

## **Efficacy of Viscosupplementation in Knee Osteoarthritis: A Clinical Trial of Three Agents**

Abdullah Al-Omran, MBBS, SSC (Ortho.)\* Quamar Azam, MD, MBBS, M.S (Orth)\*\*

### **ABSTRACT**

**Background:** In 2008, Osteoarthritis Research Society International (OARSI) cited intra-articular (IA) injection of hyaluronic acid (HA) as a useful therapeutic modality, which relieves pain and functional score and delays progress of Osteoarthritis. Currently, there are more than five HA formulations in the market approved commonly used for intra-articular (IA) injection.

**Objective:** To compare the efficacy of the three commonly used injections in a cohort population.

**Design:** A Prospective Randomized Study.

**Setting:** King Fahd Hospital of the University, Al Khobar.

**Method:** Two hundred twenty-seven patients with grade 1, 2 and 3 OA were included in the study. Three different intra-articular injections of HA were used after double blinding: Osteonil (Sodium hyaluronate, TRB Chemedica UK ltd), Durolane (stabilized form of hyaluronic acid, Bioventus) and Synvisc (hylan GF-20, Sanofi Biosurgery). The data were analyzed using Stata SE/v.12. Analysis of variance followed by a post hoc t-test (LSD) was used for inferential statistical analysis.

**Result:** Group A had 78 patients, group B 74 patients and group C 75 patients. Analysis of variance showed that the efficacy of the treatment differed significantly ( $F= 53.34$ ,  $df_1= 2$ ,  $df_2= 207$ ,  $p\text{-Value}<0.001$ ). The result of the post-hoc tests showed Synvisc Injection was the most effective showing significant improvement than both Osteonil Injection (mean diff=7.68,  $p<0.001$ , CI=4.73, 10.64) and Durolane Injection (mean diff=15.61,  $p<0.001$ , CI=12.63, 18.59). Osteonil Injection was found to be superior to Durolane Injection (mean diff=7.93,  $p<0.001$ , CI=10.89725, 4.957825).

**Conclusion:** Viscosupplement (VS) agents provide significant though temporary symptomatic relief in grade 2 and 3 OA. The efficacy of all three agents was similar with marginal superiority of one over the other. Considering excellent tolerability, viscosupplementation may be included in the armamentarium of OA.

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\* Consultant  
Associate Professor  
Chairman  
Department of Orthopedic surgery

\*\*Assistant Professor  
University of Dammam

Kingdom of Saudi Arabia  
Email: Alomran\_a\_s@yahoo.com

## **INTRODUCTION**

Osteoarthritis (OA) of the knee is one of the most common causes of disability in older age<sup>1</sup>. Because of increasing longevity, significant change in lifestyle and improved diagnostic modalities, it is diagnosed in relatively younger age group. Conservative treatment in an attempt to improve pain and functional ability is an important option in this group. Further clinical research is in progress to halt the disease. Non-operative intervention includes lifestyle modification, physical therapy, bracing, wedged insoles, anti-inflammatory medications and intra-articular injection of corticosteroid and hyaluronic acid<sup>2,3</sup>.

In September 2000, the American College of Rheumatology recommended the use of intra-articular injection of hyaluronic acid as a treatment option<sup>3</sup>. Since then, VS gained momentum in both clinical practice and research. In 2008, Osteoarthritis Research Society International (OARSI) cited intra-articular injection of hyaluronic acid as a useful therapeutic modality, which relieves pain and functional score, and delays progress of OA<sup>2</sup>. VS was shown to be chondroprotective as well<sup>4</sup>.

Hyaluronic acid (HA) is a high molecular weight (in the range of 5 to  $7 \times 10^6$  Da) glycosaminoglycan synthesized in the joint by type B synoviocytes and fibroblast<sup>5</sup>. Inflammatory effusion, abnormal synoviocytes and molecular fragmentation causes decreased concentration of HA in arthritic joints<sup>6,7</sup>. As a result, collagen network and integrity of chondral surface of knee cartilage is compromised<sup>8,9</sup>.

Currently, there are more than five approved HA formulations in the market commonly used for intra-articular (IA) injection. These preparations principally differ with respect to molecular weight, half-life within synovium, rheologic properties, pharmacodynamics and cost.

