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ORIGINAL RESEARCH

Comparison of avian and nonavian hyaluronic acid in osteoarthritis of the knee

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Background: Hyaluronic acid (HA) in knee osteoarthritis (OA) has been shown to be efficacious and safe, but long-term follow up and head-to-head comparison of products, in particular those of avian versus those of nonavian origin, are lacking.

Objective: The objective was to compare the efficacy and safety of avian and nonavian origin HA in the treatment of knee OA during a long-term follow-up.

Methods: Patients were enrolled on a consecutive basis from all referrals received from 1997 to 2007 at a large primary care referral center in London, Canada. Patients were allocated to commercially available avian and nonavian origin HA based on their own preference for product. Patients were not randomized to therapy nor did the referral center advocate one product versus another. During the period of investigation, three nonavian and two avian products were available in Canada. Injections were given once weekly over three weeks (one series) using a lateral approach. Assessments included body mass index, numbers of medications, number of chronic diseases, duration of knee OA at presentation, visual analog scale (VAS) score (0–10 cm) for rest and weight-bearing pain, patient satisfaction with treatment (5-point categorical scale), numbers of HA series to the point of analysis, previous intra-articular treatment prior to first injection series, adverse events, serious adverse events, and self-payment versus third party payment. Following the first injection series, patients returned to the clinic of their own volition. Inclusion for a second and subsequent injection series was based on a patient request but also requirement of a resting VAS score > 4.5 cm. All patients had radiographic evidence of at least grade 1 OA. Patients who crossed over to alternate avian or nonavian product were not included in the analysis following crossover. Patients could switch within class of HA product. Differences were compared using analyses of variance and were considered significant at $P < 0.05$.

Results: Four thousand four hundred twelve patients were evaluated for inclusion. Avian or nonavian HA were received by 1,726 versus 1,971 patients, respectively. There were no significant differences in demographic characteristics between groups. There were no differences in reduction of resting pain between groups between the first and 10th consecutive series of HA injections; however, there was a significantly greater improvement in weight-bearing pain ($P < 0.01$) favoring nonavian HA after the 7th series. There was also a significantly greater number of adverse events (4.8% versus 1.7%; $P < 0.01$) in the avian- compared to nonavian-treated patients.

Conclusions: Both avian and nonavian HA improve pain in patients with osteoarthritis of the knee. Some difference in weight-bearing pain favoring nonavian HA was seen later in the treatment cycle while a significantly greater number of adverse events was observed in avian HA-treated patients.

Keywords: hyaluronic acid, osteoarthritis of the knee, avian and nonavian

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Introduction

Osteoarthritis (OA) is characterized by loss of articular cartilage and a decrease in the rheologic properties of synovial fluid, which include a reduction in molecular weight and concentration of hyaluronic acid (HA) causing decreased elasticity and viscosity of synovial HA matrix.[1,2]

The HA matrix acts as a fluid shock absorber, protecting cells and the intracellular collagen network from mechanical trauma. In addition to their rheologic and mechanical functions, HA solutions inhibit the formation and release of prostaglandin and aggregation of macrophage and adhesion of granulocytes to surfaces.[1]

