation (n = 19, 4 × 3Gy)	7 days/5 days	1,2,3,4	12 months	66
Knelles 1997	Germany	Indomethacin(n = 31, 150 mg)/radiation (n = 19, 4 × 3Gy)	7 days/5 days	1,2,3,4,5,6	12 months	67
Kolbl 1998	Germany	Diclofenac(n = 25, 150 mg)/radiation (n = 25, 1 × 7 cGy preoperative)	14 days	1,2,3,4	6 months	65
Sell 1998	Germany	Diclofenac(n = 25, 150 mg)/radiation (n = 25, 3 × 3.3Gy)	3 weeks/3 days	1,2,3,4,5,6	6 months	61
Bremen-Kuhne 1997	Germany	Indomethacin(n = 31, 75 mg)/radiation (n = 19, 1 × 6Gy)	6 weeks/5 days	1,2,3,4,6	6 months	56
Martini 1995	Germany	Diclofenac(n = 25, 150 mg)/radiation (n = 25, 5 × 2Gy)	10 days/4 days	1,2,3,4,5,6	12 months	58

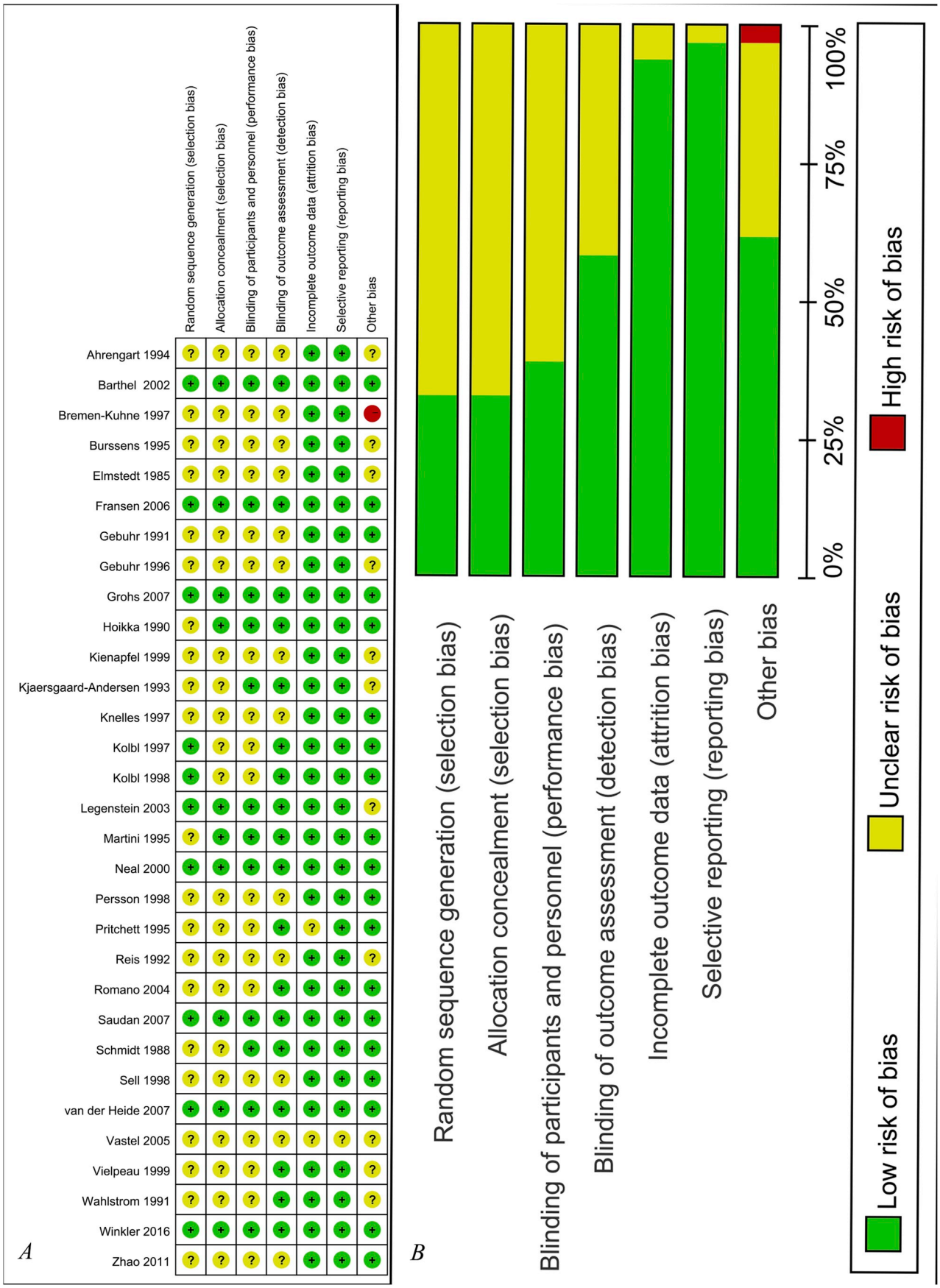

Fig. 2. Risk of bias assessment of each included study. (A) Risk of bias graph. (B) Risk of bias summary.

