Original Article

Clinical and Imaging Evaluation of Efficacy of Visco-supplementation in Degenerative Osteo-arthritis Knee – A Prospective Interventional Study

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Abstract

In this study 30 patients with osteo-arthritis (OA) knee (total 55 knees) were given weekly injections of high molecular weight (HMW) hyaluronic acid (HA) for 3 weeks. The subjective parameter was Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) score which improved from 97.67±21.4 at baseline to 61.03±24.8 at six months follow-up (p=0.0001). Also the mean range of motion (ROM) of the involved knees was 125.73± 10.8 degrees at baseline and it increased to 132.64±5.2 degrees after six months (p=0.0001) of injection treatment. The objective parameter of disease modification was MRI based semi-quantitive Whole-organ Magnetic Resonence Imaging Score (WORMS) score. The mean of total WORMS score in medial femorotibial joint (MFTJ) and patello-femoral joint (PFJ) improved from baseline (28.382±10.446; 22.64±5.969) to final follow up (27.46±10.32; 21.76± 6.182) which was quite significant (p=0.0321; p=0.0294) and implies a reduced rate of cartilage destruction after injection HA though there is no regrowth of cartilage as such.

Key words: **Osteo-arthritis knee, injection hyaluronic acid, viscosupplementation, magnetic resonance imaging, WORMS scoring.**

Introduction:

American College of Rheumatology has defined osteo-arthritis (OA) as a "heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins" like, subchondral bone thickening (sclerosis), marginal osteochondral outgrowths (osteophytes) and joint deformity[1]. In the Version 2 estimates for the Global Burden of Disease 2000 study, published in the World Health Report 2002, OA is the 4th leading cause of years lived with disability (YLDs) at global level, accounting for 3.0% of total global YLDs. Worldwide estimates indicate that 9.6% of men and 18% of women ≥60 years have symptomatic OA with impaired mobility[2].

Conservative treatment options include pharmacotherapy (analgesics and NSAIDs), orthotic support (knee braces and shoe wedges), local heat and muscular strengthening exercises. There are few potentially structure modifying drugs which include oral diacerin, glucosamine sulphate and intra-articular hyaluronic acid[3]. The term hyaluronan (as an alternative to HA) as well as the concept of visco-supplementation was first proposed by Balazas. United States Food and Drug Administration (FDA) approved injection hyaluronic acid for OA knee in 1997[4]. Visco-supplementation with HA allows for restoration of the elastoviscous properties of synovial fluid along with possible anti-inflammatory and antinociceptive properties

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and stimulation of in-vivo HA synthesis. HA is generally obtained commercially either from an avian source or from bacterial fermentation, and is of two types (a) Low molecular weight hyaluronic acid : 0.5-2 million daltons (MDa) and (b) high molecular weight / cross linked hyaluronic acid : 5-7 million daltons (MDa)[5].

Multiple studies have been conducted to evaluate the efficacy of intra-articular hyaluronic acid injections[6]. The largest and most comprehensive meta-analysis on intra-articular HA is the 2006 Cochrane review[7] which reviewed 76 trials on HA.7 At 5 to 13 weeks post injection period, improvement of 11 to 54% for pain and 9 to 15% for function was observed. In general, comparable efficacy was noted against NSAIDs and greater long term benefits were noted in comparisons against intra-articular corticosteroids. Pooled result of RCT's within the period 2004-2009 shows that effect sizes for pain relief from intra-articular HA have diminished and there was greater heterogeneity of outcomes and more evidence of publication bias[8]. This led us to review the clinical effect of intra-articular HA in a prospective study design.

MRI is now recommended by OARSI for clinical trials that involve cartilage morphology assessment as outcome variable[9]. MRI based studies by Anandacoomarasamy *et al*[10] and Wang *et al*[11] concluded that HA have a beneficial effect on knee cartilage preservation. But, other similar studies by Prasad *et al*[12] and Kosuwon *et al*[13] reported mostly a lack of response. In the above context we undertook our trial utilising for the first time, a MRI based morphological, semi-quantitive, whole-organ score viz. WORMS[14] (whole organ magnetic resonance imaging score) as the cartilage assessment tool for any HA effectiveness trial.

