

# A Comparison of Intra-Articular Hyaluronic Acid Competitors in the Treatment of Mild to Moderate Knee Osteoarthritis

AF McGrath<sup>1\*\*</sup>, AM McGrath<sup>1#</sup>, ZM Jessop MA<sup>2#</sup>, Surya Gandham<sup>3#</sup>, G Datta<sup>1</sup>, Sebastian Dawson-Bowling<sup>1</sup> and SR Cannon<sup>1</sup>

<sup>1</sup>Royal National Orthopaedic Hospital Stanmore, UK

<sup>2</sup>London Deanery, London, UK

<sup>3</sup>Royal Free Hospital, London, UK

\*These authors contributed equally and share combined first authorship

## Abstract

**Purpose:** Viscosupplementation with Hyaluronic Acid (HA) is an established intervention for pain control in patients with mild to moderate Osteoarthritis (OA) of the hip and knee. Problems include inconvenience, expense and the logistical problems associated with multiple injections, injection technique and level of skill required by the administering physician, variable clinical response and adverse reactions.

**Methods:** In this independent, prospective, randomized trial, we compare efficacy and complications associated with treatment in 182 knees using durolane<sup>TM</sup> and synvisc<sup>TM</sup> using the Visual Analogue Score, SF-36 V2 questionnaire, and Oxford knee scores. Range of movement is recorded at each visit. These assessments are repeated at 3, 6, 9 and 12 months.

**Results:** Significant improvement is seen in the VAS, SF 36 V2 and Oxford Knee Scores ( $p=0.01$ ) and reduction in the use of analgesics and anti-inflammatories is seen with both products at 3 months post injection, with a significant advantage to the durolane group ( $p=0.001$ ). At 6 months, this difference is extended even further. Adverse reactions occur significantly less with the more effective product.

**Conclusion:** We conclude that intra-articular HA a useful intervention in patients with mild to moderate OA of the knee, can produce sustained pain relief at 6 months, and can reduce the requirement for analgesia and anti-inflammatory medication during this time.

**Keywords:** Viscosupplementation; Intra-articular hyaluronic acid; Mild/Moderate osteoarthritis; Knee

## Introduction

The increase in the occurrence of osteoarthritis is in part a consequence of the ageing population, and now affects up to 6% of the population, accounting for up to 20% of consultations at primary care level and is a leading cause of disability at work [1]. An estimated 550,000 patients have moderate to severe knee osteoarthritis in the UK and in excess of 35,000 knee replacements were performed here last year. Obesity is a major risk factor, and the UK has the eighth highest obesity rate in the world.

Hyaluronic Acid (HA) is a long chain polysaccharide found in all mammals. It is present in loose connective tissue, skin, the eye and synovial fluid where it secreted continuously by the synovial membrane into the joint space and comprises the major macro-molecular part of the synovial fluid. It is highly concentrated at the surface of the articular cartilage and the superficial layers of the synovial membrane. In the synovial fluid, HA acts as both a lubricant and a shock absorber [2]. Due to the meshwork it forms with aqueous solutions, it acts as a semi-permeable barrier regulating metabolic exchanges between cartilage and the synovial fluid, and a viscoelastic shield around synoviocytes and adjacent nerve endings [3]. Through its molecular size HA hinders the free movement of lytic enzymes and inflammatory mediators, and enhances chondrocyte metabolism [4]. Osteoarthritis is associated with a decrease in concentration and average molecular weight of native HA in synovial fluid [5].

Synvisc (hylan G-F 20, Genzyme Biosurgery) is a highly cross linked, high molecular weight (6000 kDaltons) avian sourced hyaluronan. Available from 1997, prefilled syringes of 2 mls (18 mg)

HA were administered weekly for 3 weeks by intra-articular injection. A common complaint levied by clinicians and patients regarding synvisc is that treatment may require up to 3 weekly injections, requiring more organisation, resources and cost, while increasing the risk of local adverse reactions, including septic arthritis. This is in part due to the relatively faster catabolism of unmodified hyaluronan following administration.

Synvisc One, available from 2007, is a 6 mls (48 mgs) single injection for the knee, and may negate this disadvantage. Indications include mild to moderate arthritis of the knee, hip, shoulder and ankle. Reported incidence of adverse reactions is low, and no systemic reactions have been attributed to hyaluronic acid [6].

