Comparative effectiveness of glucosamine, chondroitin, acetaminophen or celecoxib for the treatment of knee and/or hip osteoarthritis: a network meta-analysis

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Abstract

Objective

To compare the efficacies of oral glucosamine, chondroitin, the combination of glucosamine and chondroitin, acetaminophen and celecoxib on the treatment of knee and/or hip osteoarthritis.

Methods

We searched electronic databases including PubMed, Embase, and Cochrane Library and the reference lists of relevant articles published from inception to October 23, 2017. A Bayesian hierarchical random effects model was used to examine the overall effect size among mixed multiple interventions.

Results

We identified 61 randomised controlled trials of patients with knee and/or hip osteoarthritis. There was no obvious difference in the results between the traditional meta-analysis and the network meta-analysis. The network meta-analysis demonstrated that celecoxib was most likely the best option (SMD, -0.32 [95% CI, -0.38 to -0.25]) for pain, followed by the combination of glucosamine and chondroitin. For physical function, all interventions were significantly superior to oral placebo except for acetaminophen. In terms of stiffness, glucosamine (SMD, -0.36 [95% CI, -0.67 to -0.06]) and celecoxib (SMD, -0.29 [95% CI, -0.51 to -0.08]) were significantly better compared to placebo. In view of safety, compared to placebo only, celecoxib and acetaminophen presented significant differences.

Conclusion

Given the effectiveness of these non-steroidal anti-inflammatory drugs and symptomatic slow-acting drugs, oral celecoxib is more effective than placebo on relieving pain and improving physical function, followed by the combination of glucosamine and chondroitin. Acetaminophen is likely the least efficacious intervention option. This information, accompanied by the tolerability and economic costs of the included treatments, would be conducive to making decisions for clinicians.

Key words

osteoarthritis, treatment, glucosamine, chondroitin, acetaminophen, celecoxib

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Introduction

Osteoarthritis (OA), which is characterised by progressive cartilage matrix degradation, subchondral bone sclerosis and osteophyte formation, is the most common degenerative joint disease and primarily affects weight-bearing joints such as the knee and hip (1, 2). Presently, OA has emerged as a major public health concern and continues to affect approximately 10% of men and 18% of women over 60 years of age (3), with total DALYs increasing by 35% and age-standardised DALY rates increasing by 4% between 1990 and 2015. It is a leading cause of pain, disability, and socioeconomic costs worldwide (4).

Pain symptoms associated with OA may result in increased walking disability and all-cause mortality (5). Therefore, the alleviation and control of pain is an important consideration in the clinical practice of OA treatments. Although there are many symptomatic interventions, most are non-specific and lack effective disease-modifying medical treatments. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used, and symptomatic slow-acting drugs (SYSADOAs) for OA are accessible in clinical practice.

Glucosamine and chondroitin are essential SYSADOAs; they are naturally occurring compounds in the body that function as the principal substrates in the biosynthesis of proteoglycan (6). Glucosamine and chondroitin are both partially absorbed and then reach the joints, where they relieve joint pain and slow the rate of joint destruction and cartilage loss (7, 8). As a result, glucosamine and/or chondroitin are available as over-the-counter products (9). However, recently, the efficacy of glucosamine, chondroitin, or the combination of the two has been widely discussed, triggering a fierce controversy. International guidelines for their management have provided an equivocal recommendation of glucosamine and chondroitin (10). However, they are not recommended according to the Osteoarthritis Research Society International (OARSI) guidelines published in 2014 (11). In addition, their effectiveness is conflicting based on several randomised controlled trials (RCTs) (12, 13). Furthermore, acetaminophen (paracetamol), commonly known as a non-prescription medication for over 50 years, is often recommended as the first-line therapy because of its cheap price and low risk of gastrointestinal adverse effects compared to other NASIDs such as aspirin (10). Celecoxib is a selective NSAID that has been considered the first specific inhibitor of cyclo-oxygenase-2 (COX-2) by the American Food and Drug Administration (FDA) in December 1998(14). Regardless of its gastrointestinal adverse effects, celecoxib has become a typical inhibitor of COX-2 and reduces its related signs and symptoms (15); it is also recommended by OARSI guidelines (11). The effects of glucosamine and chondroitin on knee and/or hip OA compared to a placebo have been studied by a previous meta-analysis (16). In addition, a meta-analysis on the efficiency and safety of acetaminophen has also been conducted (17). Most importantly, a clinical trial conducted in 2014 suggested that a certain dosage of acetaminophen can provide effective relief of signs and symptoms (18). However, available studies investigating the comparative effects between NSAIDs and SYSADOAs are limited.