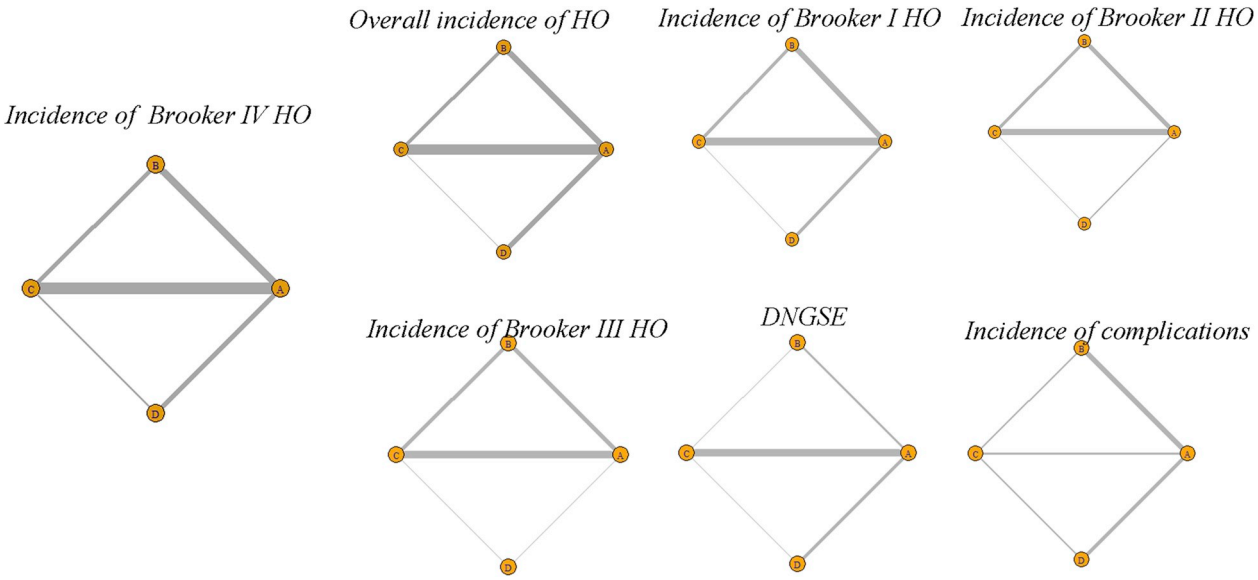

Fig. 3. Network plots of eligible comparisons of Brooker IV HO; overall incidence of HO; incidence of Brooker I HO, Brooker II HO, and Brooker III HO; DNGSE; and the incidence of complications.

4.2. Overall incidence of HO

A total of 31 studies including direct or indirect comparisons between the different strategies were included. Overall incidence of HO after THA were independently compared for each method; ORs and corresponding 95% CrIs were calculated.

As indicated in the results, compared to the control, nonselective NSAIDs, selective NSAIDs and radiation each had a significantly lower incidence rate of HO after THA (OR = 0.34, 95% CrI 0.22–0.51; OR = 0.42, 95% CrI, 0.24–0.73; OR = 0.17, 95% CrI = 0.076–0.37, respectively, Fig. 5C and Table 2). Compared with nonselective NSAIDs and selective NSAIDs, radiation had a significantly lower incidence rate of HO after THA (OR = 0.50, 95% CrI 0.25–1.0; OR = 0.41, 95% CrI, 0.17–0.97, Fig. 5 A and B and Table 2).

There was no statistical significance in the overall incidence of HO between nonselective NSAIDs and selective NSAIDs (OR = 1.2, 95% CrI 0.73–2.1, Fig. 5 B and Table 2). Of the three strategies, radiation had the lowest incidence rate of HO after THA (Fig. 5D and Table 2).

4.3. Incidence of Brooker I HO

There were no statistically significant difference in the incidence of Brooker I HO after THA for nonselective NSAIDs, selective NSAIDs and radiation compared to the control (OR = 0.77, 95% CrI 0.46–1.3; OR = 1.2, 95% CrI, 0.64–02.3; OR = 0.39, 95% CrI = 0.14–1.0, respectively, Fig. 6C and Table 2). Compared to selective NSAIDs, radiation had a significantly lower incidence of Brooker I HO after THA (OR = 0.32, 95% CrI 0.11–0.90, Fig. 6B and Table 2). Among the three strategies, radiation had the lowest incidence of Brooker I HO after THA (Fig. 6D and Table 2).

4.4. Incidence of Brooker II HO

Compared to control, nonselective NSAIDs, selective NSAIDs and radiation all had a significantly lower incidence of Brooker II HO after THA (OR = 0.46, 95% CrI 0.28–0.69; OR = 0.59, 95% CrI, 0.34–0.98; OR = 0.10, 95% CrI = 0.014–0.47, respectively, Fig. 7C and Table 2). There was no statistically significant difference in the overall incidence of Brooker II HO between nonselective NSAIDs and selective NSAIDs (OR = 1.3, 95% CrI 0.76–2.2, Fig. 7B and Table 2). Of the three strategies, radiation had the lowest incidence rate of HO after THA (Fig. 7D and Table 2).

4.5. Incidence of Brooker III HO

As indicated in the results, compared to the control, nonselective NSAIDs, selective NSAIDs and radiation all had a significantly lower incidence of Brooker I HO after THA (OR = 0.20, 95% CrI 0.049–0.44;

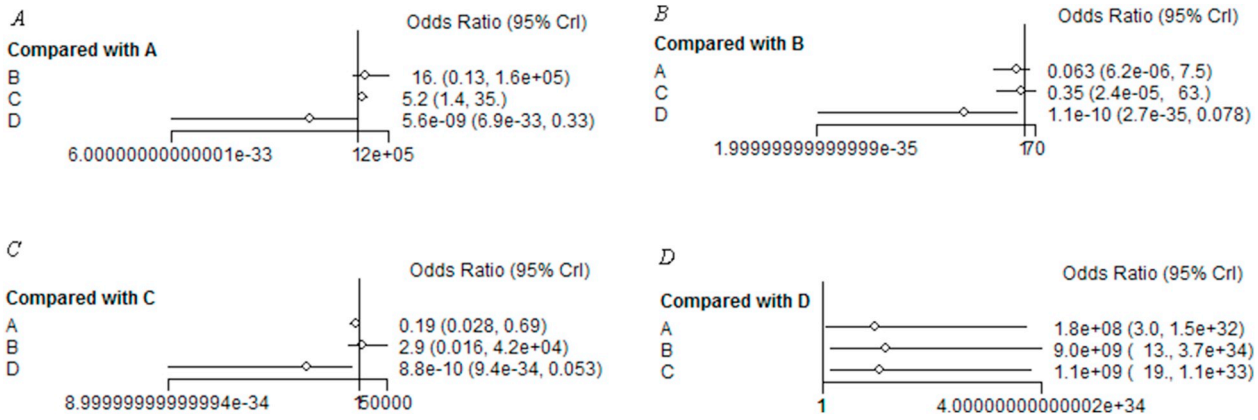

Fig. 4. The effect of different options for Brooker IV HO.