Durolane (Smith and Nephew) is a Non Animal Stabilised Hyaluronic Acid (NASHA) licensed for treatment of mild to moderate OA of the hip and knee. It is administered as a prefilled syringe containing 3 mls (60 mg) of hyaluronic acid, and has a 28 days half life. This is achieved by cross linking of molecules. The manufacturer

**\*Corresponding author:** Dr. AF McGrath, MRCSI, Bone Tumour Unit, Royal National Orthopaedic Hospital, Stanmore, United Kingdom, Tel: ++44 790 4976790; Fax: ++44 020 8909 5273; E-mail: [anthonymcgrath@nhs.net](mailto:anthonymcgrath@nhs.net)

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reports that by achieving 'mild' cross linking, of levels between 0.5 and 1.0%, maintains biocompatibility while prolonging residence time in the joint.

As it is of non animal origin there are no animal related allergic reactions or disease transmission. Product information claims a single injection can be effective for up to 6 months [7].

## Materials and Methods

We recruited 213 patients (115 female, 98 male) with mild to moderate (Kellgren grade II and III) knee OA [8,9]. Patients with other symptomatic joints were excluded. 31 patients were lost to full follow up, leaving 103 females and 79 males. Median age of patients was 58 years (range 34-82). Bilateral injections are administered in 32 patients, and the worst knee included in the study. Weight bearing anteroposterior, lateral, and tangential views are assessed for inclusion. Baseline scores and range of movement are recorded. Patients were randomized to each group. Ethics approval was not required as both treatments are already accepted for use in the United Kingdom.

Use of oral medication (anti-inflammatory and analgesia) prior to injection, and reduction following injection was noted. Anti-inflammatories included diclofenac and ibuprofen almost exclusively. Analgesics included paracetamol, often with an opiate used in addition to this, usually codeine. We considered this important, as side effects related to these products are considerable. Regular NSAID use is related to a rate of serious gastrointestinal bleeding in 7% of patients.

Clinical review was repeated at 3, 6, 9 and 12 months following injection.

## Results

31 patients lost to follow up. Outcome was measured using the VAS, Oxford Knee Score, the PCS and MCS components of the SF 36 version 2.

## Adverse Events

9 patients suffered an adverse event.

## Statistical Analysis

Preliminary data was collected from 30 patients randomised to receive Durolane or Synvisc. Differences in the primary outcome (VAS pain scores) at 3 months were used for a power calculation to determine study size. Setting  $\alpha$  at 0.05 and power at 80% we the required sample size was 125 patients. The final sample size was 168 patients. Analysis was performed with SPSS 14.0 (SPSS Inc, Chicago, Illinois 60606). After testing all scale variables for normality with Kolmogorov-Smirnov test inter-group differences were examined with the Mann-Whitney U test or unpaired student's t-test and paired data was tested using the Wilcoxon signed ranks test or the paired t-test. Normal data was presented as mean (SD) and non-normal data as median (range). Fisher's exact test was used for nominal comparisons. A value of  $p < 0.05$  was considered significant throughout.

## Outcome Measures

### Pain (Visual Analogue Score, VAS)

Baseline knee pain scores were not different between the two groups ( $p=0.697$ , Table 1). There was a significant reduction in knee pain in both treatment groups at three months post-injection. The reduction was also significant at 6 months in the Durolane group, when there was no difference in the Synvisc group ( $p=0.000$  and  $0.783$  respectively). Knee pain scores were significantly lower in the Durolane group compared with the Synvisc group at all time-points, although at nine and twelve months post-treatment scores were significantly higher than at baseline for both groups.

### Medication (change in analgesia and non-steroidals)

**Analgesia:** There was a significant reduction in the use of analgesia for up to 6 months in the Synvisc group and up to 9 months in the Durolane group (Table 2).

**NSAID:** There was reduction in NSAID used up to 12 months post treatment in both groups 1 and 2 compared to baseline pre-injection values (Wilcoxon paired test). NSAID use was lower in the Durolane group at 3 and 6 months than in the Synvisc-3 group (Table 3).

VAS pain score	Baseline (pre-injection)		3 months		6 months		9 months		12 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Synvisc	44.940	6.350	25.350	5.810	44.840	6.500	50.840	6.040	56.860	6.080
Comparison to baseline (p=)			0.008		0.783		0.001		0.001	
Durolane	45.330	6.700	19.410	6.150	26.250	7.150	53.900	5.620	53.250	5.470
Comparison to baseline (p=)			0.000		0.000		0.000		0.000	
Intergroup difference (p =)	0.697		0.000		0.000		0.000		0.000	

Intergroup difference:  $p$ =ANCOVA with adjustment for baseline (pre-injection VAS pain scores)

Table 1: Mean VAS pain scores.

