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High Molecular Weight Hyaluronic Acid Viscosupplementation for Mild to Moderate Osteoarthritis of The Knee- A Prospective Study to Evaluate Efficacy

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Abstract

INTRODUCTION: From last few decades, osteoarthritis of the knee is one of the most common degenerative joint diseases, and it not only poses a considerable problem because of its rampant frequency but also because it almost invariably leads to drastic lifestyle changes as well as huge financial and social burden. The additions of exogenous hyaluronic acid to the synovial fluid of individuals with knee osteoarthritis address the degradation of hyaluronic acid and subsequently influence the disease outcome.

METHODS: A single 6mL intra-articular injection of Hylan G-F 20 was used on a total of 61 knees of 32 patients, with a mean age of 54.0 years, and assessed in this study. The primary outcome was measured by question A1(pain score in percentage while walking) of the WOMAC at 1st, 2nd, 4th weeks, 2nd, 3rd and 6th months. Secondary outcomes were measured by the overall total and C domain (function) of WOMAC.

RESULTS: After a single dose of intra-articular injection, statistically significant improvement of symptoms was observed by the fourth week (means of A1=38.934, T=41.4754, C=42.049) after injection and the therapeutic improvement lasted through six months (means of A1=40.573, T=42.377, C=42.918) after the injection as compared on the day of treatment(means of A1=60.245, T=60.573, C=60.344).

CONCLUSION: In mild to moderate osteoarthritis of the knee, a single intra-articular injection of high molecular weight hyaluronic acid (6ml of Hylan G-F 20) was very safe and highly effective in providing statistically significant and clinically relevant pain relief within the six months, with clinically significant improvement by the 4thweek.

Keywords: Sodium Hyaluronate; Knee Osteoarthritis; WOMAC; Intraarticular therapy**;** glycosaminoglycans; Viscosupplementation; Kellgren–Lawrence.

INTRODUCTION

Knee osteoarthritis (OA) is a widespread joint condition that affects people of all races and is slightly more prevalent in women. It is most common in middle-aged to elderly adults over the age of forty and is a leading cause of physical impairment and disability among the elderly [1]. Treatment of OA

remains a serious therapeutic problem, not only due to its great prevalence but also because it frequently results in drastic lifestyle modifications and considerable economic and social costs. For a long time, the scope of treatment remained to the management of pain and improvement of the function of the affected joint with a mixture of physical measures and physiotherapy along with oral drugs and sometimes surgery.[1]

Compared to a normal healthy joint, the synovial fluid in a joint affected by OA is characterized by both diminished molecular weight and concentration of its primary functional constituent- hyaluronic acid (HA) [2], which has been associated with a decrease in the elasticity and viscosity of the synovial fluid [3-4]. This may alter the transmission of mechanical forces to the articular cartilage and subsequently increasing its susceptibility to mechanical damage or wear and tear.[5]

HA is a large glycosaminoglycan composed of repeating disaccharides of N-acetyl-glucosamine and glucuronic acid. It is a major component of the synovial fluid & cartilage and plays a key role in the trophic status and regulation of the intra-articular environment.[6] It can form a peri-cellular coat around the cells; interact with pro-inflammatory mediators and bind to cell receptors to modulate cell proliferation; migration and gene expression.[7] In OA, the overall length of the hyaluronic acid chains and concentration in the synovial fluid are decreased as compared to a healthy joint. HA may have direct or indirect effects on pain mediator substance P.[8]

In OA joints, the lower molecular weight hyaluronic acid loses its viscoelasticity and capacity to endure shear stresses. As a result, when endogenous HA synthesis is diminished, joint surfaces become progressively damaged. Although the mechanism of exogenous HA for the treatment of pain associated with knee osteoarthritis is unknown, clinical trials have shown that exogenous HA has a variety of physiological effects.[9] A combination of factors has been proposed including restoration of joint rheology; anti-nociceptive effects; anti-inflammatory effects and production of endogenous HA synthesis [10]. Viscosupplementation with HA and its derivatives can assist to replenish failing arthritic synovial fluid by increasing the synthesis of extracellular matrix proteins such as chondroitin, keratin sulphate, and proteoglycans, as well as increasing endogenous HA production.[11] Hylan G-F 20 (high molecular weight, average 6000 kDa, two cross-linked components; derivative of hyaluronan) has a peak therapeutic impact after 8 to 12 weeks, with efficacy extending up to 6 months, according to the product description. It is presently indicated for the treatment of osteoarthritis of the knee in individuals who have failed to respond to non-pharmacologic treatment and basic analgesics such as paracetamol.[12]

AIMS AND OBJECTIVES

The goal of this study was to determine if a single 6 mL dosage of intra-articular hyaluronic acid (Hylan G-F 20) injection would improve the pain and functionality of patients with mild to moderate OA of the knee.