At present, the effectiveness of SYSADOAs for OA treatment is conflicting based on the results of several RCTs (12, 13, 19). Additionally, compared to a placebo, the effects of acetaminophen have been illustrated by a previous meta-analysis. Moreover, a comparison between acetaminophen and chondroitin, particularly glucosamine and chondroitin in combination, has not been conducted. Therefore, the comparative effectiveness of these treatments for OA must be explored.

A Bayesian network meta-analysis integrates evidence from all RCTs, which increases the statistical power by combining evidence from direct and indirect comparisons and examining the relative effects that have few comparisons. Moreover, it also presents a uniform and reasonable method to identify the differences among those intervention groups (20). Based on the existing evidence, we have assessed and examined the efficacy and safety of glucosamine,

chondroitin, the combination of glucosamine and chondroitin, celecoxib or acetaminophen for primary OA.

Methods

Search strategy

We conducted this network meta-analysis following the PRISMA extension statement (21). We systematically searched electronic databases including PubMed, Embase, and Cochrane Library based on logic combinations of keywords and text words associated with OA to extract concerned RCTs from inception to October 23, 2017. The Internet-based search used the following terms: "arthritis", "osteoarthritis", "OA", "joint disease", "glucosamine", "GH", "GS", "chondroitin", "CH", "CS", "acetaminophen", "paracetamol", "celecoxib", "celebrex", and the corresponding free terms. The search was restricted to the English language and studies of human participants. We then screened the reference lists of all obtained articles, including relevant reviews, to avoid missing relevant articles. We also searched Clinical Trials.gov for progressive trials.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) RCTs; (2) studies about primary hip and/or knee OA patients with clinical and/or radiologic diagnosis; (3) studies covering at least two of the following treatments: glucosamine, chondroitin, the two in combination, acetaminophen, celecoxib, and placebo; and (4) extractable data reporting on the pain, function, stiffness and adverse events (AEs) of patients.

The exclusion criteria were as follows: (1) studies of non-randomised or uncontrolled trials; (2) treatments described unclearly; (3) studies or data reported repeatedly; and (4) trial arms with subtherapeutic doses (celecoxib not equal to 200 mg/day; acetaminophen below 3000 mg/day; <1500 mg/day of glucosamine and <800 mg/day of chondroitin (according to dosage licensed in Europe)) (22, 23).

Data extraction

Two investigators (X.Y.Z. and L.L.S.) independently assessed all trials for eligibility and extracted the data in accordance with a preconfigured form. Any disagreements were resolved through discussion with a third reviewer (L.Y.J.). For each study, the patients' characteristics including mean age, sex, mean duration of symptoms, BMI, duration of follow-up, type of outcome (pain, function, stiffness and AEs), trial design, trial size, details of intervention, treatment duration and results were individually extracted. For crossover trials, we extracted data from the first period only to avoid possible carryover effects. Data of intention-to-treat analyses were used whenever possible.

Quality assessment

The Cochrane Risk of Bias Tool was used to evaluate the methodological quality of the included studies (v. 5.3) (24). The tool evaluates seven potential risks of bias: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each item was judged by the following criteria: low risk of bias, uncertain risk of bias, and high risk of bias. Studies that included three or more high risk of bias areas were considered to have poor methodological quality. The quality of evidence on pain, function and stiffness was evaluated by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (25). The quality of evidence was presented as high, moderate, low or very low. Two reviewers independently evaluated each study.