% Reduction in analgesia use	Baseline value		3 months		6 months		9 months		12 months	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Synvisc	100	100	70.6	75 (50-100)	14.1	0 (0-75)	1.3	0 (0-25)	0.6	0 (0-25)
Comparison to Baseline (p=)			0.000		0.000		0.046		0.157	
Durolane	100	100	82.4	75 (50-100)	35.2	50 (0-50)	9.1	0 (0-25)	1.1	0 (0-25)
Comparison to Baseline (p=)			0.000		0.000		0.000		0.046	
Intergroup difference (p =)			0.0001		0.0001		0.0001		0.477	
Change=(pre-injection level-level at that time-point)										
Inter-group difference: $p$ =Mann-Whitney U test comparing distribution										
Comparison to baseline : $p$ =Wilcoxon test										

Table 2: Change in analgesic use in Synvisc and Durolane patients up to 1 year post-treatment.

NSAID use (% of baseline)	Baseline				3 months				6 months				9 months				12 months			
	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range
Synvisc	88	33	100	0-100	26	23	33	0-66	77	33	100	0-100	85.4	33.5	100	0-100	84	32.3	100	0-100
Comparison to Baseline (p=)					0.000				0.000				0.025				0.020			
Durolane	89	32	100	0-100	14	21	0	0-66	69	29	66	0-100	86.3	33.3	100	0-100	83	34	100	0-100
Comparison to Baseline (p=)					0.000				0.000				0.140				0.002			
p	0.821				0.001				0.007				0.906				0.836			
Inter-group difference: p=Mann Whitney test comparing distribution																				
Comparison to baseline : p=Wilcoxon test																				

Table 3: Change in the use of non-steroidal medication.

	Baseline		3 months		6 months		9 months		12 months	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
Synvisc	125.00 (10.64)	125 (95-135)	128.69 (3.89)	130 (110-135)	126.00 (6.38)	125 (110-135)	124.06 (7.47)	125 (100-135)	124.31 (6.45)	125 (100-135)
Comparison to baseline (p=)			0		0.435		0.293		0.184	
Durolane	125.40 (9.74)	125 (95-135)	132.27 (4.22)	135 (120-135)	129.38 (5.24)	130 (110-135)	126.02 (6.35)	130 (110-135)	126.25 (6.53)	127.5 (110-135)
Comparison to baseline (p=)			0		0		0.385		0.295	
intergroup difference (p =)	0.961		0.0001		0.0001		0.042		0.15	
inter-group difference: p=Mann whitney test comparing distribution										
Comparison to baseline: p=Wilcoxon test										

Table 4: Flexion in degrees.

	Baseline		3 months		6 months		9 months		12 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Synvisc	24.26	1.861	36.69	3.8	25.76	2.25	23.69	1.4	23	1.11
Comparison to Baseline (p=,CI)			0 neg 13.36-11.484		0 neg 0.2104--0.896		0.006 0.173 (-0.977)		0 0.907 (-1.618)	
Durolane	23.69	1.68	40.15	3.56	32.6	4.51	27.38	2.92	22.74	0.94
Comparison to Baseline (p=,CI)			0 neg (17.295)-15.614		0 neg (9.936)-7.882		0 neg (4.410)-2.954		0 0.64 (1.269)	
Intergroup difference (p=)	0.04		0.0001		0.0001		0.0001		0.492	
Intergroup difference: p=ANCOVA with adjustment for baseline level										
Comparison to baseline: p=t-test										

Table 5: Mean Oxford knee scores.

### Function (change in flexion and extension)

**Flexion:** Flexion increased at three months from 125 (95-135) to 130 (110-135) in the Synvisc group and from 125 (95-135) to 135 (120-135) in the Durolane group, and was still increased at 6 months in the Durolane group but not in the Synvisc group (p=0.0001, Table 4). Change in flexion was greater in the Durolane group than in the Synvisc group at all time-points except 12 months.

**Extension:** There was no difference in knee extension at any time.

### Oxford Knee score

Oxford knee scores were significantly better in up to 6 months in the Synvisc group, and up to 9 months in the Durolane group. Oxford scores were significantly higher in the durolane group compared to the Synvisc scores at 3, 6 and 9 months (Table 5).

### Short Form 36 version 2 (SF-36 V2)

**Mental Component Score (MCS):** (Table 6)

**Physical Component Score (PCS):** PCS was higher in both groups

up to 12 months post-injection (Table 7). PCS was significantly higher at 6 months in the Durolane group compared to the Synvisc group (35.14 vs. 42.1, p=0.000). There was no difference at 9 months. The Synvisc group scored higher than Durolane group at 12 months.