Materials and Method:

After getting the ethical clearance of the Institutional Review Board of VMMC and Safdarjang Hospital, New Delhi we conducted our study in the period from October 2010 to March 2012. By nature it was a prospective interventional one group pretest post-test study. Patients of 30-70 years and either gender diagnosed with primary OA knee of tibiofemoral joint as defined by the ACR clinical criteria[15] with Kellgren-Lawrence[16] radiological grade I, II or III having pain >40mm on >2 items of WOMAC[17] scale for at least 15 days in the month prior to start of the study were enrolled into the study after informed consent. Patients having secondary OA, ipsilateral cruciate or collateral ligament injury within past 3 months, intra-articular treatment with any product or joint lavage and arthroscopic procedure within prior 6 months, any knee surgery within prior 12 months, any overlying skin infection or joint infection, any contra-indication for MRI e.g. metal implants, claustrophobia, any allergy to avian protein (e.g. egg, chicken, feather, etc), any history of crystalline arthropathy or inflammatory arthritis or venous or lymphatic stasis were excluded from the study. Also excluded are pregnant or nursing mothers, morbid obese ones (BMI>40), patients with unstable medical condition or who are on anticoagulation therapy or simply unwilling to participate.

Methodology of Intervention:

All patients enrolled within the study received 3 doses of HMW intra-articular HA injected in the affected knee/ knees (Fig 1) at an interval of 1week with each dose equivalent to 2.5 ml, after aspiration of any joint effusion (if necessary). Any adverse effect (if any) is noted during each injection procedure. We used injection containing purified sodium hyaluronate with molecular weight of 5.03×10^3 g/mol (i.e., 5.03 million daltons) obtained by biofermentation of bacterial source viz. *Streptococcus zooepidermicus*. Pain killers or other osteo-arthritis medications were not allowed throughout the study period of 6 months, except paracetamol (maximum dose of 2g/ day), when the pain was unbearable and the number of tablets/day were noted. All the patients were encouraged to lose weight, taught quadriceps strengthening exercises and general precautions in activities of daily living (ADL) as was deemed necessary. The exercise regimen was straight leg raising, keeping knee extended with each short arc extension having 6 seconds holding time. The exercise was repeated 30 times in each sitting and was done twice a day throughout the study period.

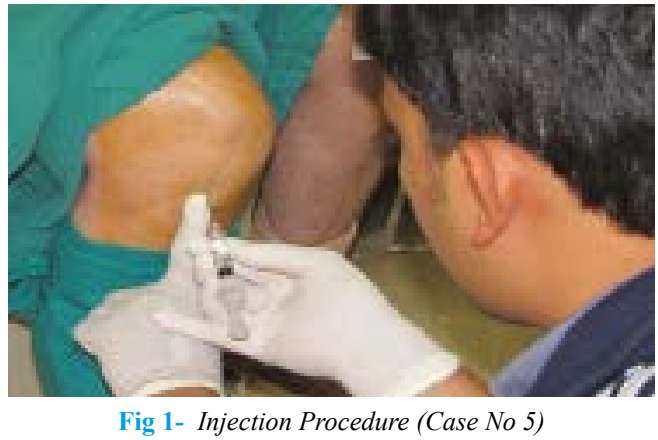

Fig 1- *Injection Procedure (Case No 5)*

Tools of Measurement:

Each patient was evaluated in terms of tools of measurement and the outcome was determined by the

assessment of both symptomatic and disease modifying efficacy parameters:

1. Symptomatic efficacy parameter was WOMAC[17] (Western Ontario and McMaster Universities Index of Osteo-arthritis) as well as ROM assessed on baseline (day 0), day 45, day 90 and day 180.
2. Disease modifying efficacy parameter was MRI grading of cartilage thickness (Fig 2) and other bony features as per WORMS[14] (whole-organ magnetic resonence imaging score) criteria assessed at baseline (day 0) and at the end of study period (180 days). MRI examination was carried out with 1.5 Tesla Philip Brilliance MRI machine in the radiology department using appropriate sequences viz. sagittal T1-weighted 3D spoiled gradient recalled echo (SPGR) with fat suppression (3D WATSc), sagittal T2-weighted TSE with frequency selective fat suppression (spectral pre-saturation with inversion recovery, SPIR), sagittal T1-weighted spin-echo (T1W-TSE), coronal T1-weighted spin-echo (T1W-TSE) and axial T1-weighted spin-echo (T1W-TSE). Five independent articular features viz. cartilage signal and morphology, sub-articular bone marrow abnormality, sub-articular cysts, sub-articular bone attrition and marginal osteophytes are scored in 3 different zones viz. medial femorotibial joint (MFTJ), lateral femorotibial joint (LFTJ) and patellofemoral joint (PFJ).

