Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis

Jasmin Arrich, Franz Piribauer, Philipp Mad, Daniela Schmid, Klaus Klaushofer, Marcus Müllner

A longer version of this article is available online at www.cmaj.ca

Abstract

Background: Osteoarthritis of the knee affects up to 10% of the elderly population. The condition is frequently treated by intra-articular injection of hyaluronic acid. We performed a systematic review and meta-analysis of randomized controlled trials to assess the effectiveness of this treatment.

Methods: We searched MEDLINE, EMBASE, CINAHL, BIOSIS and the Cochrane Controlled Trial Register from inception until April 2004 using a combination of search terms for knee osteoarthritis and hyaluronic acid and a filter for randomized controlled trials. We extracted data on pain at rest, pain during or immediately after movement, joint function and adverse events.

Results: Twenty-two trials that reported usable quantitative information on any of the predefined end points were identified and included in the systematic review. Even though pain at rest may be improved by hyaluronic acid, the data available from these studies did not allow an appropriate assessment of this end point. Patients who received the intervention experienced a reduction in pain during movement: the mean difference on a 100-mm visual analogue scale was –3.8 mm (95% confidence interval [CI] –9.1 to 1.4 mm) after 2–6 weeks, –4.3 mm (95% CI –7.6 to –0.9 mm) after 10–14 weeks and –7.1 mm (95% CI –11.8 to –2.4 mm) after 22–30 weeks. However, this effect was not compatible with a clinically meaningful difference (expected to be about 15 mm on the visual analogue scale). Furthermore, the effect was exaggerated by trials not reporting an intention-to-treat analysis. No improvement in knee function was observed at any time point. Even so, the effect of hyaluronic acid on knee function was more favourable when allocation was not concealed. Adverse events occurred slightly more often among patients who received the intervention (relative risk 1.08, 95% CI 1.01 to 1.15). Only 4 trials explicitly reported allocation concealment, had blinded outcome assessment and presented intention-to-treat data.

Interpretation: According to the currently available evidence, intra-articular hyaluronic acid has not been proven clinically effective and may be associated with a greater risk of adverse events. Large trials with clinically relevant and uniform end points are necessary to clarify the benefit–risk ratio.

CMAJ 2005;172(8):1039-43

DOI:10.1503/cmaj.1041203

Osteoarthritis affects about 10% of the population over 55 years of age. Of those, one-quarter are severely disabled.[1] The condition is characterized by degeneration of the articular cartilage and subsequent subchondral bone changes. The underlying mechanisms remain unknown, but the glycosaminoglycan–proteoglycan matrix may play a major role.[2]

Hyaluronic acid, a glycosaminoglycan, is widely used for the treatment of osteoarthritis of the knee.[3] The costs of such treatment are significant. At present, 1 syringe of hyaluronic acid costs at least Can$130 (US$110). The treatment of knee osteoarthritis is covered by the US Medicare program but not by provincial formularies in Canada. In Austria (which has 8 million inhabitants) more than 10 million euros (approximately US$12 million or Can$15 million) is spent by social insurance programs annually for hyaluronic acid preparations (excluding the cost of application).

Hyaluronic acid has beneficial effects in vitro.[4] Because of its viscoelastic quality, it may replace synovial fluid. Furthermore, it may reduce the perception of pain. Beneficial molecular and cellular effects have also been reported.[2,4] Hyaluronic acid is frequently applied by intra-articular injection, but the evidence concerning its clinical relevance is conflicting. Some experts have recommended the use of intra-articular hyaluronic acid,[5,6] whereas others have concluded that it "is not efficacious."[7]

We performed a systematic review and meta-analysis of the effect of intra-articular hyaluronic acid for the treatment of knee osteoarthritis.

Methods

We identified randomized controlled trials comparing hyaluronic acid with placebo in patients with osteoarthritis. We searched MEDLINE, EMBASE, CINAHL, BIOSIS and the Cochrane Controlled Trial Register from inception until April 2004. We predefined a variety of clinical outcomes: pain at rest, pain during or immediately after movement, joint function and adverse events. We also predefined time points of assessment in broad categories: 2–6 weeks, 10–14 weeks, 22–30 weeks and 44–60 weeks.