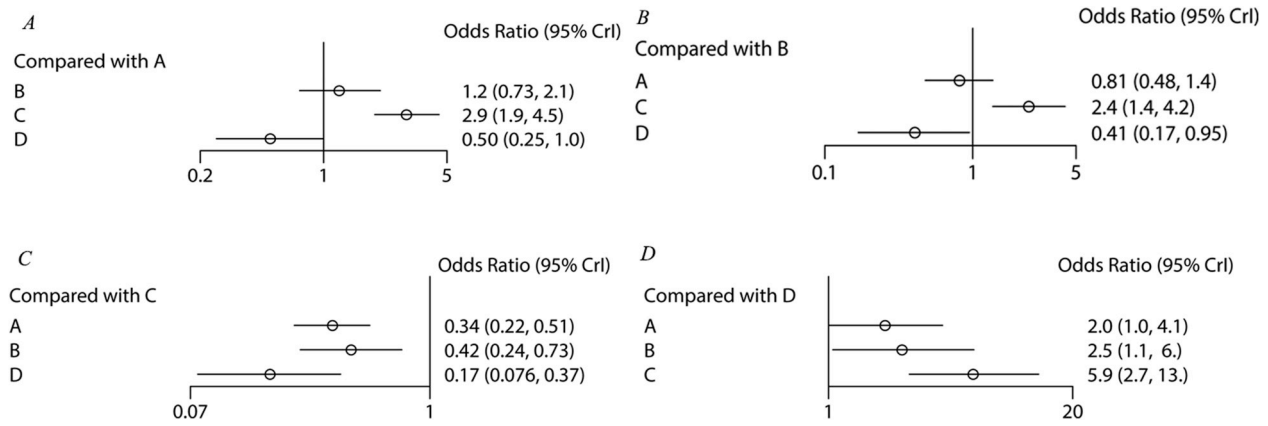

Fig. 5. The effect of different options for overall incidence of HO (A: Nonselective NSAIDs; B: Selective NSAIDs; C: Controls; D: Radiation).

OR = 0.13, 95% CrI, 0.025–0.46; OR = 1.8e-14, 95% CrI = 8.1e-46–0.040, respectively, Fig. 8C and Table 2). No statistically significant difference was found for the overall incidence of HO between non-selective NSAIDs and selective NSAIDs (OR = 1.4, 95% CrI 0.37–5.3, Fig. 8B and Table 2). Of the three strategies, radiation had the lowest incidence rate of HO after THA (Fig. 8D and Table 2).

4.6. Discontinuation caused by nongastrointestinal side effects (DNGSE)

There were no statistically significant differences between non-selective NSAIDs, selective NSAIDs and radiation compared to the control, for the incidence of DNGSE after THA (OR = 1.2, 95% CrI 0.76–1.9; OR = 0.51, 95% CrI, 0.20–1.2; OR = 0.89, 95% CrI = 0.29–2.4, respectively, Fig. 9C and Table 2). Compared with nonselective NSAIDs, selective NSAIDs had a significantly lower incidence of DNGSE (OR = 0.43, 95% CrI 0.17–0.96, Fig. 9 A, B and Table 2). Among the three strategies, selective NSAIDs had the lowest incidence rate of DNGSE after THA (Fig. 9 D and Table 2).

4.7. Incidence of complications

Fourteen studies focused on the incidence of complications after THA. As indicated in the results, compared to selective NSAIDs, non-selective NSAIDs, controls and radiation had an increased incidence in complications after THA (OR = 3.2, 95% CrI 1.9–6.0; OR = 2.2, 95% CrI 1.1–4.3; OR = 3.2, 95% CrI 1.4–7.6, respectively, Fig. 10C and Table 2). Of the three strategies, selective NSAIDs had the lowest incidence of complications after THA (Fig. 10 D and Table 2).

4.8. DGSE

Since radiation does not produce DGSE, we analyzed the DGSEs for only the selective NSAIDs, nonselective NSAIDs and controls. The results are presented in Supplement S1. The results indicate that non-selective NSAIDs were associated with an increase in the DGSE (OR = 1.85, 95 %CI = 1.55, 2.87). The SURCA value also indicated the same result.

Table 2
The efficacy and safety of different strategies for preventing HO after THA according to the network meta-analysis using odds ratios (ORs) and corresponding 95% credential intervals (Crls). P values in italics are significant.

Overall incidence of HO	Non-selective NSAIDs	1.2(0.73,2.1)	*2.9(1.9,4.5)*	0.50(0.25,1.0)
	0.81(0.48, 1.4)	Selective NSAIDs	*2.4(1.4,4.2)*	*0.41(0.17,0.95)*
	0.34(0.22,0.51)	*0.42(0.24,0.73)*	Control	*0.17(0.076,0.37)*
	2.0(1.0,4.1)	*2.5(1.1,6.0)*	*5.9(2.7,13.0)*	Radiation
Incidenceof Brooker I HO	Non-selective NSAIDs	1.6(0.87,2.9)	1.3(0.77,2.2)	0.5(0.21,1.2)
	0.63(0.35,1.2)	Selective NSAIDs	*0.82(0.43,1.6)*	*0.32(0.11,0.90)*
	0.77(0.46,1.3)	1.2(0.64,2.3)	Control	0.39(0.14,1.0)
	2.0(0.83,4.8)	*3.2(1.1,9)*	2.6(0.96,6.9)	Radiation
Incidence of Brooker II HO	Non-selective NSAIDs	1.3(0.76,2.2)	2.2(1.5,3.6)	0.23(0.031,1.0)
	0.79(0.45,1.3)	Selective NSAIDs	1.7(1.0,2.9)	*0.18(0.023,0.85)*
	0.46(0.28,0.69)	0.59(0.34,0.98)	Control	*0.10(0.014,0.47)*
	4.4(0.97,32)	5.6(1.2,43)	9.6(2.1,73)	Radiation
Incidence of Brooker III or IV HO	Non-selective NSAIDs	0.69(0.19,2.7)	*5.1(2.3,20.0)*	*9.1e-14(4.7e-45,0.22)*
	1.4(0.37,5.3)	Selective NSAIDs	*7.4(2.2,40.0)*	*1.3e-13(6.1e-45,0.35)*
	0.20(0.049,0.44)	*0.13(0.025,0.46)*	Control	*1.8e-14(8.1e-46,0.04)*
	1.1e+13(4.5.,2.1e+44)	*7.8e+13(2.9.,1.6e+44)*	*5.7e+13(25.,1.2e+45)*	Radiation
DNGSE	Non-selective NSAIDs	*0.43(0.17,0.96)*	0.83(0.53,1.3)	0.72(0.26,1.9)
	2.3(1.0,5.7)	Selective NSAIDs	2(0.82,4.9)	1.7(0.47,6.4)
	1.2(0.76,1.9)	0.51(0.20,1.2)	Control	0.89(0.29,2.4)
	1.4(0.54,3.9)	0.59(0.16,2.1)	1.1(0.42,3.4)	Radiation
Incidence of complications	Non-selective NSAIDs	*0.31(0.17,0.54)*	0.70(0.35,1.2)	1.0(0.53,1.9)
	3.2(1.9,6.0)	Selective NSAIDs	*2.2(1.1,4.3)*	*3.2(1.4,7.6)*
	1.4(0.87,2.9)	*0.45(0.23,0.94)*	Control	1.5(0.72,3.3)
	0.98(0.53,1.9)	*0.31(0.13,0.70)*	0.68(0.30,1.4)	Radiation