Materials and Methods

Study design

A prospective observational study was conducted at the Department of Orthopaedics. This study comprised a sample size of 61 knees (32 patients, 29 of whom had bilateral involvement).

Inclusion & Exclusion criteria

Inclusion criteria:
All ambulatory patients above the age of 40 years, who have been diagnosed with Primary OA of the knee according to criteria of the American College of Rheumatology, with a radiographic stage of Grade II-III osteoarthritis as per Kellgren–Lawrence grading system, at least 3 months before entering the study.

Patients are required to have been taking analgesics/non-steroidal anti-inflammatory drugs (NSAID) to control OA knee pain for at least 3 days per week for a minimum of 2 months before enrollment and have a score of ≥ 2 on Question A1 (Pain during walking) of the WOMAC at screening.[13]

Exclusion criteria:
Patients suffering from secondary arthritis, inflammatory arthritis, pregnant or lactating mother, grade I and IV radiographic stage osteoarthritis (Kellgren–Lawrence grading), clinically apparent tense effusion of the target knee, significant valgus/varus deformities, viscosupplementation in

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any joint in the past 9 months, surgery in the knee within the past 6 months, systemic or intra-articular injection of corticosteroids in any joint within 3 months before screening, localized infection at knee and allergy or hypersensitivity to any of the study medication or avian proteins were excluded.

Technique and procedure

At the screening, the patient's written and informed consent was taken and a physical examination was performed on the knee to be treated (''target knee''). A radiographic assessment was performed by getting both anteroposterior & lateral view radiographs of the knee, and grading was done accordingly.

The patients were called to the minor OT and made to lie in the supine position. The knee was painted and draped with sterile sheets. Using sterile technique, 6ml of Injection Hylan G-F 20 was injected by 18G sterile needle through the supero-lateral portal into the knee joint after aspirating and confirming the position of the needle. (Figure 1)

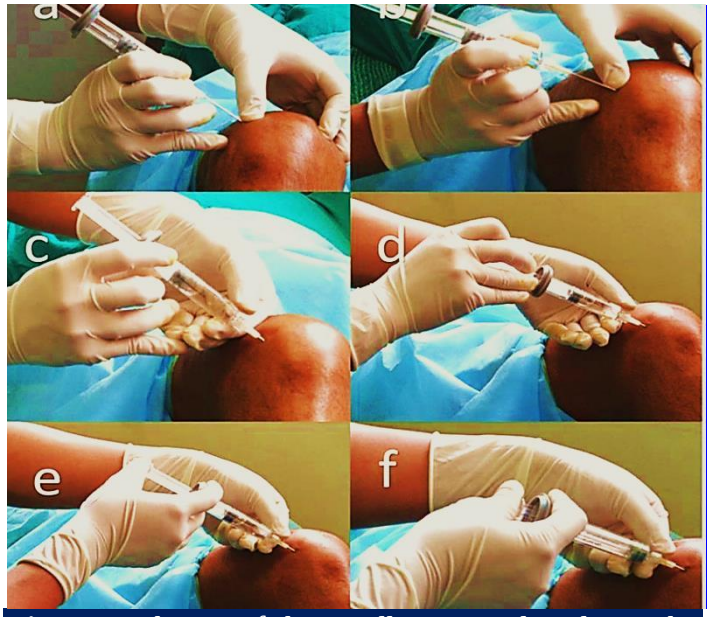

Figure 1 The tip of the needle is introduced into the supero-lateral portal of the knee after palpating (a,b,c) and confirmed by aspirating (d); followed by injection of the content into the knee JOINT (e and f)

A sterile dressing was applied at the injection site after the injection and the patient's knee was mobilized by doing flexion and extension so that the drug was uniformly distributed inside the joint. (Figure 2)

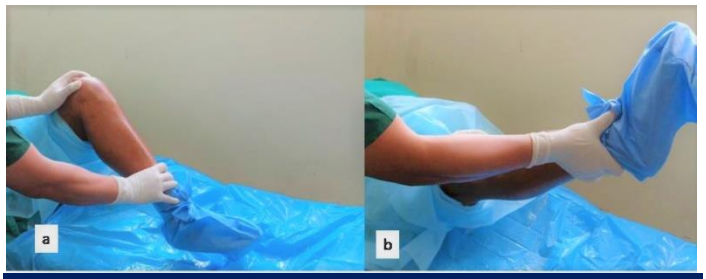

Figure 2: Cyclic steps of flexion and extension after intra-articular injection.

