Original Article

Clinical and radiological efficacy of single-dose intra-articular high-molecular-weight hyaluronic acid in knee osteoarthritis

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Abstract

Context: While visco-supplementation is being used for the treatment of knee osteoarthritis (OA), the published reports vary widely in benefits afforded by this treatment. It was therefore proposed to assess the objective parameters along with subjective outcomes. **Aims:** Our study assessed the radiological and clinical efficacy of single-dose high-molecular-weight intra-articular hyaluronic acid (HMW-IAHA) injection in knee OA. **Settings and Design:** This interventional cohort study was conducted in a calculated sample size of 44 patients with knee OA. **Materials and Methods:** Visual analog scale (VAS) and knee OA and outcome score (KOOS) were used for clinical assessment, and whole organ magnetic resonance imaging score (WORMS) for radiological assessment. The subjects were given a single dose of HMW-IAHA injection, 90 mg/3 ml, and were assessed on day 0 and day 90. **Statistical Analysis:** Statistical Package for Social Sciences (SPSS) software was used. **Results:** At the day 90 follow-up, there was an improvement in mean ± standard deviation values of VAS score (day 0: 8.53 ± 0.81, day 90: 5.97 ± 0.87), KOOS score (day 0: 27.33 ± 15.18, day 90: 57.26 ± 14.26), and the cartilage signal and morphology in the medial femorotibial joint (day 0: 11.02 ± 6.26 and day 90: 10.91 ± 6.22) and patellofemoral joint (day 0: 10.35 ± 4.36 and day 90: 10.28 ± 4.39) compartments. There was a decrease in synovitis score from 2.3 ± 1.61 to 1.3 ± 1.3 in the medial femorotibial joint compartment and total WORMS score (day 0: 66.57 ± 36.06, day 90: 65.14 ± 35.62). **Conclusions:** A single dose of intra-articular injection with high-molecular-weight hyaluronic acid produces improvement in the clinical symptoms and quality of life as well as is effective in maintaining the articular cartilage integrity and reducing synovial inflammation.

Keywords: Cartilage integrity, high-molecular-weight hyaluronic acid, intra-articular injection, knee osteoarthritis, KOOS score, visco-supplementation, WORMS score

Introduction

Knee osteoarthritis (OA) is a multi-factorial entity resulting in an imbalance between synthesis and degradation of the cartilage matrix and thus a decline in functional capacity.[1] The increased fluid content and reduced hyaluronic acid concentration in the inflammatory state reduce the synovial fluid viscosity and impair

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its biomechanical properties.[2,3] Altering these pathways and replacing the structural defects through visco-supplementation is one among the treatment modalities commonly implemented.[4] The primary aim of this study was to evaluate the efficacy of single-dose intra-articular injection of high-molecular-weight hyaluronic acid in degenerative OA knee clinically and radiologically.

Materials and Methods

Study design

The study was conducted in an out-patient care setting in northern India and was commenced on 02.04.2020 after getting approval from the Institute Ethics Committee (IEC/VMMC/SJH/Thesis/2019-10/146) dated 30.10.2019 and the Institutional Review Board on 09.10.2019 and was registered at Clinical Trials Registry India (CTRI Registration Number: CTRI/2020/03/024224). The procedures followed were in accordance with the ethical guidelines of the Indian Council of Medical Research (ICMR) and with the Helsinki Declaration of 1975, as revised in 2000. The minimum required sample size with 99% power of study and 1% level of significance was 37, and on taking the lost to follow-up as 15%, a total sample size of 44 was calculated. By nature, it was a prospective interventional cohort study conducted over 18 months after getting informed consent from the participants in the language which they understood. The clinical assessment data were collected using a pre-designed structured questionnaire through interview, and the veracity of the data was randomly cross-checked by the co-investigators. The participants were given a single injection of high-molecular-weight intra-articular hyaluronic acid (HMW-IAHA) after initial clinical and radiological assessment and followed up after 3 months.

Study population

The study population was patients of either gender, diagnosed with primary knee OA as defined by the American College of Rheumatology criteria (ACR),[5] Radiological grade II or III OA of the knee as per Kellgren Lawrence classifications[6] and body mass index <40. Patients were excluded if they had a history of bleeding disorders, ipsilateral cruciate or collateral ligament injury, intra-articular treatment with any product or joint lavage, any arthroscopic procedure or knee surgery within the prior 12 months, any overlying skin infection, venous or lymphatic stasis, or anti-coagulation therapy in the previous 7 days. Any person having a unilateral knee OA was considered as one and in those with bilateral affliction worst knee was considered.

Methodology of intervention

The eligible patients have been treated with a single dose of HMW-IAHA 90 mg in 3 ml pre-filled syringes. It is a sterile, transparent, homogeneous, viscoelastic preparation that contains 30 mg/ml of cross-linked hyaluronic acid in a buffered phosphate saline solution. Non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic medications were not allowed throughout the study period, except acetaminophen (a maximum dose of 2 g/day), if the pain was unbearable. All the patients were taught lower limb strengthening exercises and general precautions in activities of daily living.