We used random-effects models to pool the data and calculated the proportion of variation due to unexplained heterogeneity (I^2).[8] We used multivariate meta-regression analysis to assess whether an effect had been influenced by allocation concealment, blinded outcome assessment, intention-to-treat analysis or molecular mass.

Results

The electronic search of databases resulted in 1159 hits, and we retrieved 42 publications for closer inspection. Of these, 22 studies were finally included. The process of identifying trials suitable for inclusion, the clinical and methodologic characteristics of the studies and references to the included trials are presented in the expanded version of this article (at www.cmaj.ca/cgi/content/full/172/8/1039).

Trial quality

Overall, the quality of the reported trials was unsatisfactory. Only 4 trials reported concealment of allocation and blinding of the outcome observer, and presented data from an intention-to-treat analysis. Seven trials reported allocation concealment. Eight trials reported an intention-to-treat analysis, but only 6 of these presented data that could be extracted from the intention-to-treat analysis. Sixteen trials reported that the outcome observer was blinded to the intervention.

Pain at rest

Eight trials (with a total of 10 comparisons, n = 468) reported reduction of pain at rest for the treatment group relative to the control group at 2–6 weeks. Unexplained statistical heterogeneity was excessive (I^2 = 94%), and we could not identify a particular trial causing this excess variability (Fig. 1). Pooling in the face of such a high degree of heterogeneity of unknown cause is not advisable. If the data were pooled, the mean difference in the visual analogue scale was in favour of hyaluronic acid (–8.7 mm, 95% confidence interval [CI] –17.2 to –0.2, p = 0.046) (Table 1). For trials in which allocation concealment was unclear or there was no intention-to-treat analysis, the effect was overestimated by 15.6 mm (95% CI –3.2 to 34.4, p = 0.11). For trials in which outcome assessment was not blinded, the effect was also overestimated, by 13.6 mm (95% CI –0.6 to 27.7, p = 0.06).

Two high-quality trials assessed pain at rest at 10–14 and 22–30 weeks, and 2 trials (1 of which was of high quality) at 44–60 weeks; there were no significant effects at these time points (Table 1).

Pain during or immediately after exercise

Nine trials (n = 1141) reported pain reduction in the treatment group relative to the control group at 2–6 weeks. The weighted mean difference was –3.8 mm on the visual analogue scale (95% CI –9.1 to 1.4, p = 0.15) (Table 1). Again, there was an excessive degree of unexplained statistical heterogeneity (I^2 = 81%). One trial had a qualitative interaction: among patients with less severe osteoarthritis, those who received hyaluronic acid had better pain reduction than those who received placebo; however, among patients with more advanced disease, pain increased with hyaluronic acid. When this trial was excluded, the effect remained largely unchanged (weighted mean difference –4.2 mm) and heterogeneity was acceptable (I^2 = 20%).