Outcome measures

The primary outcomes of this network meta-analysis were pain intensity, function improvement and stiffness score from baseline to the end of treatment using certain dosages of celecoxib, acetaminophen, glucosamine, chondroitin, or the combination of glucosamine and chondroitin. The secondary outcome was the safety of the studies, which was investigated based on the number of patients who withdrew from the trials because of AEs. We preferentially used the scale that was recognised as the highest on the hierarchy of those suggested outcomes when more than one pain scale was given for a trial. Among these scales, global pain has precedence over pain on walking and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (26, 27). Similarly, data on function and stiffness were extracted with the same method. If the global function score was not reported, the walking disability, function subscale of the WOMAC or Lequesne Index was applied instead.

The standard mean difference (SMD) was used to calculate the difference between various intervention arms because different studies assessed the same outcome by employing different scales. SMD expresses the size of the intervention effect in each study relative to the variability observed in that study by dividing the pooled SD of the differences between two interventions (28, 29). The effect size was transformed back to the difference units of the WOMAC visual analogue scale (VAS), which is the most commonly used scale and is based on a median pooled SD of 2.5 cm to assess pain on a scale of 0 to 10 cm. A standardised WOMAC function score (0-10) was transformed by the SMD, which is based on a median pooled SD of 2.1 units. A change of 2 points on the 0–10 scale was interpreted as a clinically significant improvement (30). A negative effect size indicated a better treatment effect on pain relief and function improvement. The absolute changes in pain, function and stiffness from baseline were also evaluated by a classical meta-analysis.

Statistical analysis

Bayesian meta-analysis integrates both direct evidence from head-to-head studies and indirect evidence from all original trials. The Bayesian Markov Chain Monte Carlo is a method used to estimate posterior densities for unknown variables (31, 32). Initial values generate 50,000 simulations. Although the first 10,000 simulations are rejected because of the burn-in period, the last 40,000 simulations are used as samples to obtain the final result.

The Bayesian random effects model, which is considered much more con-

servative and appropriate than the fixed effects model, was used to examine the overall effect size among mixed multiple treatments of OA with non-informative prior distributions. Before pooling the data with a random-effects model within a Bayesian framework, the comparative effects were initially analysed by the traditional pairwise meta-analysis method. For continuous outcomes, the summary effect size was calculated as the SMD along with 95% credible intervals (CIs). For the count data, the relative risk (RR) with 95% CI was used to present the effect size. It was possible to rank the superior orders among the included interventions according to the posterior probabilities, and we reported the value as the surface under the cumulative ranking (SUCRA). The best treatment effect has a SUCRA value of 100%, whereas the worst treatment effect has a SUCRA value of 0%. Several sensitivity analyses on the primary outcomes were performed to explore the heterogeneity according to the sample size and the study quality. We also calculated the consistency of the network determined by the difference in effect sizes from direct and indirect comparisons in one loop. Publication bias was examined through visual inspection of funnel plot asymmetry. WinBUGS (v. 1.4.3, MRC Unit, Cambridge, UK), STATA (v. 13.1, StataCorp, College Station, TX), and Review Manage (v. 5.3, Oxford, UK) were used for the analyses.

Results

Study selection and characteristics

The summary of the study search and selection is presented in the Appendix Supplementary file 2: Fig. S1. Among the 3359 records identified and selected from the literature search, 3060 irrelevant articles were excluded. After screening and reading the full text of 299 articles, 58 articles (61 RCTs) met the inclusion criteria and were included in the network meta-analysis, 3 of which reported the results of two trials. Therefore, 61 RCTs were employed to assess the efficacies of oral glucosamine, chondroitin, the combination of the glucosamine and chondroitin, celecoxib and acetaminophen for patients with knee and/or hip OA.