Efficacy measures in follow-up period

Patients were followed up at 1st; 2nd; 4th week; and then at 2nd; 3rd and 6thmonths after injection. The WOMAC scale was utilized to assess efficacy results, with Question A1 (pain when walking on a flat surface) serving as the primary outcome and the total score and C (functional) domain serving as secondary outcomes.

Results

Statistical analysis was done on SPSS 20.0. The data is represented as mean and standard deviation. ANOVA-test analysis was done to compare the numerical parametric data. Chi-square analysis was done for the comparison of ordinal data. The p-value <0.05 was taken as significant.

A total of 61 target knees were injected with Hylan G-F 20 in this trial, which included 32 patients (29 of whom received bilateral injections). The patients in this research varied in age from 40 to 59 years old, with an average age of 54. The majority of the patients were between the ages of 55-60 years. Based on gender, 24 cases(75%) and 8 cases(25%) belonged to females and males, respectively.(table 1a)

Age group	No. of patients	Percentage (%)
40-45	3	9.38
45-50	7	21.87
50-55	7	27.87
55-60	15	46.88
Total	32	100

Table 1a: Age Distribution

Patients were also divided into grades of osteoarthritis using the Kellgren–Lawrence grading method in the research. 36 patients (59.02 percent) and 25 patients (40.98 percent) were assigned to grades II and III, respectively.

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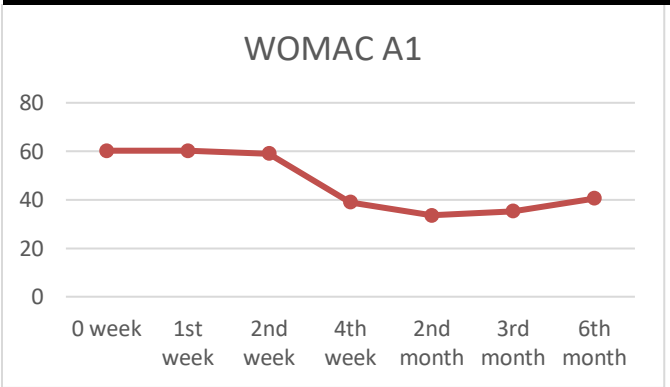
A descriptive analysis was performed on the percentage score of the **WOMAC A1** question (pain while walking on a flat surface). It showed a mean of 60.2459 at the time of treatment which decreased to 33.6066 in the 2nd month and 40.5738 in the 6th month. The mean of **C domain of the WOMAC** was 60.344 at the time of intra-articular injection and a significant decrease at 36.639 on the 2nd month but 42.918 at the 6th month. Similarly, the mean **Total WOMAC** score was 60.573 at the time of intra-articular injection and a significant decrease at 36.524 on the 2nd month but 42.3770 at the 6th month. The results of the ANOVA score and multiple comparisons at 1st week, 2nd week, 4th week, 2nd month, 3rd week, and 6th month are given in the table with standard deviation and mean difference. That is below 0.05; therefore, there is a statistically significant difference in the mean length of time in the whole course of treatment means favorable outcomes.(table 1b and 1c)

WOMAC		N	Mean	Standard Deviation	95% confidence level for mean	
					Lower limit	Upper Limit
A1	0 week	61	60.2459	12.39712	57.0709	63.4210
	1st week	61	60.2459	12.39712	57.0709	63.4210
	2nd week	61	59.0164	12.10440	55.9163	62.1165
	4th week	61	38.9344	16.78578	34.6354	43.2335
	2nd month	61	33.6066	13.60549	30.1220	37.0911
	3rd month	61	35.2459	15.39551	31.3029	39.1889
	6th month	61	40.5738	18.35071	35.8739	45.2736
	Total	427	46.8384	18.49577	45.0791	48.5977
C	0week	61	60.3443	6.32689	58.7239	61.9647
	1st week	61	60.3443	6.32689	58.7239	61.9647
	2nd week	61	55.8033	6.49056	54.1410	57.4656
	4th week	61	42.0492	10.92921	39.2501	44.8483
	2nd month	61	36.6393	10.11275	34.0493	39.2293
	3rd month	61	38.0164	10.49522	35.3284	40.7043
	6th month	61	42.9180	11.66090	39.9315	45.9045
	Total	427	48.0164	13.30351	46.7510	49.2818
T	0 week	61	60.5738	7.38119	58.6834	62.4642
	1st week	61	60.5738	7.38119	58.6834	62.4642
	2nd week	61	55.8361	7.34207	53.9557	57.7165
	4rd week	61	41.4754	11.10196	38.6321	44.3188
	2nd month	61	36.5246	10.15809	33.9230	39.1262
	3rd month	61	38.2295	10.73529	35.4801	40.9789
	6th month	61	42.3770	11.46613	39.4404	45.3137
	Total	427	47.9415	13.66737	46.6414	49.2415