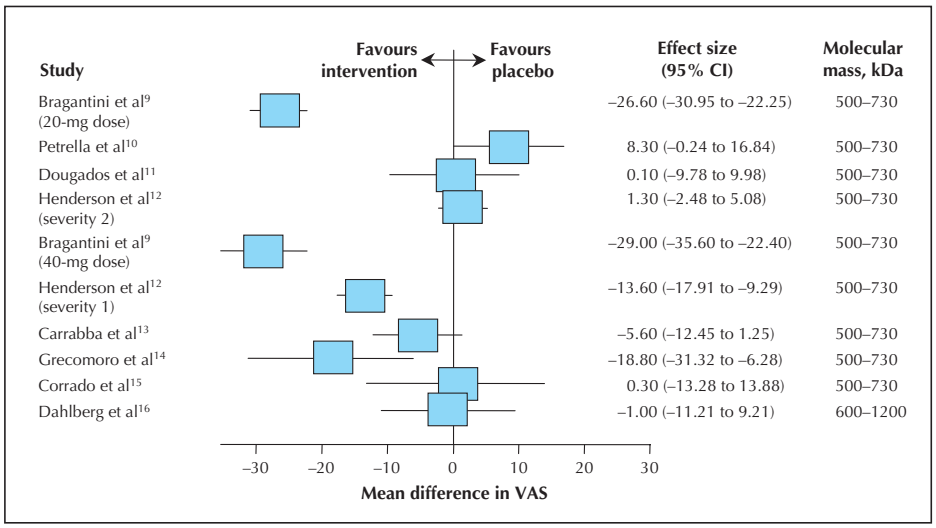

Fig. 1: Effectiveness of hyaluronic acid compared with placebo for pain at rest at 2–6 weeks. Data are presented as the study means (boxes) and 95% confidence intervals (horizontal lines). There is no summary effect, and the data are not weighted (because of excessive heterogeneity). Bragantini and associates[9] reported on 2 strata separately (20-mg and 40-mg doses), as did Henderson and colleagues[12] (severity groups 1 and 2). The trials are ranked according to the molecular mass of the hyaluronic acid preparation. VAS = visual analogue scale.

At 10–14 weeks, 5 comparisons were available (n = 877) and at 22–30 weeks, 4 comparisons were available (n = 463). In both analyses pain was lower in the intervention group (Table 1). Only one trial followed patients until 44–60 weeks (n = 95), and it showed no effect.

Joint function

Nine trials reported a measure of joint function at 2–6 weeks (n = 994). The standardized weighted mean difference between the groups at this time point was 0.00 (95% CI –0.23 to 0.23, p = 0.99) (Table 1 and Fig. 2A). There was a high degree of unexplained statistical heterogeneity (I^2 = 66%). Unclear or absent allocation concealment led to considerable inflation of the effect (by 2.6 points on the z score, 95% CI 1.2 to 3.9, p < 0.001). Other measures of quality did not influence the effect size.

Data from 7 comparisons (n = 1023) were available for function at 10–14 weeks. The standardized weighted mean difference between the groups was –0.11 (95% CI –0.31 to 0.09, p = 0.28, I^2 = 59%) (Table 1 and Fig. 2B).

Unclear or absent allocation concealment led to considerable inflation of the summary effect (by 3.0 points on the z score, 95% CI 1.1 to 4.9, p < 0.001). Other measures of quality did not influence the effect size.

Data from 22–30 weeks (4 trials, n = 542) and 44–60 weeks (2 trials, n = 143) showed no significant difference between the treatment groups (Table 1 and Fig. 2C).

Adverse events

Fifteen trials (with a total of 17 comparisons, n = 2019) reported on adverse events. Adverse events, mostly of minor clinical relevance (such as transient pain at the injection site), occurred more frequently among patients who received the intervention (summary relative risk 1.08, 95% CI 1.01 to 1.15, p = 0.021). There was no unexplained heterogeneity (I^2 = 0%).

Impact of molecular mass

The effect size is ordered in Fig. 1 and Fig. 2 according to molecular mass, but no clear association is evident (see also additional figures in the expanded online version of this article). This lack of association was confirmed by the meta-regression analyses.

Interpretation

The methodologic quality of most of the trials was poor. Treatment with intra-articular hyaluronic acid did not have a proven beneficial effect on osteoarthritis pain at rest. Pain during or after movement was slightly lower relative to placebo, but this effect is of borderline clinical relevance at best. Patients with chronic rheumatoid arthritis rated pain as "somewhat better" at a mean difference of 8 mm on a visual analogue scale and as "much better" at a 15-mm difference.[22] The summary estimates obtained in this meta-analysis fell short of being the difference defined as "somewhat better," and the confidence intervals sometimes included the range defined as "much better"; however, the latter were also compatible with increased pain. Moreover, the effect appears to have been inflated by trials of low methodologic quality. Intra-articular hyaluronic acid did not lead to improvement in joint function but may have been associated with a higher rate of side effects than placebo.

This study had several limitations. Often, only a few trials were available for a given end point at a particular time. A more significant problem, however, was the low methodologic reporting quality of the trials. Low-quality trials, particularly those not reporting allocation concealment and those not reporting blinding, are known to favour interventions.[23–27] Our data are compatible with these findings.