The aim of this study is to evaluate the clinical efficacy of intra-articular HA and compares three commonly used injections in a cohort population.

## **METHOD**

Two hundred twenty-seven patients with grade 1, 2 and 3 OA were included in the study. Informed consent was obtained from all patients. Diagnosis of osteoarthritis (OA) was based on the presence of at least three of the six clinical criteria established by American College of Radiology: more than 50 years of age, morning stiffness less than 30 minutes, crepitus, bony tenderness, bony enlargement and no palpable mass. Grading of osteoarthritis was done using Lawrence radiological scoring. All patients were double-blinded. Three different intra-articular injections: Osteonil (Sodium hyaluronate, TRB Chemedica UK ltd), Durolane (stabilized form of hyaluronic acid, Bioventus) and Synvisc (hylan GF-20, Sanofi Biosurgery) were used. The dose regimen was followed according to manufacturer's guidelines. The patients were divided to three groups: group A received Osteonil injection, group B received Durolane injection and group C patients had Synvisc injection, see table 1.

Western Ontario McMaster Score (WOMAC) was done prior to intra-articular (IA) injection and in each follow up at one, three and six months. Under all aseptic precautions, intra-articular injection was given using supero-lateral approach.

Exclusion criteria included grade 4 OA, knee with significant varus and valgus deformity of more than 15 degrees, ligament laxity and inflammatory arthritis (rheumatoid arthritis). During the study, analgesia consumption was strictly monitored according to a set protocol. Paracetamol less than 2 gm was allowed for breakthrough pain. However, any patient who required more analgesia will be permitted to do so and will be considered as failure of IA injection. Other than active physiotherapy, other therapies were not being permitted. Patients were advised to report any adverse events by telephone or attend the clinic. All adverse events were recorded.

**Statistical Analysis:** The data were analyzed using Stata SE/v.12. Descriptive analyses were used to examine the variables and were represented as means and standard deviations.

## RESULT

The mean age was  $65.8 \pm 15.8$  (45-74 years). Seventeen patients were lost in the last follow up so the statistical analysis is based on the remaining 210 patients, see table 1. The improvement was variable in terms of both duration and severity of pain relief. There was significant improvement in WOMAC score in all three groups, see table 2. Summary statistics of the variables in the study include: means score before injections, mean score after injection, and mean score of the difference (which is considered the improvement). Figure 1 is a box plot showing the improvement in functional score of the three groups.

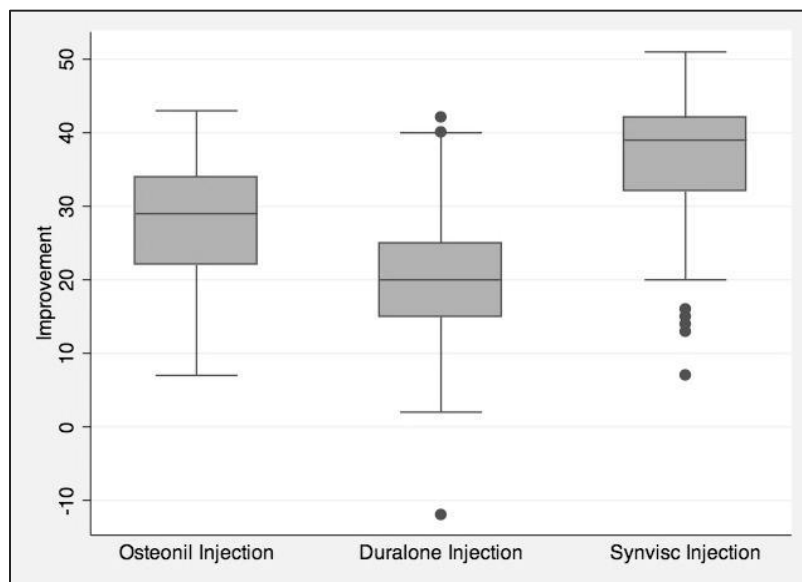
**Table 1: Randomized Allocation of Patients into Three Different Groups**

	Group A	Group B	Group C	Total
Number of Patients	78	74	75	227
Injection Received	Osteonil	Durolane	Synvisc	
Number of Patients Analyzed at the End of the Study	71	69	70	210