### Discussion

From its origins in the 1970s in the treatment of equine arthritis, positive results from numerous clinical trials in humans have led to its inclusion in many major published guidelines for treatment of OA [10-14]. The mechanism of action of administered intra-articular HA is not completely understood, but as its clinical benefit exceeds its intra-articular presence, it is thought to perhaps induce native biosynthesis of HA and other extracellular matrix components and in particular suppress the inflammatory response and inhibit substance P, in addition to contributing to shock absorption by means of its viscoelastic properties. In a paper by Ianitti et al. [15], HA was seen to actually reduce degenerative changes in a rabbit model, while in another paper he also compares 2 HA products [16], as we have done. Interestingly the well established synvisc in a study by Strand et al. [17] also performs

	Baseline		3 months		6 months		9 months		12 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<b>Synvisc</b>	52.64	3.84	55.86	2.17	52.75	3.27	52.09	3.1	52.25	3.09
<b>Comparison to Baseline (p=,CI)</b>			0	(-3.77) (-2.6794)	0.696	(-0.6984) (0.4684)	0.124	neg (4.410)-2.954	0.318	0.64 (1.269)
<b>Durolane</b>	52.21	4.67	55.12	2.28	52.75	3.51	52.5	3.35	53.22	3.03
<b>Comparison to Baseline (p=,CI)</b>			0	(-3.5753) (-2.2452)	0.068	(-1.1275) (0.0412)	0.394	(-0.9619) (0.3824)	0.018	(-1.8330) (-0.1784)
<b>Intergroup difference (p=)</b>	0.04		0.0001		0.424		0.089		0.005	
Intergroup difference: p=ANCOVA with adjustment for baseline level										
Comparison to baseline: p=t-test										

**Table 6:** Mental Component Score (MCS)

MCS scores were higher at three months than at baseline in both groups (52.64 vs. 55.86 and 52.21 vs. 55.12, p=0.000). There were no differences after three months in either group. MCS scores were higher in the Durolane group than the Synvisc group at three months and twelve months.

PCS	Baseline		3 months		6 months		9 months		12 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<b>Synvisc</b>	33.250	4.050	48.520	6.030	35.140	3.740	35.350	2.930	35.930	2.860
<b>Comparison to Baseline (p=,CI)</b>			0.00	(-16.6101) (-13.9199)	0.00	(-2.5682) (-1.2018)	0.00	(-3.1099) (-1.4591)	0.00	(-3.6067) (-1.7533)
<b>Durolane</b>	33.210	4.620	48.680	4.920	42.100	4.600	36.870	4.910	34.130	3.920
<b>Comparison to Baseline (p=,CI)</b>			0.00	(-16.6765) (-14.2735)	0.00	(-10.0176) (-7.7688)	0.00	(-4.6809) (-2.6509)	0	(-1.2541) (-0.4823)
<b>Inter-group differencep</b>	0.950		0.820		0.000		0.150		0.000	
Inter-group comparison: p=ANCOVA with adjustment for baseline level except for baseline comparison (t-test)										
Comparison to baseline: p=t-test (paired)										

**Table 7:** PCS.

less favorably as it does in our comparison with a different agent.

As a non systemic treatment, intra-articular hyaluronic acid preparations have the benefit of avoiding many of the side effect associated with traditional oral medication, for example serious gastrointestinal bleeding which can occur in up to 7% of those using non steroidal anti-inflammatory medication [18]. They are reported as having a more prolonged effect than intra-articular corticosteroids, and avoid complications associated with these [19-22].

Derived from rooster coombs, synvisc is contra-indicated in patients with no allergy to avian proteins, feathers or egg products. Unmodified HA is broken down within 12-14 hours by a combination of enzymatic and mechanical degradation, and chemically by oxygen free radicals. Cross-linking with formaldehyde and divinyl sulfone prolongs intra-articular half life up to 60 hours, which is directly related to clinical benefit, but may itself cause an immunological tissue reaction, with some authors reporting an increase of pseudosepsis (severe acute inflammatory reaction).

Reactions most commonly include localised pain and joint effusion, which tends to resolve within 3-5 days. Cases of pseudogout and rash have been reported. It has not been possible to attribute local reactions to the product itself or possible contamination and inflammation caused by the injection per se. There is some evidence that the incidence of acute local reactions increases with successive injections, and that these may be related to product specific immunogenicity [23].

As Durolane is of non animal origin there are no animal related allergic reactions or disease transmission.

## Conclusion

We have demonstrated that intra-articular HA is an effective intervention in improving pain relief in patients with knee OA. Significant differences are noted in efficacy and adverse reactions

between 2 leading competitors. We recommend its use in patients in whom selection is appropriate, and that clinicians should be aware of the differences in manufacture of the various HA products available in addition to their relative efficacy and duration of action.

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