We are aware of 3 relevant systematic reviews.[28–30] One of these was an update of the recommendations of the European League against Rheumatism (EULAR) for management of knee osteoarthritis.[30] The literature search for that review was systematic, but it covered only 2 databases (MEDLINE and EMBASE). A summary quality score was used, and the median score was 20 out of 28. This high score is surprising, considering that the standard of reporting for the 3 most important items was poor.[23] Perhaps the high scores were the result of summing individual items. The use of such scores, however, is not advisable.[31] The task force that prepared the EULAR update[30] did not perform a quantitative summary but counted the number of

Table 1: Mean difference in pain or function between treatment with hyaluronic acid and treatment with placebo at 4 time points

End point	2–6 wk	10–14 wk	22–30 wk	44–60 wk
Pain at rest, mm VAS (95% CI)	–8.7 (–17.2 to –0.2)*	–5.2 (–13.3 to 2.9)	–6.0 (–22.3 to 10.3)	–0.75 (–9.6 to 8.1)
Pain during or after exercise, mm VAS (95% CI)	–3.8 (–9.1 to 1.4)*	–4.3 (–7.6 to –0.9)	–7.1 (–11.8 to –2.4)	–0.5 (–12.5 to 11.5)
Function, z value (95% CI)	–0.00 (–0.23 to 0.23)	–0.11 (–0.31 to 0.09)	–0.16 (–0.45 to 0.13)	–0.17 (–0.50 to 0.16)

Note: A minus indicates superiority of hyaluronic acid (a reduction of pain or functional impairment). VAS = visual analogue scale, CI = confidence interval.
*Pooling is questionable because of a high degree of unexplained statistical heterogeneity.

