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


Department of Trauma and Orthopaedics, Hull Royal Infirmary, Hull. HU2 3JZ, United Kingdom

Received 26 January 2008; received in revised form 24 February 2008; accepted 25 February 2008

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.

© 2008 Elsevier B.V. All rights reserved.

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
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 intraarticular 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 intraarticular 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 within 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 α=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 with 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 203 received Sodium Hyaluronate. Patients in both groups predominantly had grade III OA (Hylan G-F 20 — 61% and Sodium Hyaluronate — 59%). There were no
significant differences in the age (42 to 82 years, mean=67.2, p=0.54) or sex (M:F=1: 2.1, p=0.61) of the patients between the two groups.

3.1. Primary outcome measure

There was a reduction in knee pain as measured by VAS in both groups at 6 months. However there was a statistically significant improvement from the baseline score at 6 months only in the Hylan G-F 20 group. Knee pain as measured by VAS improved from 6.7 to 3.1 (median=2.9) by 6 weeks (p=0.01) and was sustained until 12 months (3.7, median=3.5, p=0.04) with Hylan G-F 20. In the Sodium Hyaluronate group, pain improved from 6.6 to 5.7 (median= 5.8) at 6 weeks (p>0.05) and to 4.1 (median=4.0) at 3 months (p=0.04) but was sustained only until 6 months (5.9, median=6.0 p>0.05) (Fig. 1). When comparing the knee pain improvement from baseline between the two groups, the Hylan G-F 20 group was statistically superior (2.5 mm, p=0.02) at 6 months. This difference was as early as 6 weeks (p=0.001) and was observed until 12 months (p=0.01). However, there was no difference in the magnitude of pain relief at 3 months between the groups.

3.2. Secondary outcome measures

There was improvement in the WOMAC pain subscales in both groups compared to the baseline measurements (Table 1). The pain subscale scores were significantly better than the pretreatment scores at all assessment periods in the Hylan G-F 20 group. In the Sodium Hyaluronate group, it was significant only at 3 months, mimicking the results of the primary outcome variable. Pain subscale improvements between the two groups were significantly better in the Hylan G-F 20 group at 3 months (p=0.02), 6 months (p=0.01) and 12 months (p=0.007). Similarly there was an improvement in WOMAC physical activity subscale in both groups. However, the physical activity subscale improvement was significantly better in the Hylan G-F 20 group at 6 months (p=0.02) and 12 months (p=0.004) when compared to the Sodium Hyaluronate group (Table 2). There was improvement in the WOMAC stiffness subscale in both groups at 3, 6 and 12 months, but no statistical difference was observed between the two groups at these timescales. WOMAC improvement from baseline in both groups at 6 months is illustrated in Fig. 2.

The observed Oxford knee scores are detailed in Table 3. A significant improvement from baseline values was observed in the Hylan G-F 20 group at 6 weeks, 6 months and 12 months. In the Sodium Hyaluronate group, the improvement from the pretreatment value was significant only at 3 months. Analysis of the magnitude of improvement between the two groups suggested a significantly better outcome at 6 (p=0.009) and 12 months (p=0.02) in the Hylan G-F 20 group.

General patient satisfaction of the treatment and health related quality of life as measured by EQ-5D assessment tool at baseline, 6 weeks, 3, 6, and 12 months is provided in Table 4. Patient satisfaction was highest at 3 months in both groups. At 6 months, patient satisfaction was significantly better in the Hylan G-F 20 group. Overall, patients were generally more satisfied with their treatment in the Hylan G-F 20 group. In the Hylan G-F 20 group, EQ-5D description and valuation subscales improved from baseline at 6 weeks and was sustained until 12 months. In the Sodium Hyaluronate group, significant improvement was observed only in the description subscale at 3 months.