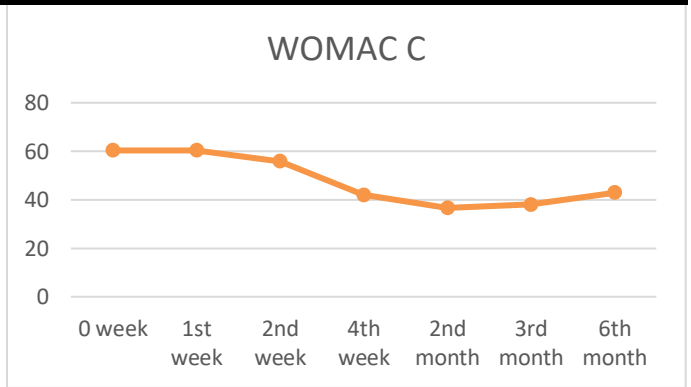


Table 1b: Descriptive analysis of the study and graphs

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		Sum of Squares	df	Mean Square	F	Sig.
WOMACA1	Between groups	56059.719	6	9343.286	43.761	.000
	Within groups	89672.131	420	213.505		
	Total	145731.850	426			
WOMACC	Between groups	39993.213	6	6665.536	79.079	.000
	Within groups	35401.672	420	84.290		
	Total	75394.885	426			
WOMACT	Between groups	41413.799	6	6902.300	75.965	.000
	Within groups	38161.738	420	90.861		
	Total	79575.536	426			

Table1b: Descriptive analysis of the study and graphs

DISCUSSION

There was a total of 8 male patients and 24 female patients (sex ratio 1:3). Osteoarthritis Synvisc-One Indian Post Marketing Study [14] had a sample size of 394 patients with 109 male and 285 female patients. Briggs KK et al [15] et al had 47 patients with 20 male and 27 female patients; while Chevalier X et al [16] et al had a sample size of 253 with 73 male and 180 female patients. Caborn D et al [17] et al. had 216 randomized patients in their study with 93 males and 123 females. In all these studies; Kellgren-Lawrence radiological Classification was used for grading of severity of OA knee. The predominance of females in all these studies indicates female sex as a universal risk factor for the development of symptomatic primary osteoarthritis in the general population.

In our study; the age range of the patients was from 40 - 59 years with a mean age of 54. Osteoarthritis Synvisc-One Indian Post Marketing Study reported 57.6 years [14]. Briggs KK et al [15] et al. reported mean age of 65 with an age range from 42 to 65 years; while Chevalier X et al [16] et al reported 63.4 with a mean standard deviation of 12.1. Caborn D et al [17] reported mean age of 62.5 with a mean standard deviation of 9.64 years. Younger mean age in our study could most probably reflect the inclusion criteria in our study as only OA of grade II and III were included. In OASIS and Caborn D et al [17] et al. symptomatic patients of all Grades were included in their study. Chevalier X et al [16] included OA of grade II; III and IV while Briggs KK et al [15] et al. included patients with OA of grade III and IV.

Ours was a prospective observational study; it was similar to OASIS (Osteoarthritis Synvisc-One Indian Post Marketing Study) which was also an open-label study[14]. However, OASIS was a multi-centric study. Chevalier X et al [16] . did a randomized; multi-centric; double-blind; placebo-controlled study; while the study was done by Briggs KK et al [15] al. was a prospective cohort study. Caborn D et al [17] et al designed a prospective; multi-centric; randomized; single-blind; parallel-group clinical trial comparison with Triamcinolone Hexacetonide.

In our study; patients were followed up at 1st week; 2nd week; 4th week; 2nd month; 3rd month and 6th-month post-injection. In OASIS; patients were followed up at 1st; 4th; 12th; 26th; 39th and 52nd weeks with a total of 7 visits[14]. In the study done by Chevalier X et al [16] .; patient follow-up was done after 1; 4; 8; 12; 18 and 26 weeks of injection. Caborn D et al [17] et al followed up patients at 1; 2; 4; 8; 12 and 26 weeks after injection. Briggs KK et al [15] et al followed up patients at 3weeks; 6 weeks; 12 weeks and 6 months.