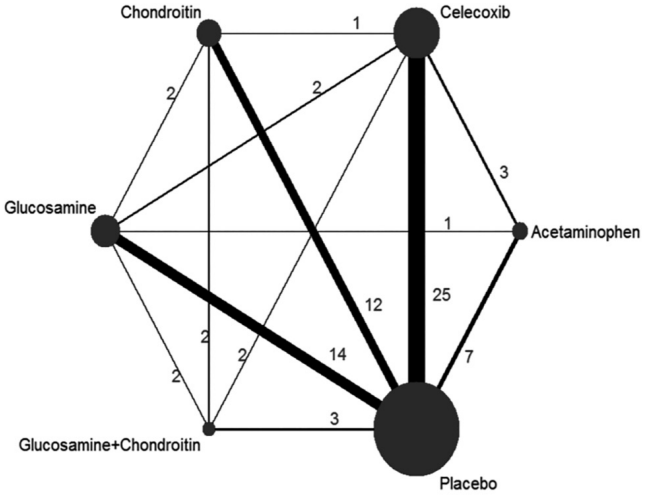

Fig. 1. Network of treatment comparisons included in the analysis for pain.
The size of every circle reflects the number of participants.
The width of every line corresponds to the number of direct comparisons; the number shown beside the line represents the number of trials.
No connecting line between 2 treatments indicates no direct comparison.

The baseline characteristics of the included studies are shown in Supplementary file 1: Table S1 (the references of the included studies are provided). Forty-seven trials covered participants with only knee OA, two trials contained participants with only hip OA, and twelve trials included patients with knee and/or hip OA.

Risk of bias

The risk of bias of the included trials is summarised in Supplementary file 1: Table S2. None of the studies had poor methodological quality. Randomisation was mentioned in all trials, and all studies were judged to have a low risk of bias for blinding to patients. The quality of evidence was measured by the GRADE system (Table I). The quality grade was downgraded primarily due to indirectness and imprecision (see details in Supplementary file 1: Tables S3-S5). The model fit well for pain, function and stiffness outcomes (Supplementary file 2: Fig. S11). Comparison-adjusted funnel plots showed no evidence of asymmetry (Supplementary file 2: Fig. S5–S7).

Pain

Figure 1 shows the network of the interventions included in this study for pain. Six nodes indicated different interventions of drugs with a specific daily dose. Celecoxib (200 mg/day) was the most commonly studied drug. However, there were few direct comparisons between chondroitin and acetaminophen or between the combination of glucosamine and chondroitin and acetaminophen.

Fifty-six studies (22,128 participants) contributed to the network meta-analysis of pain-related outcomes. Table I presents the effect sizes and the related 95% CIs of the network meta-analysis about the changes in pain score between different interventions at the last follow-up period. All treatments showed a significantly better effect compared to placebo. When the SMD was transformed, glucosamine had a value of -0.33 cm (95% CI, -0.60 to -0.10 cm), chondroitin was -0.53 cm (95% CI, -0.83 to -0.28 cm), the combination of glucosamine and chondroitin was -0.58 cm (95% CI, -0.98 to -0.18 cm), celecoxib was -0.80 cm (95% CI, -0.95 to -0.63 cm), and acetaminophen was -0.35 cm (95% CI, -0.65 to -0.05 cm). All interventions met the pre-specified minimal clinically significant improvement. Celecoxib was statistically significantly superior to acetaminophen (SMD, -0.18 [95% CI, -0.31 to -0.05]). Compared to celecoxib, glucosamine showed a worse effect (SMD, 0.18 [95% CI, 0.07 to 0.29]). According to the SUCRA related to pain, the top three ranked treatments were celecoxib (96%), the combination of glucosamine and chondroitin (67%) and chondroitin (64%) (Fig. 2). No inconsistencies were detected between the direct and indirect evidence (Supplementary file 2: Fig. S8).

Function

Forty-five articles (47 RCTs) with 19,727 patients contributed to the net-

Table I. Estimates of the treatment effect on pain, function and stiffness.