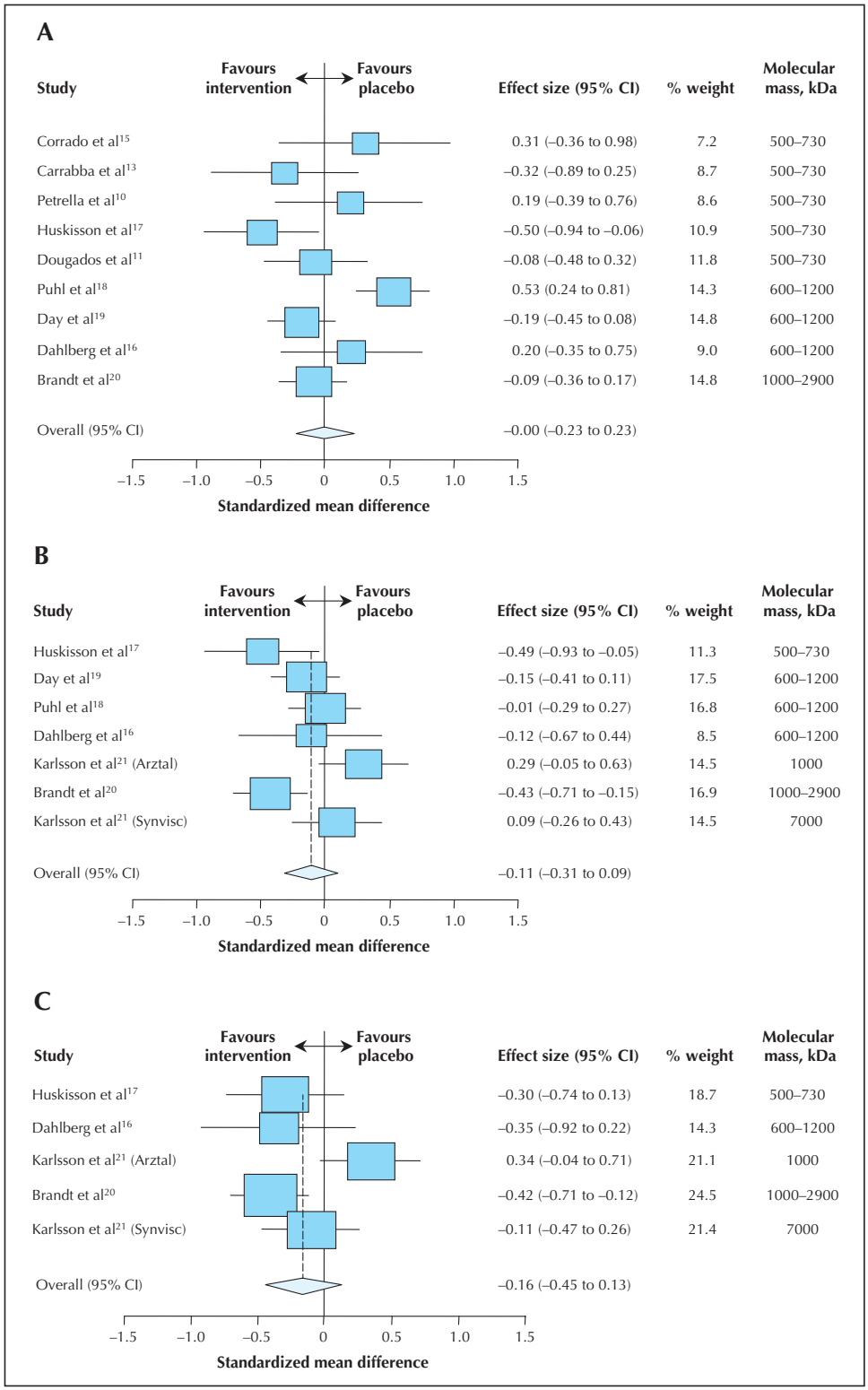

Fig. 2: Effectiveness of hyaluronic acid compared with placebo for joint function. A: At 2–6 weeks. B: At 10–14 weeks. C: At 22–30 weeks. Data are presented as standardized, weighted study mean differences (boxes), 95% confidence intervals (horizontal lines) and summary standardized, weighted mean difference with 95% confidence interval (diamond). Karlsson and collaborators[21] reported on 2 strata separately (by brand of hyaluronic acid preparation: Arztal and Synvisc). The trials are ranked according to the molecular mass of the hyaluronic acid preparation.

positive trials, an approach that may be misleading.[32] The authors' conclusion that "there is evidence to support the efficacy of HA [hyaluronic acid]" is not, in our opinion, well supported by the information presented.

The second systematic review and meta-analysis[28] covered the same search period as ours. Lo and associates[28] chose a hierarchy of relevant end points and selected the highest-ranking end point in each trial. The time of assessment was 2–3 months, but if data for this time point were not available, data were extracted on pain at 1–4 months after the first intra-articular injection. This creative approach may lump together end points that are only weakly related. The trials included in the analysis of Lo and associates[28] differed slightly from those in our analysis (see expanded online version of this article). Lo and associates concluded that at best there is a small effect.

The third systematic review and meta-analysis[29] was published recently, but the search included only studies published up to 2001. Wang and colleagues[29] used 3 end points to calculate "efficacy scores," standardizing for different pain measures and summing efficacy scores over time. These efficacy scores make clinical inferences very difficult. It is questionable if combining data from trials of highly variable length is reasonable. We found 7 additional studies, including 2 published before 2002 and 1 published before 2001. Wang and colleagues[29] stated that hyaluronic acid led to significant improvements in pain and functional outcomes with few adverse events. Even though some of their reported results were of statistical significance, they were certainly not of clinical relevance.

Experimental studies and animal studies suggest that the molecular mass of hyaluronic acid may affect pain and the underlying inflammatory mechanisms in osteoarthritis.[2,33] We observed no association between molecular mass and effect of hyaluronic acid, either by ranking the effects or by more formal methods for indirect comparisons (meta-regression analysis).

In conclusion, intra-articular hyaluronic acid should not be used for the treatment of painful osteoarthritis (except in clinical trials) until a large, long-term trial with clinically relevant and uniform end points has clarified the benefit–risk ratio. Using predefined clinically important differences could further help in the assessment of its value for patients with knee osteoarthritis. Such an approach is of particular importance when considering the public health impact of the disease and its treatment.

This article has been peer reviewed.

From the Department of Emergency Medicine, Medizin Universität Wien, Vienna, Austria (Arrich, Mad, Müllner); Hauptverband der Österreichischen Sozialversicherungsträger, Vienna, Austria (Piribauer, Schmid, Klaushofer); and Ludwig Boltzmann Institut für Osteologie and Medizinische Abteilung, Hanusch Hospital, Vienna, Austria (Klaushofer, Müllner)

Competing interests: None declared.