There was a significant decrease in the requirement of Paracetamol in the Hylan G-F 20 group at 6 months (p=0.01) and 12 months (p=0.03) as compared to the Sodium Hyaluronate group. Prior to commencement of treatment, NSAID were taken by 72% and 70% of patients in the Hylan G-F 20 and Sodium Hyaluronate groups respectively. In the Hylan G-F 20 group, 0.5% at 6 weeks, 1.1% at 3 months, and 8.6% at 6 months violated the study protocol by taking NSAID. At 12 months 30% of patients required NSAID for pain control in this group. There were 1.8% at 6 weeks, 2.2% at 3 months and 18.5% at 6 months (p=0.03) violators in the Sodium Hyaluronate group. However, at 12 months, 54% were back on NSAID (p=0.006 compared to the Hylan G-F 20 group) in the Sodium Hyaluronate group.

3.3. Adverse events

Treatment related adverse events (AE) were reported in 39 patients in the Hylan G-F 20 group and in 30 patients in the Sodium Hyaluronate group (p=0.05). In the Hylan G-F 20 group all AE were minor except one major AE. The major AE occurred in a patient aged 62 years with Grade III OA of the knee. The major AE was sepsis in the knee. The knee aspirate was sterile and the symptoms settled.
completely by 4 weeks with oral NSAID. This patient was reviewed according to the trial protocol and the outcome was included in the final analysis. 32 of the minor AE in the Hylan G-F 20 group occurred within 48 h and the rest after. All minor AE were related to the treated knee. All AE in the Sodium Hyaluronate group were minor such as injection site pain and occurred within 48 h and relating to the treated knee. No systemic AE were recorded in either of the groups. There were no other withdrawals from the study owing to AE.

Patient compliance towards treatment was 99.4% in the Hylan G-F 20 group as compared to 92.2% in the Sodium Hyaluronate group. This was due to the number of injections in each treatment regime as uniformly described by the patients. Eight patients were lost to follow up in the Hylan G-F 20 group and 11 in the Sodium Hyaluronate group. There was no difference in the cost between the therapeutic agents for the recommended treatment regime, but the total operational cost of treatment was 23% more in the Sodium Hyaluronate group due to the two additional visits to complete the course of the recommended treatment. A flow chart in accordance with the CONSORT guidelines is illustrated in Fig. 3.

4. Discussion

There was a significant reduction in pain in the Hylan G-F 20 group which occurred earlier and lasted for much longer when compared to the Sodium Hyaluronate group. Although label for Hyalgan and Synvisc suggests efficacy for 26 weeks and 52 weeks respectively, we found that the symptomatic relief lasts up to 52 weeks with Hylan G-F 20 as evidenced by VAS scores for pain at the last follow up visit.

Table 4

<table>
<thead>
<tr>
<th>EuroQol EQ-5D and treatment satisfaction scores</th>
<th>Pre injection</th>
<th>6 weeks</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D description</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylan G-F 20</td>
<td>0.65</td>
<td>0.72 (p&gt;0.05)</td>
<td>0.76 (p=0.03)</td>
<td>0.74 (p=0.03)</td>
<td>0.76 (p=0.03)</td>
</tr>
<tr>
<td>Sodium Hyaluronate</td>
<td>0.61</td>
<td>0.68 (p&gt;0.05)</td>
<td>0.69 (p=0.04)</td>
<td>0.65 (p&gt;0.05)</td>
<td>0.67 (p&gt;0.05)</td>
</tr>
<tr>
<td>EQ-5D valuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylan G-F 20</td>
<td>68</td>
<td>81 (p=0.03)</td>
<td>82 (p=0.03)</td>
<td>80 (p&gt;0.05)</td>
<td>78 (p&gt;0.05)</td>
</tr>
<tr>
<td>Sodium Hyaluronate</td>
<td>69</td>
<td>72 (p&gt;0.05)</td>
<td>72 (p&gt;0.05)</td>
<td>68 (p&gt;0.05)</td>
<td>70 (p&gt;0.05)</td>
</tr>
<tr>
<td>Treatment satisfaction (VAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylan G-F 20</td>
<td>N/A</td>
<td>7.8</td>
<td>8.1</td>
<td>7.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Sodium Hyaluronate</td>
<td>N/A</td>
<td>4.9</td>
<td>5.1</td>
<td>5.0</td>
<td>4.9</td>
</tr>
</tbody>
</table>