In this study; a single 6mL of Hylan G-F 20 was used for injection. In the study by Chevalier X et al [16] . and OASIS[14]; in addition to a single 6mL injection; repeat injection was given to selected patients. In the study done by Briggs KK et al [15] et al and D. Carbon et al[17] 3 weekly injections of Hylan G-F 20 (20mL) were given; in addition; Briggs KK et al [15] gave corticosteroid along with the first injection.

Efficacy outcomes were measured using the WOMAC scale; A1 for the primary outcome while the C (functional) domain and the total score were used to measure secondary outcomes. This scale was also used in OASIS[14] and by Chevalier X et al [16]. In

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addition to this; Briggs KK et al [15] used Visual Analog Scale and Short Form -16 were used to measure therapeutic outcomes while Caborn D et al [17] used a 100 mm VAS in addition to WOMAC

In our study; statistically, significant improvement was seen for WOMAC A1 (pain while walking on a flat surface) at 4 weeks; while for WOMAC C (functional domain) and WOMAC total; statistically significant improvements seen by 2nd week. In OASIS[14]; improvement in WOMAC A; B and C sub-score were seen by the 2nd week; Chevalier X et al [16] reported improvement by 4 weeks. Briggs KK et al [15] reported improvement in the WOMAC pain subscale by 3rd week.

A 35.39%decrease in WOMAC A1 was seen by the fourth week; a 46.89% decrease was seen in the WOMAC C domain and 48.05% seen in total score was seen in our study. OASIS[14] reported a 45.7% mean percentage change from baseline for WOMAC A1 sub-score by 26th week; and 50.8%; 41.7% and 45.5% decrease from mean baseline for WOMAC A; B and C score respectively at 52nd week. Chevalier X et al [16] reported a decrease of 36% from baseline over 26 weeks. K. K. Briggs reported a 47%reduction at 3 weeks for WOMAC total score[15].

Therapeutic improvement in WOMAC A1; C-domain and total score lasted all through 6 months in our study. In OASIS[14]; it was improvement was seen through 52 weeks of their follow-up time; Chevalier X et al [16]. reported significant; clinically relevant pain relief; as measured by WOMAC A1 (walking pain) over 26 weeks; with a modest difference compared with placebo. Briggs KK et al [15] et al study did demonstrate that with Hylan G-F 20 and corticosteroid; significant pain reduction and functional improvement were seen at early time points and up to 6 months; with greater reduction than what has been seen with HA injections or corticosteroids alone

There were no serious adverse reactions of the target knee to the study material or the study design reported. The most common adverse reactions were pain and swelling; which gradually subsided by one to two weeks and were treated with oral analgesics and anti-inflammatory drugs. Similar reports were given in the study by Chevalier X et al [16]. In OASIS [14]; no adverse reactions were reported either during the intra-articular injection or 30 minutes post-injection in the target or/and non-target knee. 23 of 394 patients experienced adverse reactions over subsequent follow-ups; of which arthralgia was the most common adverse effect. B. Cabron et al[17] reported no statistically significant differences observed between treatment groups for the overall incidence of adverse events or the incidence of any single adverse event.

CONCLUSION

A single intra-articular injection of high molecular weight hyaluronic acid (6ml of Hylan G-F 20) was safe and effective in providing statically significant and clinically relevant pain relief in mild and moderate osteoarthritis of the knee over six months; with clinically significant improvement by the fourth week.

This study conclude that viscosupplementation or intra-articular injections with hyaluronic acid in patients with symptomatic osteoarthritis knee administered a single is an effective and well-tolerated therapy with minimal complications. Viscosupplementation for treatment of osteoarthritis knee represents an alternative treatment plan for those in whom oral medications or other treatment modalities other than surgery have failed and those who want less systemic side effects arising from the systemic uses of drugs. A further clinical trial with a larger no of patients is required so that we can recommend its use on large scale and address unanswered questions related to its therapeutic use.

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Authors contribution:

Author 1: procedure, investigation, conceptualization, formal analysis and maintain follow up of the patients

Author 2,3 and 6: Investigation, assist all data analysis, methodology, project and validation

Author 4: visualization, writing original draft and editing work

Author 5: Supervise the above mention work

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