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Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee — A prospective randomized clinical trial

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Abstract

In this independent prospective randomized trial, we compared the clinical effectiveness, functional outcome and patient satisfaction following intra articular injection with two viscosupplementation agents — Hylan G-F-20 ($n=199$) and Sodium Hyaluronate ($n=193$) in patients with osteoarthritis (OA) of the knee. All patients were prospectively reviewed by blinded independent assessors at pre injection, 6 weeks, 3, 6, 12 months. Knee pain and patient satisfaction were measured on a visual analogue scale. Functional outcome was assessed using WOMAC, Oxford knee score and EuroQol EQ-5D scores. Knee pain on VAS improved from 6.7 to 3.2 by 6 weeks ($p=0.02$) and was sustained until 12 months (3.7, $p=0.04$) with Hylan G-F 20. In the Sodium Hyaluronate group, pain improved from 6.6 to 5.7 at 6 weeks ($p>0.05$) and to 4.1 at 3 months ($p=0.04$) but was sustained only until 6 months (5.9, $p>0.05$). Improvement in the WOMAC pain subscale was significantly superior in the Hylan G-F 20 group at 3 months ($p=0.02$), 6 months ($p=0.01$) and 12 months ($p=0.007$). There was no significant difference in the EQ-5D scores at 6 weeks and 3 months between the two groups. The numbers of treatment related adverse events were higher (39 vs. 30) in the Hylan G-F 20 group. One patient in the Hylan G-F 20 group who had a serious adverse event was also included in the final analysis. Although both treatments offered significant pain reduction, it was achieved earlier and sustained for a longer period with Hylan G-F 20. From this study, it appeared that the clinical effectiveness and general patient satisfaction are better amongst patients who received Hylan G-F 20.

Keywords: Viscosupplementation; Osteoarthritis; Knee; Hyaluronic acid; Randomized

1. Introduction

Osteoarthritis (OA) is the most widespread joint disease affecting the elderly population [1,2]. Hyaluronic acid (HA) is a principal constituent of the normal synovial fluid and contributes significantly to its rheological properties and joint homeostasis [3,4]. The synovial fluid in the osteoarthritic joint has both a lower concentration and lower average molecular weight of HA [3,5]. The rationale of intra articular injection of HA in the osteoarthritic joint is to restore the viscoelastic properties [5–8].

The therapeutic efficacy and safety of intra articular injection of HA in the treatment of osteoarthritis of the knee has been well established in the literature [9–16]. A recent Cochrane review has concluded in favour of HA class products in the treatment of OA of the knee [17]. The aim of therapy is to reduce pain and improve functional outcome by supplementing the endogenous synovial fluid [18,19]. The viscoelastic properties and the molecular weight of such preparations influence the magnitude of therapeutic benefits achieved [20–23].

There are multiple viscosupplementation products marketed with variations of source, molecular weight and dose regimes. Although there are many studies to demonstrate the beneficial effects of viscosupplementation, the question about the magnitude and longevity of the therapeutic effects remains unanswered [10,17]. Furthermore, there is a paucity of clinical trials comparing the relative efficacy of different HA products in the treatment of OA of the knee [24–26].

In recent years, viscosupplementation with Hylan G-F 20 and Sodium Hyaluronate has been successfully used for short

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term relief of arthritic symptoms in the knee [11,23,27–33]. The aim of this study is to compare the clinical effectiveness, functional outcome and patient satisfaction following intra articular injection with Hylan G-F 20 and Sodium Hyaluronate in patients with symptomatic primary OA of the knee.

2. Material and methods

2.1. Patient recruitment

Patients with primary osteoarthritis of the knee affecting the tibio-femoral +/− the patello-femoral compartment were consulted by senior orthopaedic surgeons who discussed their preferred management strategy. All patients who opted for viscosupplementation therapy were referred to a dedicated injection clinic where they were counselled to participate in the study. The inclusion criterion was a minimum pain score of 6 on a visual analogue scale (VAS) (0–10, 10 as worst pain) in the affected knee. Exclusion criteria were surgery to the knee, previous intra articular treatment with corticosteroids, local anaesthetic agents or viscosupplementation agents to the target knee. Patients who had bilateral disease warranting treatment on both knees were excluded from the trial as they received the same treatment agent in both knees. The study was approved by the local research committee and an informed consent was obtained from all study subjects.

2.2. Viscosupplementation agents

Two types of viscosupplementation therapy agents were used. Synvisc® (Genzyme Biosurgery, Oxford, UK), classed as a medical device in the United Kingdom, is composed of cross-linked derivatives of hyaluronan (Hylan G-F 20) with an average molecular weight of 6 million Daltons for its fluid component. Hyalgan® (Fidia Farmaceutici S.p.A, Italy) is a viscous solution consisting of a fraction of purified natural sodium hyaluronate with a molecular weight of 0.50–0.73 million Daltons.