Interventions	Pain, SMD (95% CI)			Function, SMD (95% CI			Stiffness, SMD (95% CI)		
	Network meta-analysis	Direct comparison	GRADE	Network meta-analysis	Direct comparison	GRADE	Network meta-analysis	Direct comparison	GRADE
Glucosamine									
Chondroitin	0.08(-0.06,0.22)	0.03(-0.10,0.16)	High	0.04(-0.09,0.18)	0.05(-0.08,0.17)	High	-0.32(-0.85,0.20)	-0.07(-0.22.0.09)	High
Glucosamine+Chondroitin	0.09(-0.09,0.27)	0.10(-0.05,0.24)	High	0.05(-0.12,0.22)	0.12(-0.01,0.24)	High	-0.14(-0.69,0.39)	0.09(-0.07,0.24)	Moderate
Celecoxib	0.18(0.07,0.29)	-0.04(-0.44,0.37)	Moderate	0.14(0.02,0.25)	-0.06(-0.56,0,44)	Moderate	-0.06(-0.44,0.29)	0.13(-0.02,0.29)	Moderate
Acetaminophen	0.01(-0.15,0.15)	-0.09(-0.36,0.17)	Low	-0.04(-0.21,0.12)	-0.05(-0.32,0.22)	Moderate	-0.28(-0.84,0.26)	NA	Moderate
Placebo	-0.13(-0.24,-0.04)	-0.10(-0.25,0.05)	High	-0.17(-0.28,-0.07)	-0.12(-0.26,0.01)	High	-0.36(-0.67,-0.06)	-0.30(-0.60,-0.00)	High
Chondroitin									
Glucosamine+Chondroitin	0.02(-0.17,0.19)	0.05(-0.17,0.27)	High	0.01(-0.17,0.18)	0.08(-0.05,0.20)	High	0.18(-0.44,0.79)	0.15(-0.00,0.31)	High
Celecoxib	0.10(-0.03,0.23)	0.15(-0.00,0.31)	High	0.09(-0.03,0.21)	0.16(0.00,0.31)	High	0.26(-0.23,0.74)	0.20(0.05,0.36)	High
Acetaminophen	-0.07(-0.24,0.09)	NA	Moderate	-0.08(-0.26,0.09)	NA	Moderate	0.04(-0.61,0.68)	NA	Moderate
Placebo	-0.21(-0.33,-0.11)	-0.21(-0.36,-0.07)	High	-0.22(-0.33,-0.11)	-0.22(-0.36,-0.08)	High	-0.04(-0.50,0.42)	0.03(-0.09,0.15)	Moderate
Glucosamine+Chondroitin									
Celecoxib	0.09(-0.07,0.25)	0.00(-0.11,0.12)	High	0.08(-0.07,0.24)	0.04(-0.12,0.19)	High	0.08(-0.40,0.56)	0.06(-0.06,0.17)	High
Acetaminophen	-0.09(-0.29,0.11)	NA	Moderate	-0.09(-0.30,0.11)	-0.24(-0.52,0.04)	High	-0.14(-0.79,0.51)	NA	Moderate
Placebo	-0.23(-0.39,-0.07)	-0.10(-0.22,0.33)	High	-0.23(-0.38,-0.08)	-0.12(-0.24,0.01)	High	-0.21(-0.69,0.26)	-0.07(-0.21,0.07)	High
Celecoxib									
Acetaminophen	-0.18(-0.31,-0.05)	-0.18(-0.31,-0.05)	High	-0.18(-0.33,-0.03)	NA	Low	-0.22(-0.70,0.26)	-0.25(-0.54,0.03)	Moderate
Placebo	-0.32(-0.38,-0.25)	-0.32(-0.37,-0.27)	High	-0.31(-0.38,-0.25)	-0.32(-0.37,-0.27)	High	-0.29(-0.51,-0.08)	-0.28(-0.36,-0.21)	High
Acetaminophen									
Placebo	-0.14(-0.26,-0.02)	-0.14(-0.21,-0.06)	High	-0.14(-0.27,0.01)	-0.16(-0.31, 0.00)	High	-0.08(-0.53,0.38)	-0.17(-0.34,0.01)	High

CI: Confidence interval; NA: Not applicable; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

work meta-analysis of physical function outcomes (Supplementary file 2: Fig. S2). All interventions except for acetaminophen were statistically significantly better than oral placebo in the aspect of function improvement (Table I). After being transformed, the difference for glucosamine was -0.36 units (95% CI, -0.59 to -0.15 units), chondroitin was -0.46 units (95% CI, -0.69 to -0.23 units), the combination of glucosamine and chondroitin was -0.48 units (95% CI, -0.80 to -0.17 units), celecoxib was -0.65 units (95% CI, -0.80 to -0.53 units), and acetaminophen was -0.29 units (95% CI, -0.57 to -0.02 units). According to the SUCRA of function (Fig. 2), celecoxib was the best treatment (96%), followed by the combination of glucosamine and chondroitin (65%), chondroitin (62%) and glucosamine (44%), with placebo as the worst treatment (1%). No inconsistencies were detected between the direct and indirect evidence (Supplementary file 2: Fig. S9).