p values against pre injection scores.
In recent years viscosupplementation with HA products features constantly in the management strategy of primary osteoarthritis of the knee. Various treatment guidelines published by the American Academy of Orthopaedic Surgeons and American College of Rheumatology recommend viscosupplementation injections early in the treatment paradigm, before and during non-selective NSAID and COX-2 inhibitors therapy and when those therapies are contraindicated, ineffective or cause adverse events [41,42]. Results from various clinical trials and Cochrane review form a solid body of evidence in support of intra articular administration of HA products for the treatment of OA of the knee [5,10,17,27]. Wang et al. [10] in their recent meta-analysis of randomized controlled trials confirmed that intra articular injection of cross-linked and non-cross-linked HA can decrease symptoms of osteoarthritis of the knee. Furthermore, the use of intra articular viscosupplementation in patients with knee osteoarthritis without mechanical symptoms gives results comparable with arthroscopic washout [43].

Several HA based products are available for the treatment of OA of the knee. These preparations differ significantly in their molecular weight, rheologic properties, residence times in the joint and concentration. The effect on patello-femoral arthritis has also been reported in the literature [44]. Whilst there is a general acceptance of the beneficial effects of HA, there still exists an ongoing debate about the degree of efficacy of these individual products [15,17]. Additionally there have been controversies in the therapeutic efficacy of cross-linked/non cross-linked and high/low molecular weight products [10,15,20,21,45]. This has prompted the need for well designed prospective randomized trials to resolve the continued uncertainty about the magnitude of therapeutic effects of various products.

Results similar to our study demonstrating efficacy for up to 1 year in favour of cross-linked HA have been reported in the literature [46,47]. One series reports an improvement in the pain within one month after initiating Hylan G-F 20 injections in 99% of the patients [29]. In other studies, therapeutic effect with Sodium Hyaluronate was observed as early as 1 week after the first injection [48]. In our study, the effect was maximal at 3 months in this group. The severity of pain at baseline has been correlated to the degree of improvement with HA injections with patients having severe pain at baseline demonstrating a greater response in some studies [23,49]. This heterogeneity in the degree of efficacy from various studies may relate to factors in the study design and composition of the HA preparations used. Longer efficacy has been reported with repeat courses of Sodium Hyaluronate at 4 to 6 month intervals [48].

The impact of age and radiological degree of osteoarthritis in the clinical efficacy is unclear. Some studies suggest that patients older than 65 years and with those of advanced radiographic stage arthritis were less likely to benefit from intra articular injection of HA [10,50]. However there are other studies which suggest the contrary in favour of older population with more severe knee disease as these patients may be more sensitive in detecting an analgesic effect [49,51]. From our study, we are unable to provide any additional information as the number of patients with severe disease (KL Grade IV) is low. This probably reflects the fact that those patients with advanced disease might have opted for an initial surgical solution, thus creating a selection bias in our study.

Although our study was powered only for the primary outcome variable, significant differences were also observed in the secondary outcome measures even if some of these tools are not specific to assess outcome of OA of the knee. There exists a significant difference in the magnitude of efficacy between these two classes of agents in favour of the higher molecular weight agent. Hylan G-F 20 has rheologic properties that are qualitatively similar to normal synovial fluid and show a slower export rate out of the joint [52]. The suggestion that the mechanical and viscoelastic properties of the HA products contribute to the therapeutic effects seems logical. However, the half-life of these products is in the measure of hours. The persistence of these benefits for much longer may be also due to biological properties than physical properties alone [52,53].

EQ-5D is a generic health related quality of life assessment tool. The scores probably do not reflect the treatment response alone, but the general health of the patient. In our study the valuation subscale scores improved following treatment. But the magnitude of improvement did not correspond with the primary outcome variable. This is probably due to the associated co-morbidities and/or other joint involvement which influence EQ-5D scores. However, the therapeutic efficacy of HA treatment and the superiority of the Hylan G-F 20 group is sufficiently demonstrated by disease specific scores such as the WOMAC and Oxford knee scores. The gain in quality adjusted life years (QALY) between the two groups must be analysed extensively before any cost benefit assumptions can be made. This is beyond the scope of this study.

