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No Difference Between Intra-Articular Injection of Hyaluronic Acid and Placebo for Mild to Moderate Knee Osteoarthritis: A Randomized, Controlled, Double-Blind Trial

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ABSTRACT

The main goal of our study was to examine the effectiveness and safety of Fermathron plus, a specific brand of hyaluronic acid (HA), in patients with mild to moderate knee osteoarthritis. In a randomized, controlled, double-blind trial, 196 patients with symptomatic knee osteoarthritis (mean age ± SD, 59.4 ± 9.9 years, Kellgren–Lawrence grade 1–3) were given either 3 weekly intra-articular injections of HA or saline (placebo). Although pain and functional scores (WOMAC scale) improved significantly from baseline up to 6 months, HA was not superior to placebo at any follow-up (VAS pain 50 m walking from 56.4 to 38.1, $P < .001$, and 58.2 to 39.6, $P < .001$, respectively). No subgroup analysis resulted in superior outcomes. No serious adverse events were noticed.

Patients suffering from osteoarthritis (OA) of the knee experience pain, joint stiffness and are limited in daily activities, sports and work. Treatment options for patients with mild or moderate knee osteoarthritis (OA) vary from life style advice or analgesia to exercise therapy, NSAIDs, corticosteroid injections or glucosamine suppletion. These symptom-relieving treatments may have their own disadvantages such as gastrointestinal complications or being very labor intensive for both the patient and the professional [1–4]. In the joints of OA patients, the natural supply of hyaluronan (a naturally occurring long-chain, unbranched polysaccharide which is the most characteristic component of synovial fluid) is reduced both in molecular weight and concentration [5,6].

The debate on the effectiveness of viscosupplementation therapy for these patients, which involves single or repeated intra-articular injections with exogenous hyaluronic acid (HA), is still unresolved. One systematic review found HA to be effective in improving pain, activity levels, and function in patients with symptomatic knee OA [7]. A more recent systematic review found a bias in results from HA studies with a potential conflict of interest [8].

There are 7 meta-analyses published on intra-articular HA treatment for knee OA. One found favorable results [9], while 4 found that intra-articular HA was not proven to be clinically effective and even might be associated with a greater risk of adverse events [10–13]. One meta-analysis concluded that short-term pain relief was superior with intra-articular corticosteroids but long-term pain relief was superior with intra-articular HA [14], and 1 concluded that HA was not more efficacious than oral NSAIDs but HA might have a safer profile [15]. In a Cochrane review, Bellamy et al [2] concluded that HA had beneficial effects on pain, function and patient global assessment, especially at the 5 to 13 week post injection period.

A reason for these contradicting results might be the large differences in available HA products including source, molecular weight, concentration and volume of HA [11]. Also, the lack of consensus on the optimal treatment protocol regarding the number of injections and the interval between injections, as well as the use of repeated treatment cycles make it difficult to establish HA effectiveness.

Although national guidelines by the American Academy of Orthopedic Surgeons, the National Institute for Clinical Excellence (United Kingdom) and the Dutch Orthopedic Society do not recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee [16–18], intra-articular HA is widely used in clinical orthopedic practice. While health insurance companies in the Netherlands and most other European countries will not reimburse this treatment, many patients are paying to have this treatment. Treatment protocols usually prescribe 3 to 5 intra-articular injections at weekly intervals, with only specifically designed HA products being used with a single injection treatment. Since no study has proven superior efficacy of 5 intra-articular injections over the more commonly used 3 injections regime, we routinely use a protocol of 3 intra-articular injections at a weekly interval and an HA product with a medium molecular weight (2200 kd). A

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recent systematic review on the effectiveness of different HA products was unable to prove superiority of high molecular weight HA products over low or medium molecular weight HA products. Treatment with different HA products resulted in a 40% to 50% improvement of symptoms compared to baseline, while this improvement was 30% for placebo treatment. This review concluded that more studies were needed to give more evidence of the efficacy of different HA products [11].

The main goal of our study was to examine the effectiveness and safety of Fermathron plus, a specific brand of HA. We hypothesized the HA group to have superior pain relief compared to the placebo group in patients with mild to moderate knee OA, without serious adverse events occurring in the treatment group.