Stiffness

Twenty-nine articles (30 RCTs) with 12,404 participants contributed to the network meta-analysis of stiffness outcomes (Supplementary file 2: Fig. S3). Compared to placebo, glucosamine (SMD, -0.36 [95% CI, -0.67 to -0.59]) and celecoxib (SMD, -0.29 [95% CI, -0.51 to -0.08]) were significantly superior. Other comparisons showed no statistical significance in terms of stiffness (Table I). The SUCRA rank was presented as follows (Fig. 2): glucosamine (82%), celecoxib (73%), the combination of glucosamine and chondroitin (58%), acetaminophen (37%), chondroitin (31%) and placebo (20%). No significant inconsistencies were detected between the direct and indirect evidence (Supplementary file 2: Fig. S10).

Safety

Forty-one articles (44 RCTs) reported the withdrawal of patients due to AEs, and 38 studies reported the number of patients with AEs (Supplementary file 2: Fig. S4). Diarrhoea, abdominal pain, nausea and headache were the most commonly reported AEs. Compared to glucosamine, the celecoxib treatment option exhibited a relatively higher incidence of AEs (RR, 1.82 [95% CI, 1.12 to 2.95]), whereas acetaminophen showed a similar value (RR, 1.97 [95% CI, 1.11 to 3.52]). The safety and tolerability analyses are presented in Table II.

Sensitivity analysis

To confirm the robustness of the result, we also conducted sensitivity analyses for those outcomes. A sensitivity analysis of the sample size and methodological quality of the included studies did not show any major changes in pain, function and stiffness outcomes (Supplementary file 1: Table S6).

Discussion

We estimated the effectiveness of different interventions including glucosamine, chondroitin, the combination of glucosamine and chondroitin, celecoxib and acetaminophen. In our study, we performed four individual outcome-oriented network meta-analyses. The pooled effect sizes suggested that all interventions may alleviate pain symptoms and improve function. The recommended dosage of oral celecoxib is more effective than placebo on relieving pain and improving physical function, followed by the combina-

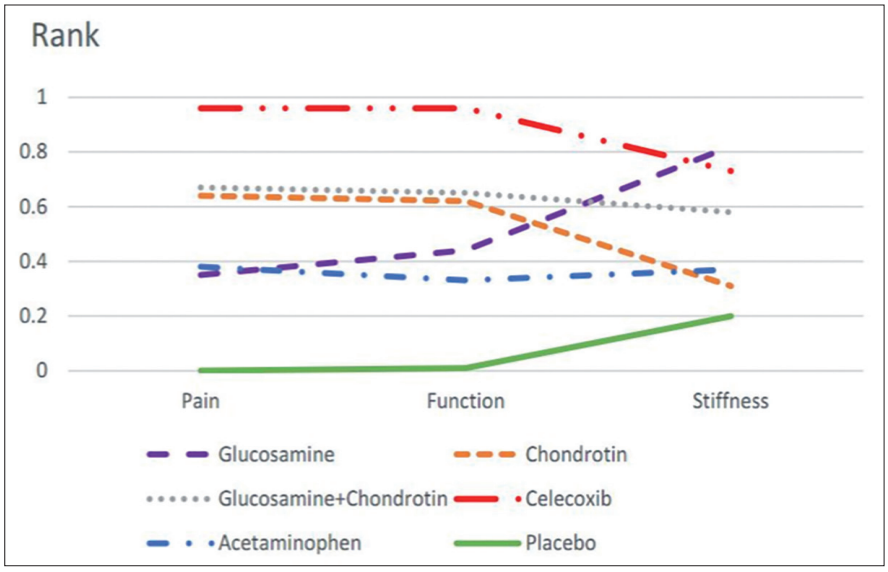

Fig. 2. The rank of efficacy of pain, function and stiffness.
Data were pooled as the RR (relative risk) and its related 95% CI; G+C=glucosamine+ chondroitin.