**Table 2: Summary Statistics of the Variables WOMAC Score**

		Group A N=71	Group B N=69	Group C N=70	
<b>Mean Before Injection</b>	Mean (SD) of Functional Score	75.9 (6.7)	73.1 (8.3)	82.4 (9.1)	<b>210 (17 lost for follow up)</b>
	Range of Functional Score	65 – 92	61 – 93	55 – 91	
<b>Mean After Injection</b>	Mean (SD) of Functional Score	48.0 (4.6)	53.1 (7.4)	46.8 (4.6)	
	Range of Functional Score	45 – 74	40 – 79	40 – 67	

<b>Mean</b>	Mean (SD) of 28 (7.7)	20.1 (9.6)	35.7 (9.4)
<b>Difference</b>	Range of 7 – 43	-12 – 42	7 – 51
	Functional Score		Functional Score



**Figure 1: Box Plot Showing the Improvement in Functional Score**

The treatments used in the study led to an improvement. The Analysis of Variance showed that the efficacy of the treatment differed significantly ( $F= 53.34$ ,  $df1= 2$ ,  $df2= 207$ ,  $p\text{-Value}<0.001$ ), see table 3. Reviewing the results of the post-hoc tests, see table 4, Synvisc Injection was the most effective showing higher improvement than both Osteonil Injection (mean diff=7.68,  $p<0.001$ ,  $CI=4.73, 10.64$ ) and Durolane Injection (mean diff=15.61,  $p<0.001$ ,  $CI=12.63, 18.59$ ). Osteonil Injection was superior to Durolane Injection (mean diff=7.93,  $p<0.001$ ,  $CI=10.89725, 4.957825$ ), see table 3.

**Table 3: ANOVA between Groups and within Groups**

	SS	Df	MS	F	Sig
<b>Between groups</b>	8470.89089	2	4235.44545	53.34	0.0000
<b>Within groups</b>	16435.7234	207	79.3996299		
<b>Total</b>	24906.6143	209	119.170403		

**Table 4: Pairwise Comparison between Groups**

Group	Std. Err.	t	P> t	[95% Conf. Interval]
<b>Durolane vs Osteonil</b>	1.506328	-5.26	0.000	-10.89725, -4.957825
<b>Synvisc vs Osteonil</b>	1.500861	5.12	0.000	4.72678, 10.64465
<b>Synvisc vs Durolane</b>	1.511622	10.33	0.000	12.6331, 18.5934

## DISCUSSION

Balazs et al pioneered the concept of VS in 1960s and believed that an ideal VS agent should meet four specific criteria: i) permeability to metabolites and macromolecules, ii) non-immunogenic, iii) similar molecular weight to native synovial fluid and iv) long half-life<sup>10</sup>. First clinical use of VS was done in 1980s and was approved for knee arthritis by Food and Drug Administration (FDA) in 1997. Hyaluronic acid exerts its effect by inhibition of migration, chemotaxis and phagocytosis of leukocytes<sup>11,12</sup>. Animal studies demonstrated both direct inhibitions of nociceptors and indirectly via decreasing the synthesis of bradykinin, substance P (a modulator of inflammation) etc. Ghosh et al further showed its chondroprotective effect by stimulating synoviocytes and fibroblasts to synthesize HA<sup>13-15</sup>. The present study found significant improvement in terms of pain relief, stiffness and functional activity in the three groups compared with baseline. The Analysis of Variance showed that the efficacy of the treatment differed significantly in the three groups. Synvisc injection was found most effective showing higher improvement than both Osteonil injection and Duralone injection. Osteonil injection was also demonstrated to be superior to Duralone injection. The result is comparable to previous study of Balazs et al<sup>10</sup>. The superiority of Synvisc noted in our study could be attributed to the higher molecular weight as was explained in the earlier literature<sup>10-11</sup>.