Contributors: All authors were involved in the conception and design of the article. Jasmin Arrich and Philipp Mad were responsible for data acquisition. Jasmin Arrich, Philipp Mad and Marcus Müllner were responsible for data interpretation. Marcus Müllner was responsible for the statistical analysis and wrote the first draft of the article. Franz Piribauer, Daniela Schmid, Klaus Klaushofer and Marcus Müllner revised the article. All authors approved the final version for publication.

Acknowledgements: We are grateful to Walter Grunt and Maximilan Gstöttner (Oberösterreichische Gebietskrankenkasse, Linz, Austria) for providing Austrian expenditure data for hyaluronic acid in 2001. We also thank Melanie Carr for editorial assistance.

The study was partly funded by the Hauptverband der Österreichischen Sozialversicherungsträger (Main Association of Austrian Social Security Institutions).

References

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-7.
2. Lajeunesse D, Delalandre A, Martel-Pelletier J, Pelletier JP. Hyaluronic acid reverses the abnormal synthetic activity of human osteoarthritic subchondral bone osteoblasts. *Bone* 2003;33:703-10.
3. Jordan KM, Sawyer S, Coakley P, Smith HE, Cooper C, Arden NK. The use of conventional and complementary treatments for knee osteoarthritis in the community. *Rheumatology (Oxford)* 2004;43:381-4.
4. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther* 2003;5:54-67.
5. Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2000;59:936-44.
6. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;43:1905-15.
7. Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis: hope, hype, and hard truths. *Arch Intern Med* 2002;162:245-7.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
9. Bragantini A, Cassini M, De B, Perbellini A. Controlled single-blind trial of intra-articularly injected hyaluronic acid (Hyalgan®) in osteoarthritis of the knee. *Clin Trials J* 1987;24:333-40.
10. Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee. *Arch Intern Med* 2002;162:292-8.
11. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. *Osteoarthritis Cartilage* 1993;1:97-103.
12. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Ann Rheum Dis* 1994;53:529-34.
13. Carrabba M, Paresce E, Angelini M, Re KA, Torchiana EEM, Perbellini A. The safety and efficacy of different dose schedules of hyaluronic acid in the treatment of painful osteoarthritis of the knee with joint effusion. *Eur J Rheumatol Inflamm* 1995;15:25-31.
14. Grecomoro G, Martorana U, Di Marco C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: a controlled clinical trial versus placebo. *Pharmatherapeutica* 1987;5:137-41.
15. Corrado EM, Peluso GF, Gigliotti S, De DC, Palmieri D, Savoia M, et al. The effects of intra-articular administration of hyaluronic acid on osteoarthritis of the knee: a clinical study with immunological and biochemical evaluations. *Eur J Rheumatol Inflamm* 1995;15:47-56.
16. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. A one-year double-blind, placebo-controlled study. *Arthritis Rheum* 1994;37:521-8.
17. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)* 1999;38:602-7.
18. Puhl W, Bernau A, Greiling H, Köpcke W, Pförringer W, Steck KJ, et al. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. *Osteoarthritis Cartilage* 1993;1:233-41.
19. Day R, Brooks P, Conaghan PG, Petersen M. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. *J Rheumatol* 2004;31:775-82.
20. Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. *Clin Orthop* 2001;(385):130-43.
21. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford)* 2002; 41:1240-8.
22. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol* 1993;20:557-60.
23. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
24. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693-708.
25. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101-5.
26. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350:834-43.
27. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609-13.
28. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003;290:3115-21.
29. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004;86-A:538-45.
30. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003;62:1145-55.
31. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;282:1054-60.
32. Bushman BJ. Vote counting procedures in meta-analysis. In: Cooper H, Russel HL, editors. *The handbook of research synthesis*. New York: Sage Foundation; 1994: p. 194-213.
33. Gomis A, Pawlak M, Balazs EA, Schmidt RF, Belmonte C. Effects of different molecular weight elastoviscous hyaluronan solutions on articular nociceptive afferents. *Arthritis Rheum* 2004;50:314-26.

Correspondence to: *Dr. Marcus Müllner, Universität Klinik für Notfallmedizin, Medizin Universität Wien, Währinger Gürtel 18-20/6D, Allgemeines Krankenhaus Wien, A-1090, Austria; fax +43 (1) 40400 2512; marcus.muellner@meduniwien.ac.at*