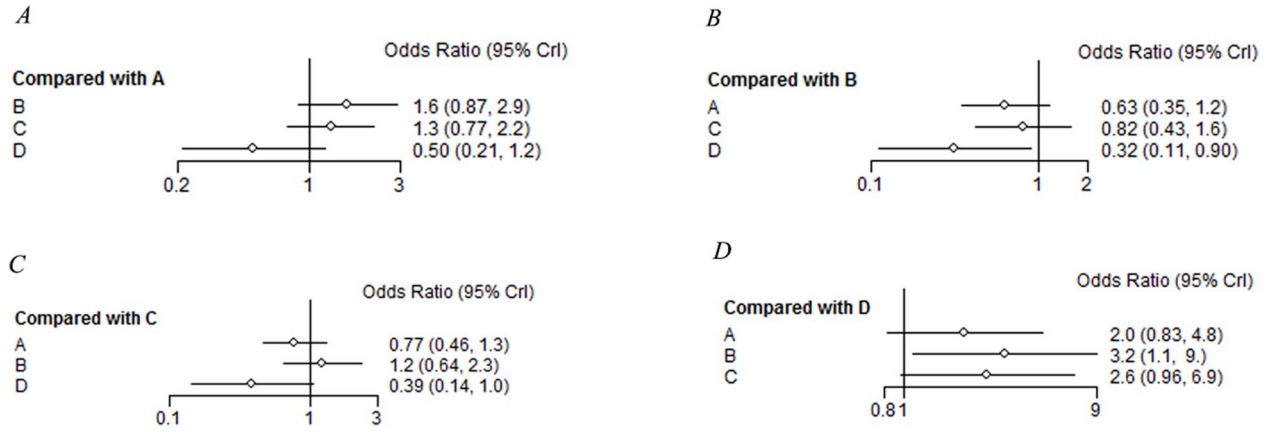

Fig. 6. The effect of different options for Brooker I HO.

4.9. Relative rankings of the four treatments

The relative rankings of the four strategies for the incidence of Brooker IV HO are shown in Fig. 11. Radiation ranked the lowest for the incidence of Brooker IV HO. Radiation ranked best among the relative rankings of the four strategies for the overall incidence of HO and incidence of Brooker I, II and III HO (Fig. 12A and B, C and D), which means it has the lowest incidence rate of HO after THA. Regarding the DNGSE and the incidence of complications, the use of selective NSAIDs and radiation ranked the lowest and second-lowest of the four strategies (Fig. 12E and F).

4.10. Comparisons between direct and indirect evidence

When we compared the effects of radiation and placebo on the incidence of Brooker II HO, there was no significant difference between the incidence of Brooker II HO for direct evidence. In contrast, the OR from indirect evidence indicated that radiation had a significantly lower incidence rate of Brooker II HO than the placebo ($P = 0.02$, Fig. 12C). There was no significant difference between direct and indirect evidence for the six other outcomes (incidence of Brooker IV HO, overall incidence of HO, incidence of Brooker I and III HO, DNGSE, DGSE and the incidence of complications, Fig. 12A and B, D, E, F).

4.11. Small-study effect and testing inconsistency

Fig. 13 shows that the funnel plot was symmetrical, indicating there was no small-study effect in this network meta-analysis (see Fig. 14).

5. Discussion

In this meta-analysis, we compared four strategies (nonselective NSAIDs, selective NSAIDs, radiation and controls) for preventing heterotopic ossification after THA. A total of 31 RCTs were included in this meta-analysis. The results show that radiation was the most efficient option for preventing HO after THA. Radiation was ranked as the first choice for preventing the incidence of Brooker IV HO, overall incidence of HO, and Brooker I, II and III HO after THA. However, compared with nonselective NSAIDs, selective NSAIDs had a significantly lower incidence of NDGSE.

This is the first network meta-analysis to compare different strategies, including NSAIDs and radiation, for preventing HO after THA. In his meta-analysis involving 993 patients, Pakos et al. reported that the risk of developing HO with RT was less than half that with NSAIDs [27]. In our study, the risk of overall HO incidence was reduced to 50% and 40% when compared with nonselective NSAIDs and selective NSAIDs, respectively. This study was intended to investigate the efficacy and safety of radiation compared to NSAIDs for patients with major hip fracture. These procedures would likely be clinically different among patients with different underlying biologies. Thus, we cannot conclude what impact radiation may have on THA-only patients. In addition, Milakovic et al. [24] demonstrated that overall incidence of HO decreased after radiation compared with a control group. They also concluded that multiple fractions seem to be more effective than single-fraction radiotherapy in preventing HO progression. Kan et al. [15] compared NSAIDs versus placebo as prophylaxis for HO after THA among 21studies with 5995 patients. They found that NSAIDs may

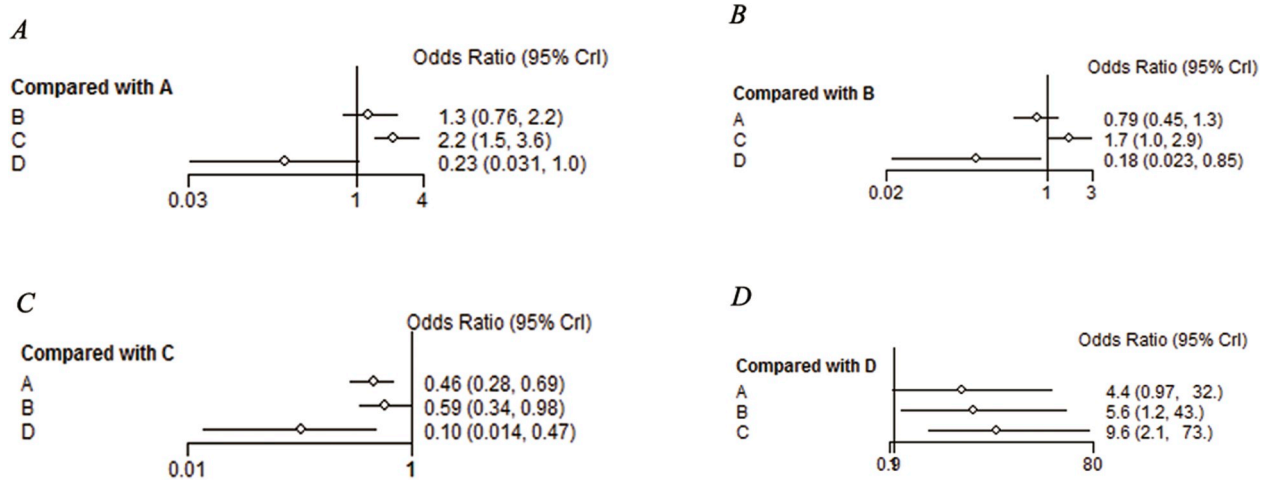

Fig. 7. The effect of different options for Brooker II HO.