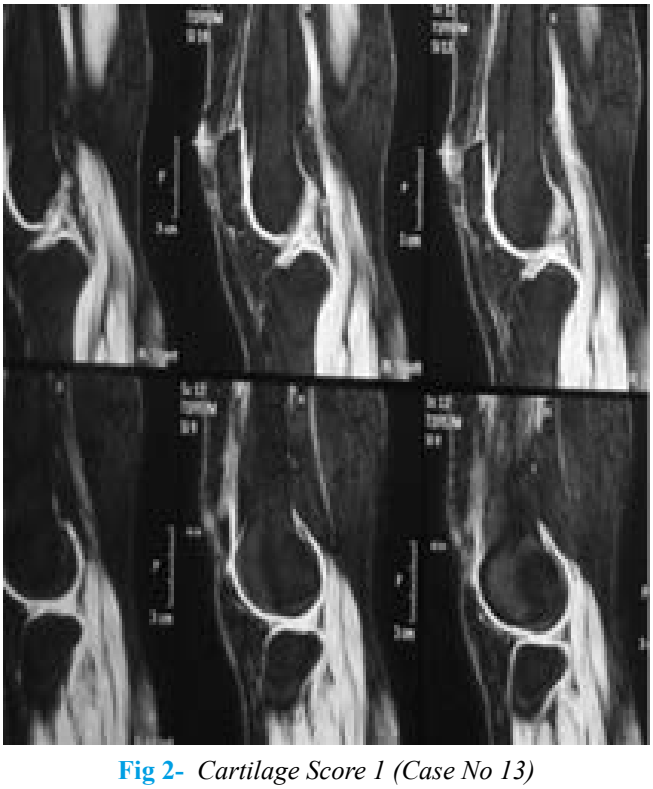

Fig 2- *Cartilage Score 1 (Case No 13)*

Statistical Analysis:

Data obtained of all patients who completed the stipulated follow-up were compiled and analysed using MS excel as well as SPSS version 17. Descriptive statistics including mean and standard deviation (SD) were found for each quantitative variable. Also frequency distributions were found for each of the qualitative variable. For quantitative data, the mean values across various follow-ups were compared using the Student's paired t test. The results were considered significant at 5% level of significance, i.e. $p<0.05$.

Results:

Forty-three consecutive patients with primary OA of the knee satisfying the inclusion and exclusion criteria participated in the study but only 30 completed the 6 months follow-up. Consequently, we had a total study population of 30. Among the total number of 30 patients, 25 had bilateral involvement and the rest 5 had unilateral involvement. Hence, the total knee count comes out to be 55.

The total WOMAC score is obtained on summation of the pain, stiffness and function subscores of each of the 30 patients. The values were 97.67±21.37, 52.87±15.69, 48.70±18.51 and 61.03±24.79 at baseline, second visit, third visit and final visit respectively (Table 1). Thus, there is significant decrease in WOMAC score on comparing baseline with any of the subsequent visits ($p=0.0001$). But, in between the third and fourth visit there is increase in WOMAC score with high statistical significance ($p=0.0001$) emphasizing that the effect of visco-supplementation is gradually plateauing at 3-6 months.

Table 1: *WOMAC Score at Baseline, 45 Days, 90 Days and 180 Days Follow-up*

Days	No of cases	Mean	Standard deviation
Baseline (WOMAC 1)	30	97.67	21.37
45 days (WOMAC 2)	30	52.87	15.69
90 days (WOMAC 3)	30	48.70	18.51
180 days (WOMAC 4)	30	61.03	24.79

The mean ROM was found to be 125.73±10.819, 131.73±735, 132±4.495 and 132.64±5.169 (Table 2). 5.169 degrees respectively at first, second, third and fourth visits. Thus, there was significant increase in ROM when baseline value was compared to the values at second, third and fourth visits ($p=0.0001$), although there was slight decrease in mean ROM in between the third and fourth visits which was not significant ($p=0.742$).