Viscosupplementation is the process whereby an injection of exogenous HA into synovial joints, in order to restore the normal rheologic environment in osteoarthritic joints. Injected HA is cleared from the joint in less than one day, but the benefits of single treatment cycle can last several months[3,4] and can increase the viscosity and decrease the clearance time from the joint. HA has been modified to form hyalines, which are chemically cross-linked molecules with an average molecular weight as high as 23×10^6 daltons and intra-articular half-lives of between 1.5 to 9 days.[5] Viscosupplementation has been proposed to increase the benefit to the patient in terms of pain and function but also can increase the risk of adverse events. Higher viscosity and longer intraarticular half-lives may increase long-term efficacy in terms of duration and intensity of pain relief,[6,7] however, higher adverse event rates have been reported.[8] Further, meta-analyses have found more pronounced pain reduction in controlled trials of hyalines than in trials with HA.[9,10] Conversely, case reports have suggested that injection of hyalines may lead adverse events including increased symptomatic flares of pain and swelling within 48 hours of injection.[11–13] The SVISCOT-1[14] (first Swiss viscosupplementation trial) was a multicenter, patient blinded, randomized controlled trial designed to determine comparative efficacy and safety of preparations in patients with knee OA. Three preparations of HA were compared, including high molecular weight, cross-linked hyaline derived from rooster comb (Synvisc®; Genzyme, Cambridge, MA, USA), a noncross-linked medium range molecular weight HA derived from rooster comb (Avian HA) (Orthovisc®; Anika Therapeutics, Woburn, MA, USA), or a noncross-linked low molecular weight HA obtained through bacterial fermentation (bacterial HA) (Ostenil®; TRB CHEMEDICA, Geneva, Switzerland). In this study, a single cycle of intraarticular injections separated by one week were delivered in a randomized fashion. No differences in outcomes were observed among any of the three treatments. There was however a trend towards more local adverse events in the hyaline group compared to the other HA groups and this became more pronounced with a second injection cycle. Hence, the intention of the current study was to compare avian and nonavian HA treatments of varying molecular weight over a long-term follow up.

Methods

Patients with knee OA, according to the American College of Rheumatology criteria,[15,16] with Kellgren–Lawrence grades 1–3 radiographic evidence of knee OA, were administered avian or nonavian HA products as per their request in a large primary care referral center. Exclusion criteria for treatment included significant renal or hepatic comorbidity, treatment with anticoagulants or immunosuppressants and intraarticular injection with HA and steroids within the past 12 months.

Informed consent was obtained and the study was approved by the University of Western Ontario Ethics Review Board. In patients with bilateral knee disease, the more painful knee was treated. Both avian and nonavian HA products were delivered at 2 mL one week apart over three consecutive weeks. Products utilized included avian (ie, Synvisc), and nonavian (ie, Suplasyn®). Cycles of treatment were separated by at least 26 weeks (and were recorded up to 10 series) at which time patients could return for elective reassessment for injection but had to satisfy the criteria of a resting visual analog scale (VAS) score > 4.5 cm.

Injections were performed by three experienced physicians using anterolateral approach along the patella tendon with the knee flexed at 90°. Both patient and physician were aware of the treatment assigned. No attempts at concealment were utilized. Patients were encouraged to use other forms of analgesia if needed for the acute phase of injection (within 24 hours following the injection), which could include acetaminophen up to 4 mg per day. No analgesics were permitted for the 48 hours prior to the study visit. Pre-injection assessments included VAS at rest and with weight-bearing pain (0–10 cm), numbers of medications taken, number of chronic diseases, body mass index (BMI), duration of OA prior to initial presentation, patient satisfaction with treatment using a 5-point categorical scale (1 = no satisfaction, 5 = extremely satisfied), numbers of series to the point of analysis (10 years or at cross-over to another class, or failure to return), previous intraarticular injection with HA prior to their first injection series at the referral center, adverse events (ie, pain or erythema reported to the

study physician) and whether patients had self-payment or third party payment. The primary outcome measure was the resting VAS for pain.