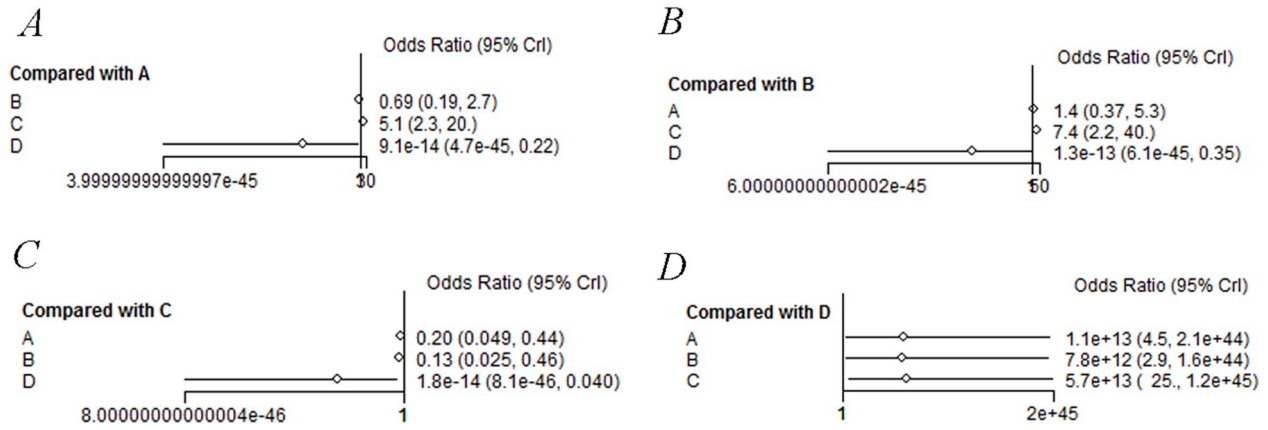

Fig. 8. The effect of different options for Brooker III or IV HO (A: Nonselective NSAIDs; B: Selective NSAIDs; C: Controls; D: Radiation).

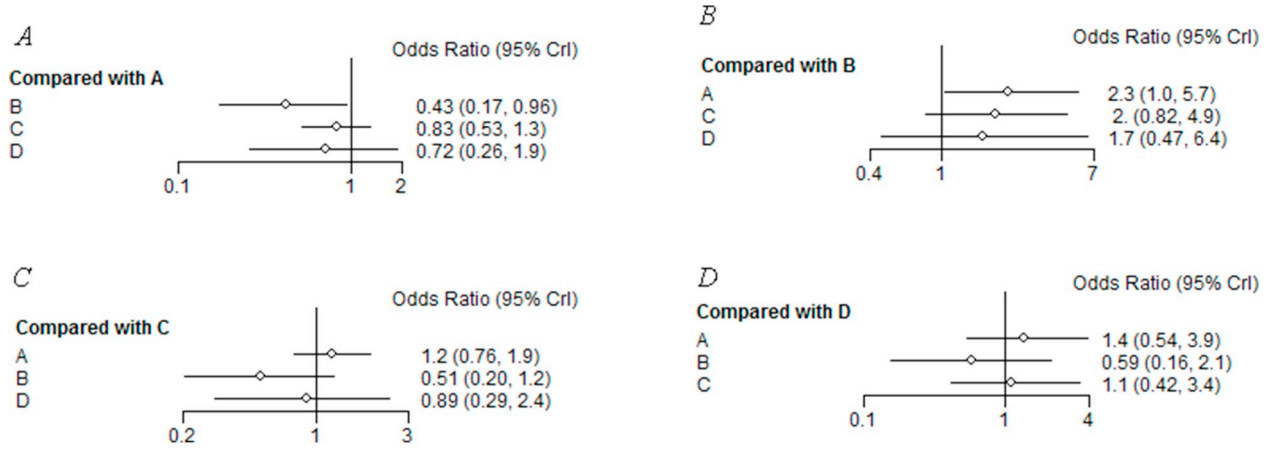

Fig. 9. The effect of different options for DNGSE (A: Nonselective NSAIDs; B: Selective NSAIDs; C: Controls; D: Radiation).

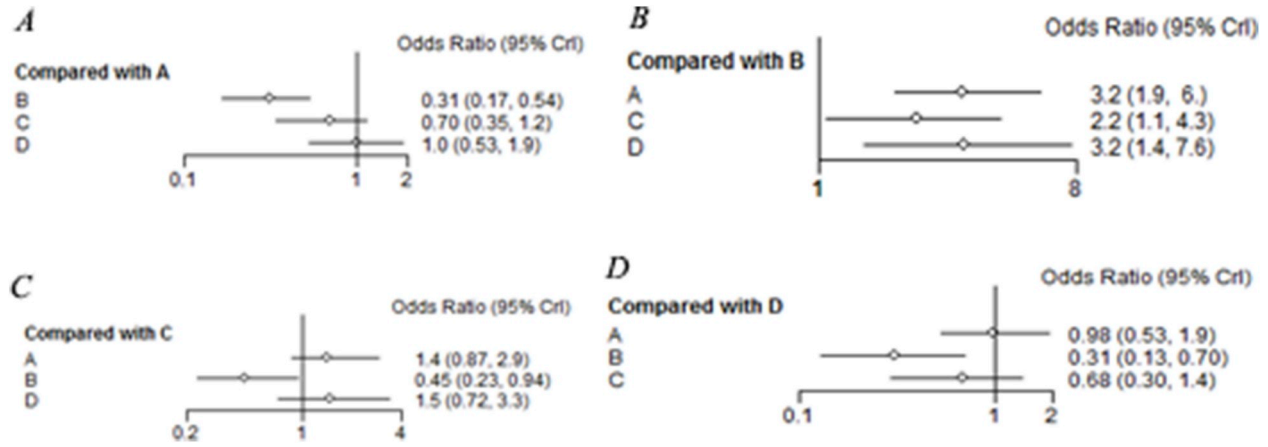

Fig. 10. The effect of different options for the incidence of complications (A: Nonselective NSAIDs; B: Selective NSAIDs; C: Controls; D: Radiation).