Patients and Methods

We conducted a multi-center, double-blind, placebo controlled clinical trial after obtaining medical ethical review board approval (IRB ID NL19495.015.07), in which we compared the effectiveness and safety of HA to placebo treatment in patients with mild to moderate knee OA. Although investigator initiated and driven, financial support was provided to conduct this trial (Biomet Europe), together with material support (both the investigational device and placebo materials were supplied by Hyaltech Inc.). The trial was carried out according to the 1964 Helsinki Declaration principles, and its subsequent endorsement. A priori power analysis ($\alpha = .05$, $\beta = .8$ to detect an estimated 20% higher number of responders in the intervention group) resulted in 186 patients (93 patients per group) but we aimed to include 200 patients to compensate for possible loss to follow up. After written informed consent all patients were randomized to either the treatment (HA) group or the control group using a computer-generated randomization list produced by a third party (Medical Statistics Unit, University of Edinburgh, UK). All patients were followed up with a maximum of 6 months after the third (final) injections. Both groups received 3 injections administered at weekly intervals with the HA group receiving a 1.5% solution of sodium hyaluronate (Fermathron plus, Hyaltech Ltd., Edingburgh, UK), produced from the bacterium *Streptococcus equi* by a process of continuous fermentation. This HA has a molecular weight of 2.2 Md and aims to restore the viscoelasticity of the depleted endogenous HA by decreasing anti-inflammatory cytokines which are present with OA. The treatment syringes (2 ml) contained for each milliliter 15 mg sodium hyaluronate, 8.5 mg sodium chloride, 0.28 mg disodium hydrogen orthophosphate dihydrate, 0.044 mg sodium dihydrogen phosphate dehydrate and water for injections (Eur. Ph. *q/s*). The syringes (2 ml) for the placebo group contained for each milliliter 8.5 mg sodium chloride, 0.28 mg disodium hydrogen orthophosphate dihydrate, 0.044 mg sodium dihydrogen phosphate dihydrate and water for injections (Eur. Ph. *q/s*). All devices were supplied as sterile, pre-filled syringes containing a clear colorless solution and only carrying numbers corresponding to the randomization list. Between June 2009 and March 2012, 196 patients (HA group: n = 99, placebo group: n = 97) in good general health with knee OA according to the American College of Rheumatology diagnostic criteria [19] were included from 2 different hospitals (Fig. 1). Knee OA was confirmed with a standard anterior-posterior (AP) radiograph taken within the previous 12 months. Patients with evidence of knee OA grade 0 or IV as described by Kellgren–Lawrence were excluded. We also excluded bilateral knee OA patients if they had ≤25 mm difference in visual analogue scale (VAS) pain score on the 50 m walk test and patients with a VAS score of <30 or >89, patients with hip OA or any other condition interfering with the assessment of effectiveness. Patients with prior HA treatment (any joint), and patients who had within the preceding 3 months intra-articular injections of any type or arthroscopic surgery of the treated knee, were also excluded. Patients were required to rely on acetaminophen as the only escape medication for the duration of the study. Before the first injection an index knee examination was done, including range of motion (ROM), VAS 100 mm pain scores (pain after 50 m walking and pain at rest), the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score and recording of limitations in

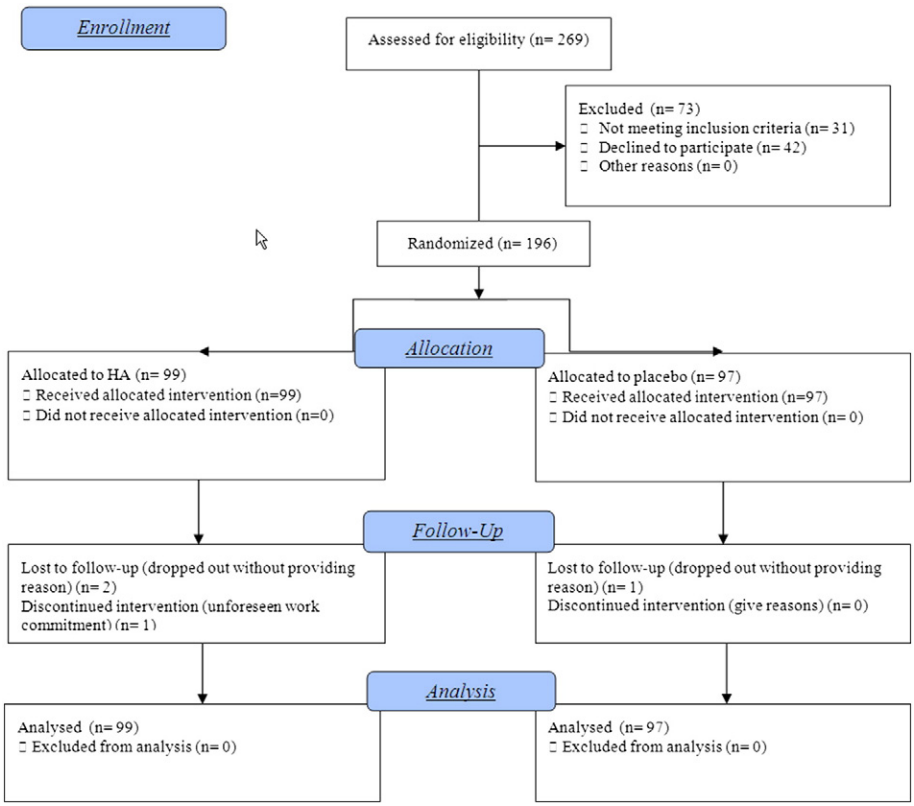

Fig. 1. Consort 2010 study flow.