Table II. Adverse event results.

Comparison	RR (95%CI)
Chondroitin *vs*. Glucosamine	1.67 (0.93,3.01)
G+C *vs*. Glucosamine	1.70 (0.86,3.37)
Celecoxib *vs*. Glucosamine	1.82 (1.12,2.95)
Acetaminophen *vs*. Glucosamine	1.97 (1.11,3.52)
Placebo *vs*. Glucosamine	1.05 (0.66,1.66)
G+C *vs*. Chondroitin	1.02 (0.53,1.96)
Celecoxib *vs*. Chondroitin	1.09 (0.69,1.72)
Acetaminophen *vs*. Chondroitin	1.18 (0.67,2.08)
Placebo *vs*. Chondroitin	0.63 (0.41,0.96)
Celecoxib *vs*. G+C	1.07 (0.61,1.88)
Acetaminophen *vs*. G+C	1.16 (0.59,2.29)
Placebo *vs*. G+C	0.62 (0.35,1.09)
Acetaminophen *vs*. Celecoxib	1.08 (0.72,1.63)
Placebo *vs*. Celecoxib	0.58 (0.47,0.71)
Placebo *vs*. Acetaminophen	0.53 (0.36,0.78)

Data were pooled to obtain the relative risk and its related 95% CI; G+C: glucosamine+chondroitin.

tion of glucosamine and chondroitin. Acetaminophen is likely the least efficacious option. In terms of stiffness improvement, glucosamine showed a superior effect compared with placebo, whereas acetaminophen did not significantly differ from placebo. There was no significant difference of safety in the comparisons between SYSADOAs and placebo. Compared with placebo and glucosamine, celecoxib and acetaminophen was a risk factor of AEs, whereas celecoxib and acetaminophen were recommended in clinical practice. Our network meta-analysis indicated that glucosamine and the combination of glucosamine and chondroitin showed a greater significant improvement in pain and function from baseline information. Conversely, a traditional meta-analysis suggested that glucosamine and chondroitin can present a certain efficacy in treating OA symptoms (33, 34). However, the findings of a Bayesian network meta-analysis indicated that glucosamine, chondroitin and the combination of the two did not result in a relevant reduction of joint pain compared to placebo (16). The evidence of previous study was limited and the result may not be reliable, because only one RCT of combined group was included. Nevertheless, in our study, four RCTs covering the combination of glucosamine and chondroitin were measured, which could support the similar findings of the latest RCT (19). A recent meta-analysis indicated that celecoxib would lead to significant improvements in pain compared to placebo (35). Cao and colleagues combined 24 RCTs and indicated that oral 200mg daily celecoxib was effective for pain relief (36). The finding was similar to our analysis. Machado and colleagues conducted a pair-wise meta-analysis and reported that acetaminophen had a significant but small effect on hip and/or knee OA patients compared to placebo within 12 weeks(17). We also found that acetaminophen was the least efficacious drug when comprehensively evaluated. Another network meta-analysis indicated that celecoxib was significantly superior to placebo but inferior to acetaminophen, which was contrary to our findings (30). In our study, dosage was restricted and the RCTs included met these criteria, and such results could be comparable and reasonable.

All of the treatments in our analysis were based on the recommendations from the latest clinical practice guidelines. We compared typical SYSADOAs and NSAIDs in the treatment of OA. Chondroitin and glucosamine are believed to play a significant role in relieving joint pain and slowing the rate of cartilage loss. As shown in previous studies, glucosamine inhibited prostaglandin release, and chondroitin stimulated collagen synthesis (37-39). However, the standard intervention focused on symptom relief with analgesics and NSAIDs. Presently, acetaminophen is the most commonly prescribed over-the-counter drug, and celecoxib was first specific inhibitor of cyclo-oxygenase-2 (40). Indeed, previous meta-analyses have compared the use of SYSADOAs for OA disease (16, 33). Several network meta-analyses were estimated for knee OA but were only concerned about different NSAID treatments (16, 30, 41, 42). Given the above reasons, we selected and then conducted a more comprehensive mixed comparison of those treatments on knee and/or hip OA.