Statistical analysis included percent change in VAS pain score both at rest and with weight bearing compared to baseline between those who had avian versus nonavian HA therapy. One-way analyses of variance were used to compare the two groups. Significance was accepted at $P < 0.05$. An *a priori* sample size estimate was calculated based on a resting VAS pain difference between groups of 3.0 cm. A 3 cm difference in VAS score corresponds to a difference in effect size of about four standard deviations between avian and nonavian HA that was obtained using data derived for meta-analysis by Low and colleagues.[12] We estimated that a sample size of 200 patients per treatment arm would provide >90% power to detect differences ($P < 0.05$). Analyses were conducted using an intent-to-treat approach where all patients in both groups were included in the analysis in which they were allocated to treatment. Analyses were conducted using Sigma Stat™ (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Between June of 1997 and June 2007, a total of 4,412 patients were evaluated for inclusion. Patients (avian versus nonavian) were aged 64 ± 7 versus 65 ± 6 years, were 57% female overall, had a BMI of 31 ± 2 and 30 ± 2 in both groups, and had similar marital, educational, and employment status. Overall, patients had 3 ± 2 chronic diseases and took 3 ± 1 oral or topical OA medications at the time of first series. No significant changes in BMI, number of chronic diseases and numbers of oral or topical OA medications were observed over 10 consecutive series. Overall, patients, had OA symptoms for 8 ± 4 years prior to first injection series. Grade of OA at entry was 1 ± 2. There were no differences in baseline demographic characteristics, the grade of OA, VAS score for rest or weight-bearing pain between both avian or nonavian HA source groups (Table 1). A total of 1,726 versus 1,971 patients received avian versus nonavian HA injections over 10 consecutive series. No difference in the reduction in resting and weight-bearing VAS pain was observed between the avian and nonavian groups after the first series (Table 2). Specifically, pain reduction of 4.8 cm versus 5.1 cm ± 2.0 cm was observed from first to second series and that was for resting VAS pain for avian versus nonavian, respectively. VAS resting pain after the 10th consecutive series revealed no significant difference in VAS change from first injection series compared to baseline. However, weight-bearing VAS pain decreased in both groups at 8.8 ± 1.8 cm versus 7.2 ± 2.6 cm, to 6.1 ± 1.4 cm versus 6.1 ± 1.9 cm for the avian versus nonavian groups, respectively ($P < 0.01$). Interestingly, this significant difference emerged after the 7th series (−7.8 ± 1.1 cm vs −6.2 ± 1.4 cm) (Table 2). Patient global satisfaction was similar in both groups between the 1st and baseline injection series with no significant difference between the 10th and 1st injection series change. There was no significant difference in the time returned for HA treatment (6 ± 3.1 versus 6 ± 3.0 months) for avian versus nonavian groups, respectively. There was no significant difference in time between return for the 2nd series and the 10th series in either group. There were an increased

Table 1 Patient demographic and clinical characteristics at baseline

Characteristics	Avian (n = 1726)	Nonavian (n = 1971)	*P*-value*
Age (years, mean ± SD)	64.22 ± 7.43	65.76 ± 6.68	
Men	65.31 ± 7.54	66.50 ± 7.00	0.314
Women	63.42 ± 7.29	65.19 ± 6.40	
Sex			
Male	81 (42.0%)	73 (43.7%)	0.750
Female	112 (58.0%)	94 (56.3%)	
Marital status			
Single	6 (3.1%)	5 (3.0%)	0.945
Married	147 (76.2%)	129 (77.2%)	
Divorced	15 (7.8%)	10 (6.0%)	
Widowed	23 (11.9%)	22 (13.2%)	
Education			
Elementary	8 (4.1%)	30 (18.0%)	0.400
Secondary	90 (46.6%)	76 (45.5%)	
College	35 (18.1%)	27 (16.2%)	
University	38 (19.7%)	21 (12.6%)	
Postgraduate	22 (11.4%)	13 (7.8%)	
Employment status			
Full-time	52 (26.9%)	34 (20.4%)	0.062
Part-time	26 (13.5%)	14 (8.4%)	
Retired	108 (56.0%)	106 (63.5%)	
Unemployed	7 (3.6%)	13 (7.8%)	
BMI ($kg \cdot m^{-2}$)	30.62 ± 2.01	29.87 ± 2.60	0.414
Grade OA (%)			
1	45	42	0.550
2	38	35	
3	9	10	
4	11	13	

Abbreviations: BMI, body mass index; OA, osteoarthritis; SD, standard deviation.