The incidence of local and treatment related adverse events varies from 1% to 8% of the patients in the literature [12,28,54,55]. This wide variation is attributed to the molecular weight of the HA products. The fact that cross-linked HA products are associated with increased adverse events has been well established in the literature. Significantly, this incidence is higher in patients who have had more than one course of Hylan G-F 20 [11,56]. This has previously been attributed to extra articular delivery of the HA product. The mechanism for an increased incidence with previous Hylan G-F 20 treatment is unclear. Antigenicity and an immunological response have been proposed as the likely reason in the literature [54,55,57,58]. Marino et al. [59] suggest that the flares which occur after Hylan G-F 20 treatment may be Type 4 (cell mediated) hypersensitivity reactions and not Type I (antibody mediated) reactions. In our series the incidence of adverse events was higher in the Hylan G-F 20 group (4% more). There was only one major adverse event (0.5%) in this group compared to none in the Sodium Hyaluronate group. The earlier and long lasting pain relieving effect in the Hylan G-F 20 group is reached at a price of minimal increase in rate of adverse effects. There were no other withdrawals from the study due to adverse events.

Analgesia requirement was monitored in our study with advice to avoid NSAID for 6 months from commencement of treatment. There were violators in both groups due to heterogeneity of the therapeutic effect from the treatment. However, the numbers of protocol violators were higher in the
Sodium Hyaluronate group particularly at 6 months which probably reflects the shorter therapeutic relief obtained. The consumption of analgesics and NSAID was less in the Hylan G-F 20 group at all assessment periods. There are other reports of patients discontinuing analgesics and NSAID during and at 1 year after treatment with Hylan G-F 20 [29,47,51].

In this trial we compare two HA preparations from either end of the spectrum representing high/low molecular weight and cross-linked/non cross-linked products. We acknowledge the fact that the number of injections (3 vs. 5) in each of the groups is a source of a treatment bias. However, to achieve the maximal effect, we were obliged to follow the manufacturer’s recommendations. Furthermore, we did not include two saline injections in the Hylan G-F 20 group due to its unknown effect on the final outcome. As a result, the patients were not blinded to the treatment. We ensured that the assessors were totally blinded for the treatment regime. Our study population consisted of patients who opted for viscosupplementation therapy. By this methodology, we did not alter the preferred management strategy of treatment of OA of the knee of individual clinicians although this introduces a potential selection bias. We believe this to be a representation of current practice in the United Kingdom. The effectiveness of viscosupplementation treatment could not be proved in this trial due to the lack of a third placebo control group. However other studies such as the Cochrane review have established the beneficial effect of viscosupplementation [17]. Health economic analysis calculating the costs of each treatment including the adverse events must be performed before any definitive assumptions can be made regarding the true cost effectiveness of these treatment regimes. This is of particular relevance before any recommendations can be made to the economically conscious NHS.

Viscosupplementation is a valuable tool in the armamentarium of orthopaedic surgeons and rheumatologists who provide secondary care for patients with symptomatic OA. Although both treatments offered significant pain reduction, it was earlier and sustained for a longer period in patients with Hylan G-F 20 as seen in other studies. Both treatments were well tolerated, however, a local reaction of pseudo-sepsis was observed with Hylan G-F 20 in one patient. One patient with a serious adverse event in the Hylan G-F 20 group was also included in the final outcome analysis. Few recent publications have reported similar reactions particularly in patients with repeat injections. The shorter treatment regime of Hylan G-F 20 reduces the overall operational cost, both for the patient and the hospital. From this study, it appears that the clinical effectiveness and general patient satisfaction are better amongst patients who received Hylan G-F 20.

Acknowledgement

We thank Dr A Taylor PhD, University of Leeds for his support in the statistical analysis.

No Financial support received.

References