SYSADOAs provide lasting pain relief and function improvement in OA treatment (43, 44) and beneficial effects that develop slowly over time(45). Chondroitin and glucosamine were tested in

several clinical trials in osteoarthritis. In spite of the controversy surrounding the SYSADOAs, they were commonly used to control symptoms of OA in western countries. So, an understanding of chondroitin and glucosamine consumption is of significance for public health. The evidence in our study presented that SYSADOAs have a comparable efficacy in both outcome of pain and function improvement, especially for the combination of glucosamine and chondroitin. Furthermore, glucosamine seems greater in stiffness score and much safer in terms of AEs. Given the reasons above, we do not oppose the use of glucosamine and chondroitin, which were not recommended according to the Osteoarthritis Research Society International (OARSI) guidelines published in 2014. In fact, we recommend that the future guidelines reconsider the oral treatment option of chondroitin and glucosamine for the clinical treatment of OA. Considering the aspect of safety, the current study provides valuable information to help physicians make treatment decisions for patients with OA.

Notably, a comprehensive and rigorous literature search strategy was performed in our network meta-analysis, which insured that it was unlikely to miss other relevant trials. To minimise bias, the study selection, quality assessment and data extraction were completed independently by two reviewers. Several sensitivity analyses of RCTs with more than 100 patients per arm were conducted to make the results more sensible and comprehensive. In accordance with the pre-specified inclusion criteria, the articles included in our study had achieved our expected methodological quality.

Unlike conventional meta-analyses, our analysis integrated all available high-quality RCT evidence concerning typical oral medicines of SYSADOAs and NSAIDs to assess their effects on treating knee and/or hip OA. The integration of direct and indirect comparisons led to a more precise outcome than a pairwise meta-analysis (46). This method provided indirect effect estimate where direct comparisons were not available. The accuracy and robustness of the results were validated by the model fit and absence of inconsistency. Funnel plots also showed no asymmetry, and the risk of publication bias was not recognised. What is more, GRADE was used to evaluate the quality of the evidence, which provide a more comprehensive evidence-based review.

Some limitations must be acknowledged. Firstly, variation length of follow-up time point might contribute to the evidence of significant heterogeneity. Fortunately, no obvious evidence of inconsistency was observed in this network meta-analysis. Secondly, the tolerability of specific kinds of AEs (diarrhoea, abdominal pain, nausea, headache) cannot be proven due to the inadequate reporting of adverse event data. Thirdly, radiological grounds probably mean more sensitivity and included mild cases (47). We were unable to conduct subgroup analysis for OA grade because of original data restraints. Moreover, the results between the direct and indirect comparisons identified inconsistencies for pain (glucosamine *vs*. celecoxib and glucosamine vs. acetaminophen) and function (glucosamine *vs*. celecoxib). This may be due to the limited numbers of head-to-head comparisons between these interventions. Researches among SYSADOAs and NSAIDs are still required due to the limitations on the quality and quantity of the current available evidence.

Conclusion

There were no obvious differences in the results between the traditional meta-analysis and the network meta-analysis. For the two typical options of NSAIDS, acetaminophen had a significant but small effect in patients with hip or knee OA, whereas celecoxib was relatively outstanding. Glucosamine and chondroitin were categorised as SYSADOAs that provide lasting pain relief and function improvement in OA. SYSADOAs are generally safe and well tolerated, in view of the well-established beneficial effects of NSAIDs and SYSADOAs, long-term use of the combination of chondroitin and glucosamine should be given preference.

In fact, combination therapy is common in practice. Treatment interventions such as the combination of SYSADOAs and NSAIDs were usual in clinical experience; furthermore, our study will help highlight the potential role of the glucosamine and chondroitin combination in the future. Therefore, the above information, along with the safety profile and relative costs of included treatment, should be conducive to clinicians when making care decisions tailored to individual patient needs.

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