Glucosamine for pain in osteoarthritis: why do trial results differ?

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CRD summary
This review concluded that glucosamine hydrochloride is not effective in treating osteoarthritic pain, and that definitive conclusions could not be drawn on the efficacy of glucosamine sulphate because of significant variation between the studies. Given the limitations of the included studies and the poor reporting of the review process, the reliability of the authors' overall conclusion is unclear.

Authors' objectives
To assess studies using glucosamine to treat pain in osteoarthritis and investigate potential sources of heterogeneity.

Searching
MEDLINE, the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched from 1966 to February 2006, with no restriction on language; the search terms were reported. In addition, several websites were searched, references of relevant articles and conference proceedings of relevant societies were screened, and manufacturers were contacted.

Study selection
Randomised, double-blind, placebo-controlled trials of parenteral or oral glucosamine for pain from osteoarthritis of the knee or hip, with a follow-up of more than 4 weeks, were eligible for inclusion. Studies assessing glucosamine in combination with another agent were only eligible for inclusion if they compared treatment with glucosamine alone with a placebo group. Studies were excluded if they assessed chondroitin alone or only chondroitin and glucosamine combinations. All of the included studies were of glucosamine for osteoarthritis of the knee. The majority of studies used glucosamine sulphate at the equivalent of 1,500 mg/day and a rescue medication. Treatment durations in the included studies ranged from 4 weeks to 3 years.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed according to the Jadad criteria, which include items on allocation concealment, intention-to-treat analysis and withdrawals. The included studies were given a score of between 1 and 5, and were rated as adequate, intermediate or inadequate for allocation concealment.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Primary outcomes were identified as defined by the authors of the included studies, or where several outcomes were reported, the first was extracted. Odds ratios were converted into effect sizes (ESs), with 95% confidence intervals (CIs), according to published methods; an ES of 0.2 was considered small, 0.5 moderate, and 0.8 large.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
ESs were pooled using a random-effects model. Heterogeneity was investigated through the the $I^2$ test and meta-regression. Sensitivity analyses were conducted on glucosamine preparation, industry involvement, study quality, use of rescue medication, study duration, study publication data and various participant characteristics. Post-hoc analyses were undertaken for glucosamine dosing regimen and the use of Rottapharm products, and Fisher's exact test was used to assess further associations. Publication bias was assessed using Egger's test and funnel plots.
Results of the review
Fifteen RCTs (n=2,613) were included in the review. The sample sizes ranged from 24 to 630 participants.

The included studies scored between 1 and 5 on the Jadad scale, with 5 studies scoring 5 and 6 studies scoring 4. Five studies were rated as adequate for allocation concealment, six as intermediate and four as inadequate. Participant withdrawals ranged from 4.4 to 40.1%.

The overall ES for glucosamine compared with placebo was 0.35 (95% CI: 0.14, 0.56), favouring glucosamine. Sensitivity analyses indicated a greater ES in studies using glucosamine sulphate (0.44, 95% CI: 0.18, 0.70) compared with studies using glucosamine hydrochloride (0.06, 95% CI: -0.08, 0.20). There were significant differences in ESs for industry involvement, but no significant differences for other study characteristics.

Post-hoc analyses indicated greater ESs for the 4 studies using daily dosing (0.59, 95% CI: 0.01, 1.18) compared with the 9 studies using three times a day dosing (0.12, 95% CI: 0.02, 0.23), and a significant difference in ESs for studies using Rottapharm products (0.55, 95% CI: 0.29, 0.82) compared with those using other products (0.11, 95% CI: -0.16, 0.38). There was no significant association between industry involvement and allocation concealment when using Fisher’s exact test.

There was significant heterogeneity ($I^2=80\%$) overall and levels of heterogeneity were reported in the review for other study characteristics. There was no evidence of publication bias when using Egger’s test, but potential bias was detected with funnel plots.

Authors’ conclusions
Glucosamine hydrochloride is not effective in treating osteoarthritic pain. Definitive conclusions about the efficacy of glucosamine sulphate could not be drawn because of the significant heterogeneity amongst the studies, which appeared to result mainly from bias due to industry involvement.

CRD commentary
The review question was clear and was supported by appropriate inclusion criteria for the participants, interventions and study design. A relevant literature search was conducted using three electronic databases and other relevant sources. Attempts were made to reduce the possibility of language bias and to minimise the potential for relevant papers to be missed, by including papers in any language and unpublished manuscripts. Validity was assessed according to published criteria. However, details of the review process for the study selection, validity assessment and data extraction were not reported, thus the potential for reviewer error and bias cannot be ruled out. Appropriate methods were used to investigate heterogeneity but, as there was significant heterogeneity, the pooling of the results was not appropriate, as the authors acknowledged. Furthermore, since all of the included studies assessed osteoarthritis of the knee, the results may not be generalisable. There were several limitations of the included studies, such as poor reporting of allocation concealment and high levels of participant withdrawal, and CIs were wide for many of the studies. In addition, it is unclear from the review which outcomes were included from each study and which measurement tools were used. Given the above considerations, the reliability of the authors’ overall conclusion is unclear, although their inconclusive statement concerning glucosamine sulphate appears reasonable.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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