Two notable findings of our study were that the benefits were more pronounced and encouraging in grade 2 and 3 osteoarthritis and the improvement was most remarkable between 2 to 18 weeks; however, the analgesic effect continued up to six months. The requirement of NSAIDS significantly decreased in all patients. Authors recommend that VS should be included in the armamentarium of OA in early stage rather than waiting for degenerative changes. The efficacy result of the current study is comparable to Wang et al who evaluated 20 randomized controlled studies and found significant improvement in pain management and functional activity up to six months<sup>16</sup>. Furthermore, he noted that cross linked Hyalan has better efficacy. Other recent studies, Wobig et al, Scale et al, Waddell et al and Raman et al concluded that VS improves rest pain, improves weight bearing and decreases the need for pain medications<sup>17-20</sup>.

The strength of the study is randomized comparison of three different VS agents, a fixed protocol and a follow up after 12 months. However, the study sample is small; thus, further prospective studies are recommended. None of our patients had any serious adverse events; however, local reaction at the injection site consisting of pain, swelling, warmth or redness was noted in eleven (4.84%) patients. The rate of acute painful reaction is described to be 2%-8% in different studies<sup>15,17,19</sup>.

Our study however, contrasts with that of Karlsson et al and Kotevoglou et al who noted no significant difference between low or high molecular weight preparations<sup>21,22</sup>. The present study did not compare the efficacy of HA with intra-articular corticosteroids. Other studies compared the efficacy of intra-articular steroids with hyaluronic acid and concluded that both provide effective symptomatic relief<sup>23,24</sup>. VS has long duration of action while corticosteroids have rapid onset of action.

Our study contrasts with Chen et al who have done a prospective, randomized control study on 50 patients using transcutaneous electric nerve stimulation (TENS) and proved that TENS is

more effective than intra-articular HA injection for patients with knee osteoarthritis<sup>25</sup>. The American Academy of Orthopedic Surgeons no longer favor the use of HA for osteoarthritis based on evidence from 3 quality and 11 moderate quality research studies that met the inclusion criteria. Despite these recommendations, many studies including ours revealed that HA is valuable for osteoarthritic patients<sup>26</sup>.

## CONCLUSION

**VS agents provide significant though temporary symptomatic relief in grade 2 and 3 OA. Its use reduces the concomitant medication burden. The efficacy of all three agents was similar with marginal superiority of Synvisc over other two drugs. Considering its overall tolerability, VS may be included in the armamentarium of OA treatment.**

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**Competing Interest:** None.                      **Sponsorship:** None.

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## REFERENCES

1. Adams ME, Brandt KD. Hypertrophic Repair of Canine Articular Cartilage in Osteoarthritis after Anterior Cruciate Ligament Transection. *J Rheumatol* 1991; 18(3):428-35.
2. Allen E, Krohn K. Adverse Reaction to Hylan GF-20. *J Rheumatol* 2000; 27(6):1572.
3. Altman RD. Intra-Articular Sodium Hyaluronate in Osteoarthritis of the Knee. *Semin Arthritis Rheum* 2000; 30(2 Suppl 1):11-8.
4. Amiel D, Toyoguchi T, Kobayashi K, et al. Long-Term Effect of Sodium Hyaluronate (Hyalgan) on Osteoarthritis Progression in a Rabbit Model. *Osteoarthritis Cartilage* 2003; 11(9):636-43.
5. Bagga H, Burkhardt D, Sambrook P, et al. Longterm Effects of Intraarticular Hyaluronan on Synovial Fluid in Osteoarthritis of the Knee. *J Rheumatol* 2006; 33(5):946-50.
6. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the Treatment of Osteoarthritis of the Knee. *Cochrane Database Syst Rev* 2006; (2):CD005321.
7. Berg P, Olsson U. Intra-Articular Injection of Non-Animal Stabilised Hyaluronic Acid (NASHA) for Osteoarthritis of the Hip: A Pilot Study. *Clin Exp Rheumatol* 2004; 22(3):300-6.