2.3. Study design

This was an independent single centre prospective randomized study where patients were randomized on entry to the study to either receive Hylan G-F 20 or Sodium Hyaluronate.

A process of simple randomization with no restrictions was applied to generate a random allocation sequence by a computerised random number generator. Following consent, patients were allocated the next available number on the trial by researchers. The patients were then assigned to the treatment groups based on their trial number by the surgeon (AD) at the dedicated injection clinic. The outcome investigators were blinded for the treatment received by the patient. Hylan G-F 20 was administered as a series of 3 weekly injections and Sodium Hyaluronate as a series of 5 weekly injections as per the manufacturer's recommendations. All injections were performed using the default blind technique by the same surgeon (AD), who did not participate in the evaluation of the patients. Any synovial fluid that was present in the knee was aspirated before the injection.

Analgesia consumption was strictly monitored according to a set protocol. All patients were requested to be 24 h analgesia free before baseline measurement. After the first dose of viscosupplementation, all patients were advised to avoid non steroidal anti inflammatory drugs (NSAID) for 6 months. Paracetamol (<2000 mg/day) was allowed for 'break-thru' pain, and Aspirin (<300 mg/day) was allowed as a platelet inhibitor. All patients were advised to stop analgesics for 24 h before each assessment. All patients received standardised physical therapy. Our study design is compliant with the CONSORT recommendations.

2.4. Outcome assessment

All patients were prospectively reviewed by independent assessors who were blinded for the treatment at pre injection, 6 weeks, 3, 6 and 12 months. Weight bearing radiographs were reviewed at baseline to grade the degree of OA using the Kellgren–Lawrence (KL) system [34]. The follow up was 12 months. Knee pain on a VAS (0–10, 10 as worst pain) was recorded at each visit by the patient. The primary outcome variable was the inter-group difference in the knee pain as measured by VAS at 6 months. Measures of secondary effectiveness were WOMAC 3.1 (Likert) and Oxford knee scores [35–37]. Patient satisfaction was quantified on VAS. Health related quality of life was measured using EuroQol-5D index.

Applicable to a wide range of health conditions and treatments, the EQ-5D provides both a compact descriptive profile and a single index value that can be used in the clinical and economic evaluation of the health care. The EQ-5D has been found to be acceptable, valid, and reliable in population studies and with other patient groups [38,39]. It consists of five dimensions — mobility, self care, usual activity, anxiety/depression, and pain/discomfort. Each dimension has 3 levels of statement representing degrees of perceived problem. In addition to the five dimensions, the EQ-5D also incorporates a visual analogue scale (VAS) on which patients are requested to rate their health on a scale of 0 (worst imaginable health) to 100 (best imaginable health). A total of 245 theoretically possible health states can be defined and weights for these states were derived from a national representative survey of UK population [40].

2.5. Adverse events

Safety was assessed at each visit. AE were classified into those occurring within 48 h of injection and those occurring at any other time. Furthermore they were subdivided as minor or major depending of the severity of symptoms. In addition, patients were asked to report any adverse events by telephone or attend the hospital for further advice and management. All adverse events, however minor, were recorded.

2.6. Statistics

The sample size was calculated from a two arm pilot study which was performed with 10 patients in each group. The pilot study was performed over 6 months. Using a power of 80% and $\alpha=0.05$, the required sample was 156 per group for a total of 312 patients. The final sample required was 344 patients to accommodate a 10% expected dropout. An end point analysis of the intent-to-treat patients was undertaken using the last recorded observation carried forward. Comparison of data between the groups was performed on a personal computer using SPSS® 11.0 for Windows®, © SPSS Inc., Chicago Illinois 60606. All scale variables were tested for normality with the Kolmogorov–Smirnov test. Student's *t*-test was used for parametric and Mann–Whitney *U* test for non parametric data. Fisher's exact test was used for all nominal comparisons. A p value of <0.05 was considered significant for all statistical tests.

3. Results

We identified 392 patients who met our criteria and participated in the study. Following randomization, 199 patients received Hylan G-F 20 and 193 received Sodium Hyaluronate. Patients in both groups predominantly had grade III OA (Hylan G-F 20 — 61% and Sodium Hyaluronate — 59%). There were no

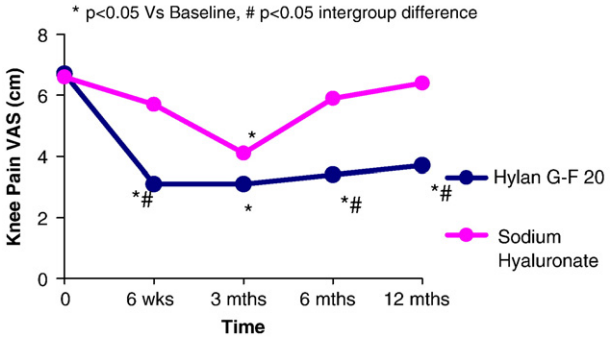

Fig. 1. Knee pain (VAS) in both groups.