Efficacy and safety of viscosupplementation with Hylan G-F 20 for the treatment of knee osteoarthritis: a systematic review
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CRD summary
This review assessed intra-articular injections of Hylan G-F 20 for the treatment of knee osteoarthritis. The available evidence suggested that Hylan G-F 20 injections decreased pain and improved knee function in the short term. The authors' conclusions are supported by the data presented, but differences between included studies, suggest they should be viewed with caution.

Authors' objectives
To review the efficacy, effectiveness and safety of intra-articular injections of Hylan G-F 20 for the treatment of painful knee osteoarthritis (OA).

Searching
The manufacturers of Hylan G-F 20 supplied primary data to the authors. The data were supplemented by searches of MEDLINE (from 1966 to 1999), EMBASE (from 1988 to 1999), HealthSTAR (from 1976 to 1999), Current Contents (1999) and the Cochrane Library (Issue 4, 1999). The search strategy was reported in the review. In addition, the authors examined the references of retrieved articles and other relevant reviews.

Study selection
Study designs of evaluations included in the review
Randomised controlled studies (RCTs) and observational studies were eligible for inclusion.

Specific interventions included in the review
Comparisons of intra-articular injections of Hylan G-F 20 with placebo (saline solutions) or other conventional treatments were eligible for inclusion. Other conventional treatments used in the included studies were sodium hyaluronate (low molecular weight hyaluronan), non-steroidal anti-inflammatory drugs (NSAIDs) and conventional appropriate care (defined according to American College of Rheumatology guidelines).

Participants included in the review
The inclusion criteria were not specified in terms of the participants. The mean age of the participants in the included studies ranged from 41 to 77 years.

Outcomes assessed in the review
Studied reporting health outcomes were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The inclusion criteria were applied independently by two reviewers and, in the case of disagreement, a consensus was reached.

Assessment of study quality
The validity of the RCTs was assessed using the Chalmers scale. For observational studies, the criteria proposed in the Centre for Reviews and Dissemination Report 4 were used. The maximum score range for quality was 0 (worst) to 1 (best). References for the quality checklists were reported in the paper. The authors did not state how many reviewers performed the validity assessment.
Data extraction
Two reviewers independently abstracted all data using a standard protocol. In the case of disagreement a consensus was reached. The data extracted from the included studies were listed in the review.

For each study, continuous outcomes were expressed as the incremental and marginal difference between the treatment and control groups. For dichotomous outcomes, the relative risk and number-needed-to-treat were calculated.

Methods of synthesis
How were the studies combined?
The studies were discussed in a narrative synthesis. The authors stated that the data were pooled when the available data allowed for it, and after investigation of the comparability of the studies. Dichotomous outcomes (relative risks) were pooled in fixed-effect and random-effects models.

How were differences between studies investigated?
The studies were grouped according to the type of control group.

Results of the review
Fourteen studies (1,735 patients and 298 knees) were identified: 7 RCTs, 6 case series (including 2 before-and-after studies) and 1 cross-sectional, descriptive study.

Hylan G-F 20 versus placebo injections (4 RCTs; n=386): a single course of Hylan G-F 20 produced a significant decrease of painful symptoms of knee OA (as measured on the visual analogue scale), and a short-term improvement in joint function (up to 3 to 6 months post-treatment). The authors noted that significant decreases in symptoms, compared with baseline, were often reported in both the treatment and control groups.

Hylan G-F 20 versus NSAIDs and other conventional therapies (3 RCTs; n=407): 2 RCTs found no evidence that intra-articular injections of Hylan G-F 20 were more effective than oral NSAIDs. Hylan G-F 20 did not seem to provide additional benefits over conventional therapy, as reported in one RCT.

Hylan G-F 20 versus other intra-articular hyaluronan products (1 RCT, 1 descriptive, cross-sectional study; n=169): the injection of a single course of intra-articular Hylan G-F 20 appeared to be more effective than injections of other low molecular weight hyaluronan products for the reduction of acute OA symptomatology. The authors noted that these results should be interpreted with caution because of the small sample size of the RCT and the design limitations of the other study.

Studies without a control group (2 before-and-after studies, 4 post-intervention assessment studies; n=781): 2 studies were retrospective and some did not define improvement versus baseline. Overall, around 40% of the patients showed an improvement in their symptoms, and 70% did not require a total knee arthroplasty at the end of the study (1 to 2 years).

Multiple courses of Hylan G-F 20 (5 longitudinal, descriptive studies): 2 studies were extensions of RCTs, however, the quality of the evidence was limited. The studies mainly described similar results after multiple courses in comparison with the baseline treatment course.

Safety: the available data suggested that local adverse effects of Hylan G-F 20 were in general infrequent, mild and transient. Adverse events appeared in 0 to 8.3% of the patients/knees treated in the included studies. Generally, no systemic events were reported, except for gastrointestinal events. Some studies reported mild and/or unspecific events such as itching, calf cramps and haemorrhoids. There was little evidence that patients receiving multiple courses of Hylan G-F 20 were at a greater risk of adverse events.

Cost information
The authors stated that evidence incorporating the cost-analysis associated with Hylan G-F 20 treatment seemed to show that the cost-effectiveness and cost-utility ratios favour Hylan G-F 20 when compared with appropriate
conventional care without this treatment.

**Authors’ conclusions**
The available evidence suggests that treatment with Hylan G-F 20 ameliorates knee OA pain and improves knee function in the short term. The delay of the need for knee replacement, as well as the durability of the effect over the longer term, has only been demonstrated in uncontrolled studies. There is insufficient evidence to reach firm conclusions about multiple courses of Hylan G-F 20 treatment. The authors also state that treatment with Hylan G-F 20 seems to be reasonably safe.

**CRD commentary**
The authors posed a clear review question and presented suitable inclusion criteria. The search was comprehensive and included data from the manufacturers of Hylan G-F 20. However, publication bias was not assessed. The review process was adequately described and appropriate methods were used to assess the validity of the included studies. Details of the studies were well presented in tabular format and the studies were mainly combined in a narrative. Only one group of studies were pooled, and the relative risks and 95% confidence intervals were not reported in the text. Differences between the studies were also not discussed. The authors’ conclusion follows from the data presented, but should be viewed with caution due to the problems stated.

**Implications of the review for practice and research**
Practice: The authors state that while Hylan G-F 20 appears to be an effective therapeutic option for patients with knee OA, its clinical role in relation to NSAIDs might be determined by a risk-benefit assessment in individual patients.

Research: The authors did not state any implications for further research.

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