8. Strauss EJ, Hart JA, Miller MD, et al. Hyaluronic Acid Viscosupplementation and Osteoarthritis: Current Uses and Future Directions. *Am J Sports Med* 2009; 37(8):1636-44.
9. Bernardeau C, Bucki B, Lioté F. Acute Arthritis after Intra-Articular Hyaluronate Injection: Onset of Effusions without Crystal. *Ann Rheum Dis* 2001; 60(5):518-20.
10. Balazs EA, Denlinger JL. Viscosupplementation: A New Concept in the Treatment of Osteoarthritis. *J Rheumatol Suppl* 1993; 39:3-9.
11. Brockmeier SF, Shaffer BS. Viscosupplementation Therapy for Osteoarthritis. *Sports Med Arthrosc* 2006; 14(3):155-62.
12. Forrester JV, Balazs EA. Inhibition of Phagocytosis by High Molecular Weight Hyaluronate. *Immunology* 1980; 40(3):435-46.
13. Tamoto K, Tada M, Shimada S, et al. Effects of High-Molecular-Weight Hyaluronates on the Functions of Guinea Pig Polymorphonuclear Leukocytes. *Semin Arthritis Rheum* 1993; 22(6 Suppl 1):4-8.
14. Tobetto K, Yasui T, Ando T, et al. Inhibitory Effects of Hyaluronan on [14C]Arachidonic Acid Release from Labeled Human Synovial Fibroblasts. *Jpn J Pharmacol* 1992; 60(2):79-84.
15. Ghosh P. The Role of Hyaluronic Acid (Hyaluronan) in Health and Disease: Interactions with Cells, Cartilage and Components of Synovial Fluid. *Clin Exp Rheumatol* 1994; 12(1):75-82.
16. Wang CT, Lin J, Chang CJ, et al. Therapeutic Effects of Hyaluronic Acid on Osteoarthritis of the Knee. A Meta-Analysis of Randomized Controlled Trials. *J Bone Joint Surg Am* 2004; 86-A (3):538-45.
17. Wobig M, Dickhut A, Maier R, et al. Viscosupplementation with Hylan G-F 20: A 26-Week Controlled Trial of Efficacy and Safety in the Osteoarthritic Knee. *Clin Ther* 1998; 20(3):410-23.
18. Scale D, Wobig M, Wolpert W. Viscosupplementation of Osteoarthritic Knees with Hylan: A Treatment Schedule Study. *Curr Ther Res* 1994; 55(12): 20-32.
19. Waddell DD, Bricker DC. Clinical Experience with the Effectiveness and Tolerability of Hylan G-F 20 in 1047 Patients with Osteoarthritis of the Knee. *J Knee Surg* 2006; 19(1):19-27.
20. Raman R, Dutta A, Day N, et al. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the Treatment of Osteoarthritis of the Knee -- A Prospective Randomized Clinical Trial. *Knee* 2008; 15(4):318-24.
21. Karlsson J, Sjögren S, Lohmander LS. Comparison of Two Hyaluronan Drugs and Placebo in Patients with Knee Osteoarthritis. A Controlled, Randomized, Double-Blind, Parallel-Design Multicentre Study. *Rheumatology (Oxford)* 2002; 41(11):1240-8.
22. Kotevoglou N, Iyibozkurt PC, Hiz O, et al. A Prospective Randomised Controlled Clinical Trial Comparing the Efficacy of Different Molecular Weight Hyaluronan Solutions in the Treatment of Knee Osteoarthritis. *Rheumatol Int* 2006; 26(4):325-30.
23. Caborn D, Rush J, Lanzer W, et al. A Randomized, Single-Blind Comparison of the Efficacy and Tolerability of Hylan G-F 20 and Triamcinolone Hexacetonide in Patients with Osteoarthritis of the Knee. *J Rheumatol* 2004; 31(2):333-43.
24. Leopold SS, Redd BB, Warme WJ, et al. Corticosteroid Compared with Hyaluronic Acid Injections for the Treatment of Osteoarthritis of the Knee. A Prospective, Randomized Trial. *J Bone Joint Surg Am* 2003; 85-A (7):1197-203.

25. Chen WL, Hsu WC, Lin YJ, et al. Comparison of Intra-Articular Hyaluronic Acid Injections with Transcutaneous Electric Nerve Stimulation for the Management of Knee Osteoarthritis: A Randomized Controlled Trial. Arch Phys Med Rehabil 2013; 94(8):1482-9.
26. American Academy of Orthopedic Surgeons. Treatment of Osteoarthritis of the Knee – 2nd Edition. Available at: <http://www.aaos.org/Research/guidelines/GuidelineOAKnee.asp>. Accessed in January 2014.