reduce the incidence of HO after THA and increase DGSE. In our meta-analysis, when compared with placebo, nonselective NSAIDs, selective NSAIDs and radiation all reduced the overall incidence of HO (by 66%, 58% and 83%, respectively). We also identified the efficacy of each of the four strategies in preventing HO with different classifications along the Brooker scale. We found that radiation was much more effective than selective NSAIDs, nonselective NSAIDs and controls in preventing clinically significant HO (Brooker Grade 3 or 4). A higher Brooker grade HO may affect the postoperative functioning of the hip and cause more problem. The results reported here are in agreement with the results reported by Pakos et al. [27]. There was no significant difference between selective NSAIDs and non-NSAIDs in terms of the overall incidence of HO. Xue et al. [44] conducted a pairwise meta-analysis and found that the selective NSAIDs are equally effective as nonselective NSAIDs for preventing HO after THA.

However, the results of the present study are in conflict with other traditional meta-analyses. A meta-analysis by Vavken et al. [39] found no evidence of a statistically significant or clinically important difference between NSAIDs and radiation in preventing HO.

We compared DNGSE and the incidence of complications between the four strategies. The results indicated that there were no significant differences between the four strategies in terms of DNGSE. The only

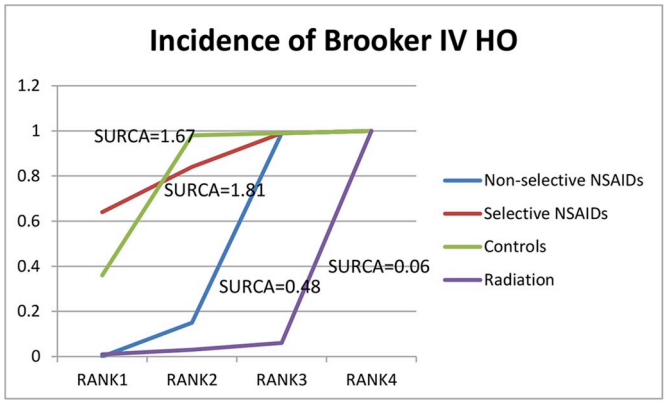

Fig. 11. Cumulative probability of the ranks of each treatment with respect to Brooker IV HO.

difference found for DNGSE was between selective NSAIDs and non-selective NSAIDs (OR = 0.43, 95 %Crl = 0.17–0.96). We further analyzed the DGSE and found that compared with nonselective NSAIDs, selective NSAIDs were associated with a reduction in DGSE. For the incidence of complications, we found that selective NSAIDs were the safest strategy for preventing HO after THA. Radiation was also a relatively safe method.

An economic evaluation of NSAIDs and radiation should be performed for clinical application. One published article compared the effectiveness, safety and costs of NSAIDs and radiation. The conclusion of the article was that the rate of complications was the most influential economic variable for patients. The cost-effectiveness analysis recommended the use of NSAID [40]. Since there was insufficient data to directly compare the economic costs of the two options, there is a need for more studies to identify the most cost-effective strategy for preventing HO after THA.

This network meta-analysis had some limitations. Some inconsistent results were observed in the calculations (incidence of Brooker II HO), which may have affected the validity of our results. There was a lack direct comparisons between selective NSAIDs and radiation. Therefore, the evidence for comparing selective NSAIDs and radiation was relatively low. Unpublished RCTs were not included in this network meta-analysis, and thus, it may underestimate the summary statistics. The number of eligible RCTs for direct comparison was small. Variations in regimens of selective and nonselective NSAIDs used between the studies may have cause some heterogeneity.

Further studies should focus on determining the radiation dose required for preventing HO after THA. In addition, studies should be performed to provide direct evidence for a comparison between selective NSAIDs and radiation for HO prevention after THA.