Table 2: *ROM at Baseline, 45 Days, 90 Days and 180 Days Follow-up*

ROM	No of cases	Mean in degrees	Standard deviation
Baseline	55	125.73	10.819
45 days	55	131.73	4.735
90 days	55	132.73	4.495
180 days	55	132.64	5.169

The mean of total WORMS score in MFTJ and PFJ improved from baseline (28.382±10.446; 22.64±5.969) to final follow-up (27.46±10.32; 21.76±6.182) which was quite significant (p=0.0321; p=0.0294). Although, there was decrease in WORMS score in LFTJ from first visit (24.73±7.509) to final visit (23.73±7.509), the difference was not statistically significant (p=0.1209) (Table 3).

Table 3: *Progression of WORMS Score at Baseline and Six Months Follow-up*

WORMS score	MFTJ	LFTJ	PFJ
Total WORMS score at first visit	28.382 ± 10.446	24.73 ± 7.509	22.64 ± 5.969
Total WORMS score at six month	27.46 ± 10.32	23.73 ± 7.509	21.76 ± 6.182
P value	0..0321	0.1209	0.0294

As a whole the injection procedure was quite safe and without any serious adverse effect. Three patients (10%) had transient pain on the first day of injection that required rescue analgesics and ice therapy. Significantly, the first two patients participating in this study were among them. This suggests an initial learning curve of the injection procedure.

Discussion:

Altman and moskowitz[18] in their study noted that HA treated patients had lower mean WOMAC pain, stiffness and physical function subscore at week 26 when compared with oral naproxen (though not statistically significant). Similarly, Phiphobmonkgol *et al*[19] also reported that all three efficacy parameters of WOMAC scale became significantly better than baseline after the second injection of HA (out of a 3 injection regime like our study), showed further improvement at 8 weeks and maintained thereafter up to 6 months of follow-up. Our findings closely corroborates that of literature with significant WOMAC score improvement occurring up to 3 months with the effect maintained till the end of study.

Literature predicts significant improvement in joint function as measured by flexion movement (ROM) of the knee[20,21]. The present study also reports similar improvement in knee flexion movement when the baseline value is compared with subsequent visits. Leardini *et al*[22] noted that the improvement occurred from the first injection itself; progressive improvement is seen up to 2 months and then it was maintained, although not to the same degree, for as long as 1 year. The present study also noted maximum benefit at about 45 days, after which the benefit is sustained for almost 6 months.

We found that the MRI based WORMS score at six months improves from baseline at patellofemoral and medial tibiofemoral joint while there is somewhat deterioration at lateral tibiofemoral joint, which implies a reduced rate of cartilage destruction after injection of hyaluronic acid though there is no regrowth of cartilage as such. This corroborates well with Anandacoomarasamy *et al*[10] who demonstrated that both the cartilage and the synovial membrane were improved when measured arthroscopically 6 months after the injection. Listrat *et al*[23] in their arthroscopy based study observed that cartilage destruction was significantly reduced in HA treated knee. MRI based studies done by Anandacoomarasamy *et al*[10] and Wang *et al*[11] reported preserved cartilage both on volumetric and cartilage defect scores after treatment with hyaluronic acid up to a six months follow-up.

Results of retrospective study of 336 patients treated by 5 Canadian rheumatologists over 2.5 years suggested that incidence of local side effects depends upon the injection technique: with a medial approach and a partially flexed knee, the incidence was 5.2%; with a straight medial approach, 2.4%; and with a straight or lateral approach (as practised by us), 1.5%[24]. The higher incidence of local pain in our study may be due to increased pain perception in the Indian population[25].

Conclusions:

From this study we can conclude that injection HA is a safe and effective treatment for OA knee. The beneficial effect of viscosupplementation reaches peak at 3 months and is maintained up to 6 months. There is no severe adverse effect of injection hyaluronic acid. Only a few case of local pain are reported which can be managed quite effectively. Regarding disease modification role viscosupplementation maintains the cartilage integrity at least in MFJ and PFJ of OA knee joint for a period of minimum 6 months. Though there is suggestion of structural improvement of cartilage on injection HA, further studies are needed with randomisation, control group and larger number of study population to settle the dispute.

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