Table 2 Percent improvement in resting VAS pain with first and 10th HA series

	First series		10th series	
	Avian	**Nonavian**	**Avian**	**Nonavian**
Resting pain (reduction from baseline)	–4.8 ± 2.0	–5.1 ± 2.0	–5.2 ± 2.2	–5.5 ± 2.1
Weight-bearing (reduction from baseline)	–6.1 ± 1.4	–6.1 ± 1.9	–7.2 ± 2.6	–8.8 ± 1.8*

VAS resting and weight-bearing pain scores (improvement from baseline).
Note: *$P < 0.01$.

number of concomitant therapies in the avian versus nonavian groups (4 ± 2 versus 1 ± 2) between the 3rd and 10th series ($P < 0.05$). These included more use of analgesics and non-steroidal anti-inflammatory drugs.

There was a significantly greater number of adverse events at 4.8% versus 1.7% for the avian versus nonavian HA groups ($P < 0.01$) between the second and 10th series, respectively. Adverse events included (in descending order of prevalence): pain, effusion, erythema with over 80% of adverse events being pain. There were no serious adverse events.

Discussion

Our aim was to compare the long term effect of avian versus nonavian HA for knee OA clinically and in terms of patient satisfaction and adverse events. Previous meta-analyses have suggested no significant difference in efficacy among cross-linked and noncross-linked products, but with more adverse events among cross-linked products.[14,17] Previous studies have been primarily industry-sponsored, which could have influenced the results. The SVISCOT-1 trial[14] was an industry-independent viscosupplementation trial. The results of this study suggested that there was no rational for use of cross-linked product versus noncross-linked in OA of the knee. Similarly, we did not observe any significant difference between avian and nonavian products in our primary pain outcome. However, there was a significant difference in weight-bearing VAS pain after the 7th injection series, which favored the nonavian product. We also observed significant difference in the number of adverse events with the avian versus nonavian product similar to previous studies. This was primarily related to pain which has been described in some studies to be more prevalent in avian-based products.[5] Between the 7th to 10th treatment cycles, we found a significantly higher number of local adverse events for those who received avian product. Interestingly, most patients continued with their current treatment cycle product with very few discontinuing or switching to an alternate HA product. The increased local reaction risk was also noted in previous trials[13,18,19] and meta-analysis.[5] The occurrence of statistically significant differences in adverse events between avian and nonavian after the 7th cycle may suggest perhaps the repeated exposure to avian source may play a role in the development of local adverse events. This is in agreement with the findings of Juni and colleagues.[14] As there was no difference in exposure avian or nonavian product prior to the 1st injection series at the referral center, it appears that accumulated effects would have been the result of the treatments administered during the current study. There were no serious adverse events recorded in either treatment group over ten cycles suggesting that regardless of treatment effect, HA of both avian and nonavian source is not only effective but is also safe. As the study did not compare to placebo, we are unable to draw any conclusions regarding the advantage of viscosupplementation over placebo. However, recent meta-analysis[5] and a Cochrane review[13] have identified the efficacy of HA in improving clinical outcomes in OA of the knee. We also did not blind patients or clinicians to treatment allocation, which could have affected the results. However, patients were free to choose treatments without bias from either avian or nonavian HA origin and, hence, given the large numbers of subjects exposed to both treatment groups, concealment bias should not have been an issue.

Several HA-based products are available for the treatment of OA of the knee. The preparations differ significantly in their molecular weight, concentration, rheologic properties, manufacturing processes and residence times in the joint. Studies comparing the efficacy and therapeutic benefit of either cross-linked or noncross-linked lower or higher molecular weight products have not shown any significant difference[14,17,20] although there has been some evidence of higher adverse event rate in those of cross-linked origin.[21] The current study of nonavian-based products showed small difference in efficacy after 10 consecutive series of HA but fewer adverse events, which suggests that these considerations should be made available to clinicians when considering appropriate therapy for their patients. Our study population consisted of patients who opted for viscosupplementation therapy. As we did not infer any particular

treatment choice among patients, the implications of our findings to real-world practice are likely. While it appears the clinical effectiveness of both sources of HA product is similar in the long term with some favoring of nonavian for weight-bearing pain, there appears to be an advantage for using nonavian HA for local adverse events.

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Disclosures

The authors report no conflicts of interest.

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