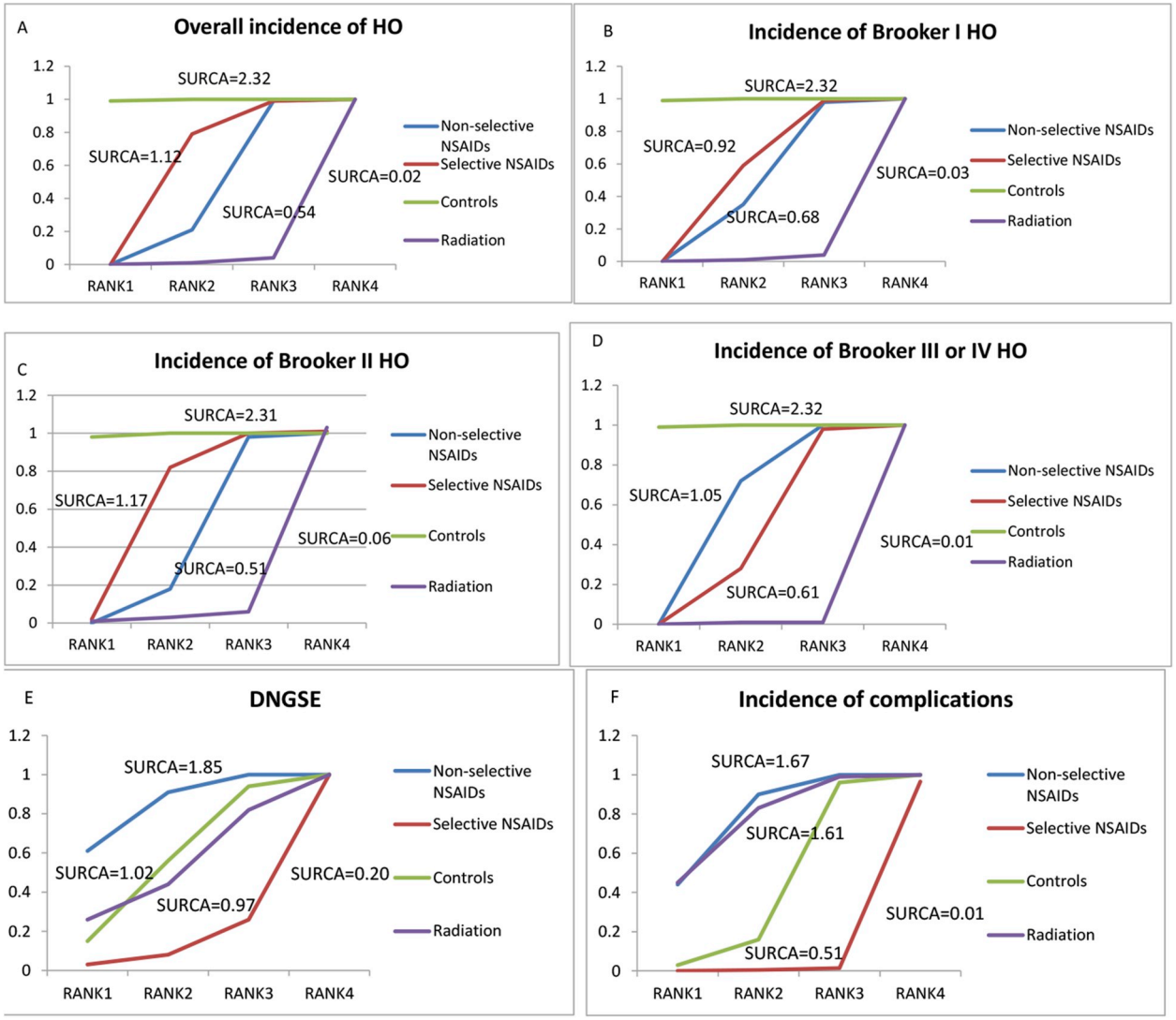

Fig. 12. Cumulative probability of the ranks of each treatment with respect to each outcome.

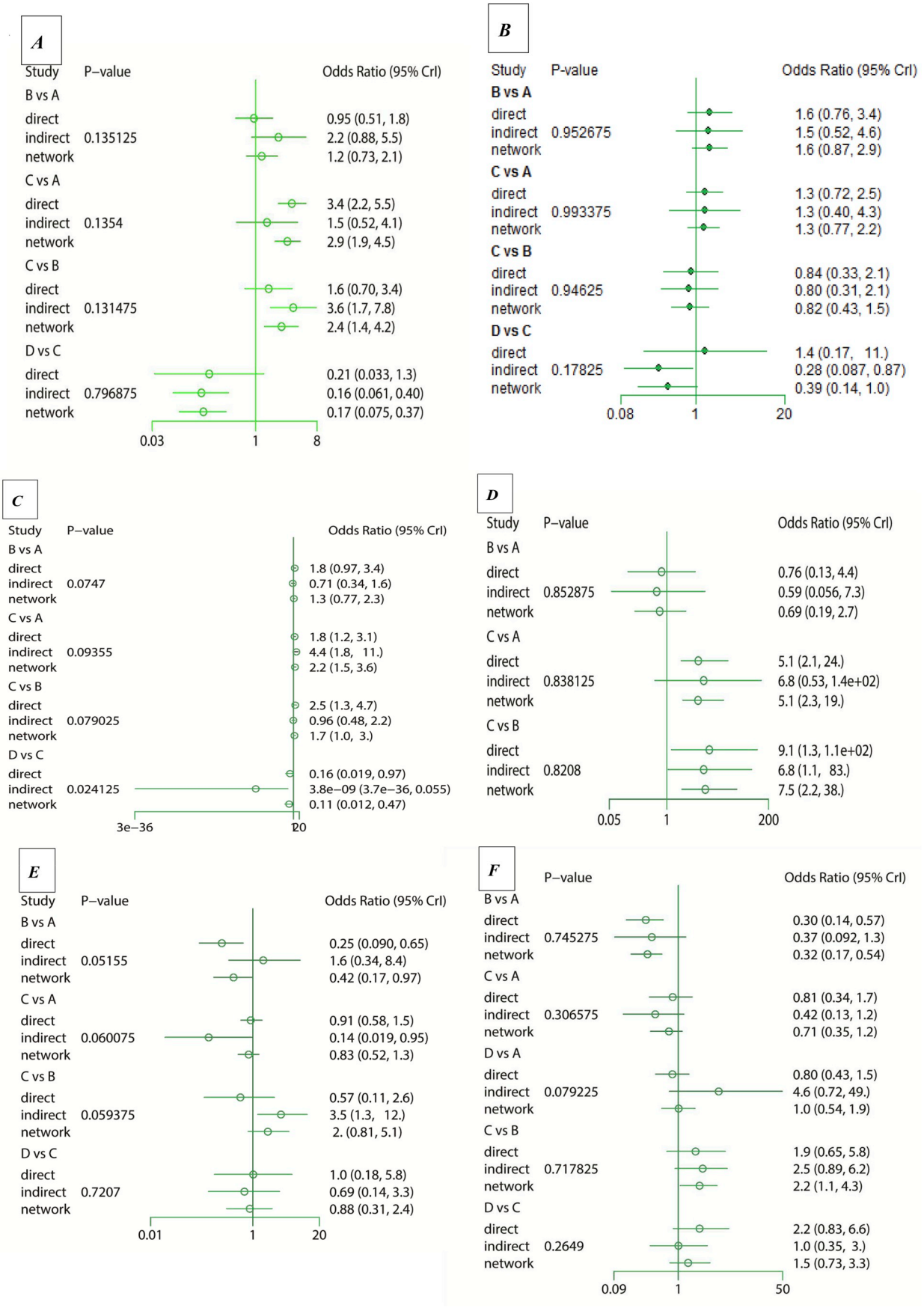
A
Study P–value Odds Ratio (95% CrI)
B vs A
direct 0.95 (0.51, 1.8)
indirect 0.135125 2.2 (0.88, 5.5)
network 1.2 (0.73, 2.1)
C vs A
direct 3.4 (2.2, 5.5)
indirect 0.1354 1.5 (0.52, 4.1)
network 2.9 (1.9, 4.5)
C vs B
direct 1.6 (0.70, 3.4)
indirect 0.131475 3.6 (1.7, 7.8)
network 2.4 (1.4, 4.2)
D vs C
direct 0.21 (0.033, 1.3)
indirect 0.796875 0.16 (0.061, 0.40)
network 0.17 (0.075, 0.37)
0.03 1 8
B
Study P-value Odds Ratio (95% CrI)
B vs A
direct 1.6 (0.76, 3.4)
indirect 0.952675 1.5 (0.52, 4.6)
network 1.6 (0.87, 2.9)
C vs A
direct 1.3 (0.72, 2.5)
indirect 0.993375 1.3 (0.40, 4.3)
network 1.3 (0.77, 2.2)
C vs B
direct 0.84 (0.33, 2.1)
indirect 0.94625 0.80 (0.31, 2.1)
network 0.82 (0.43, 1.5)
D vs C
direct 1.4 (0.17, 11.)
indirect 0.17825 0.28 (0.087, 0.87)
network 0.39 (0.14, 1.0)
0.08 1 20
C
Study P–value Odds Ratio (95% CrI)
B vs A
direct 1.8 (0.97, 3.4)
indirect 0.0747 0.71 (0.34, 1.6)
network 1.3 (0.77, 2.3)
C vs A
direct 1.8 (1.2, 3.1)
indirect 0.09355 4.4 (1.8, 11.)
network 2.2 (1.5, 3.6)
C vs B
direct 2.5 (1.3, 4.7)
indirect 0.079025 0.96 (0.48, 2.2)
network 1.7 (1.0, 3.)
D vs C
direct 0.16 (0.019, 0.97)
indirect 0.024125 3.8e−09 (3.7e−36, 0.055)
network 0.11 (0.012, 0.47)
3e−36 20
D
Study P–value Odds Ratio (95% CrI)
B vs A
direct 0.76 (0.13, 4.4)
indirect 0.852875 0.59 (0.056, 7.3)
network 0.69 (0.19, 2.7)
C vs A
direct 5.1 (2.1, 24.)
indirect 0.838125 6.8 (0.53, 1.4e+02)
network 5.1 (2.3, 19.)
C vs B
direct 9.1 (1.3, 1.1e+02)
indirect 0.8208 6.8 (1.1, 83.)
network 7.5 (2.2, 38.)
0.05 1 200
E
Study P–value Odds Ratio (95% CrI)
B vs A
direct 0.25 (0.090, 0.65)
indirect 0.05155 1.6 (0.34, 8.4)
network 0.42 (0.17, 0.97)
C vs A
direct 0.91 (0.58, 1.5)
indirect 0.060075 0.14 (0.019, 0.95)
network 0.83 (0.52, 1.3)
C vs B
direct 0.57 (0.11, 2.6)
indirect 0.059375 3.5 (1.3, 12.)
network 2. (0.81, 5.1)
D vs C
direct 1.0 (0.18, 5.8)
indirect 0.7207 0.69 (0.14, 3.3)
network 0.88 (0.31, 2.4)
0.01 1 20
F
P–value Odds Ratio (95% CrI)
B vs A
direct 0.30 (0.14, 0.57)
indirect 0.745275 0.37 (0.092, 1.3)
network 0.32 (0.17, 0.54)
C vs A
direct 0.81 (0.34, 1.7)
indirect 0.306575 0.42 (0.13, 1.2)
network 0.71 (0.35, 1.2)
D vs A
direct 0.80 (0.43, 1.5)
indirect 0.079225 4.6 (0.72, 49.)
network 1.0 (0.54, 1.9)
C vs B
direct 1.9 (0.65, 5.8)
indirect 0.717825 2.5 (0.89, 6.2)
network 2.2 (1.1, 4.3)
D vs C
direct 2.2 (0.83, 6.6)
indirect 0.2649 1.0 (0.35, 3.)
network 1.5 (0.73, 3.3)
0.09 1 50

Fig. 13.

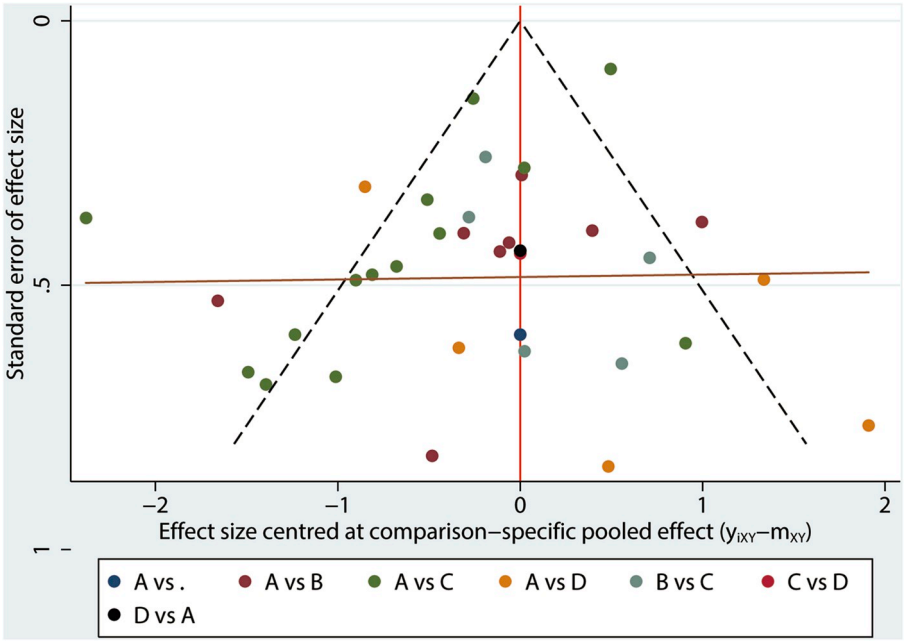

Fig. 14.

In conclusion, radiation was found to be the most efficient and relatively safe option for preventing HO after THA. Selective NSAIDs were found to have the lowest incidence rate of DNGSE and incidence of complications. This is the first and largest network meta-analysis comparing the different strategies for preventing HO after THA. Further studies should focus on the optimal dose of radiation for preventing HO after THA.

Provenance and peer review

Not commissioned, externally peer reviewed.

Ethical approval

None.

Author contribution

Liyang Cai and Zhan Wang: data collections, data analysis and writing.

Xiangli Luo and Wei She: data collections and data analysis.

Hui Zhang: data analysis and writing.

Hui Zhang: study design, data collections.

Conflicts of interest

Each author certifies that neither he, nor any member of his immediate family, has funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Research registration number

None.

Guarantor

Hui Zhang.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2018.12.011.

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