Outcome measures

Clinical assessment of each patient was performed before giving intra-articular injections and 3 months after injection using visual analog scale (VAS)[7] and the knee injury and osteoarthritis outcome score (KOOS).[8] For assessing cartilage integrity, the whole organ magnetic resonance imaging (WORMS) tool[9] was used, where the radiological images were assessed before and after injections by different radiologists. VAS is used to evaluate the intensity of subjective pain, where the pain was rated on a scale of 0–10 (0 no pain, 10 the most severe pain). KOOS is a 42-item patient-reported questionnaire with subscales like pain, symptom, ADL function, sports and recreation function, and quality of life for scoring, which helps to assess short- and long-term consequences of knee injury in OA. A Likert scale is used to record the responses, and all items had five possible answer options scored from 0 (none) to 4 (extreme) and each of the five scores is calculated as the sum of the subscale items included. The scores from each dimension were then transformed to a 0–100 scale, where 100 indicated no knee problems and 0 indicated extreme knee problems.

The radiological assessment was performed with 3 Tesla Philips MRI scanners and a sense coil for the following sequences: sagittal T2, T2 FS, PDFS, Coronal T1, PDFS, and Axial PDFS according to WORMS criteria. Images obtained through the scan were scored concerning 14 independent articular features in four zones, namely, medial femorotibial joint (MFTJ), lateral femorotibial joint (LFTJ), patellofemoral joint (PFJ), and S region. A total combined score of all the components for the entire knee was taken as the final WORMS score.

Statistical analysis

The data were entered into a spreadsheet, and categorical variables were presented in the form of numbers and percentages. The quantitative data were presented as the mean (standard deviation/SD) and as the median with 25th and 75th percentiles. The data normality was checked using the Kolmogorov–Smirnov test. In cases where data were not normal, the Wilcoxon signed-rank test was used for analysis across follow-up. The final analysis was performed with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0. The results were considered significant at a 5% level of significance (i.e., P value <0.05).

Results

Of the 47 participants who were enrolled in the study after satisfying the inclusion and exclusion criteria, a total of 44 participants were followed up after 3 months and the mean (SD) age was 52.02 (9.5). Among the participants, 73% were females

and 27% were males. A mean body mass index (BMI) of 25.85 (2.94) was observed among participants as given in Table 1.

Of the 44 participants who followed up in the study, the pain severity assessed using VAS improved from 8.53 (0.81) on day 0 to 5.97 (0.87) by day 90. The KOOS score showed an overall and component-specific improvement in follow-up visits. The total KOOS score on day 0 was 27.33 (15.18), which improved to 57.26 (14.26). The detailed improvement in each of the five components of KOOS is given in Table 2. There was a statistically significant improvement in the *P* value in each subscale (<.0001).

The total WORMS score [Table 3] improved between day 0 and day 90 from 66.57 (36.06) to 65.14 (35.62), respectively (*P* value <.0001). The synovitis component of the WORMS score [Table 4] changed from 2.91 (2.18) on day 0 to 1.77 (1.85) on day 90 (*P* value <.0001). The highest contribution in the synovitis component was from the MFTJ zone. However, the improvement was present in all four (MFTJ, LFTJ, PFJ, and S region) zones but was not significant except for the MFTJ compartment. The cartilage integrity as shown by the cartilage signal and morphology feature of WORMS [Table 4] showed improvement from day 0 to day 90 in MFTJ, LFTJ, and PFJ, but the improvement could not be statistically established with a *P* value of <0.05.

Table 1: Demographic characteristics and baseline values

Demographic characteristics	Baseline values
Age	
Mean (standard deviation)	52.02 (9.5)
Median (minimum, maximum)	50 (45, 60)
Gender (%)	
Male	27%
Female	73%
Body mass index	
Mean (standard deviation)	25.85 (2.94)
Median (minimum, maximum)	25.6 (24.35, 26.65)

Table 2: Changes in KOOS score and its components before and after injections

Components of KOOS	Day 0 (*n*=44) Mean (SD)	Day 90 (*n*=44) Mean (SD)	*P*
Pain	27.58 (16.45)	60.01 (16.33)	<0.0001
Symptom	28.74 (17.43)	62.89 (16.76)	<0.0001
Activities of daily living	28.64 (16.56)	58.71 (15.17)	<0.0001
Sports and recreation function	26.48 (16.09)	54.66 (14.4)	<0.0001
Knee-related quality of life	25.2 (13.61)	50 (14.07)	<0.0001
Total KOOS score	27.33 (15.18)	57.26 (14.26)	<0.0001

Table 3: Changes in WORMS score from day 0 to day 90

WORMS and components score	Day 0 (*n*=44) Mean (SD)	Day 90 (*n*=44) Mean (SD)	*P*
Total WORMS score	66.57 (36.06)	65.14 (35.62)	<0.0001
Cartilage signal and morphology	31.2 (13.69)	31.18 (13.7)	0.317
Bone marrow abnormality	7.55 (5.21)	7.55 (5.21)	1
Subarticular cyst	2.86 (3.33)	2.86 (3.33)	1
Bone attrition	3.45 (4.47)	3.45 (4.47)	1
Osteophytes	16.41 (14.77)	16.25 (14.6)	0.317

Discussion

Many of the previous studies have suggested that IAHA injections can promote endogenous hyaluronic acid production in synovial fluid in OA-affected knees, thus improving the cartilage structural composition and integrity.[10] A substantial decrease in the quality of evidence has caused inconsistency in published literature in considering visco-supplementation as a mainstream treatment for knee OA.[11]

In our study population, the patient's ages were in a range of 36–76 with a mean age of 52.02 (9.5). 73% of the participants of the study were females. These demographic characteristics were typical of knee OA as supported by previous works of the literature.[12,13] The BMI of the study population ranged from 20.9 to 34.2 (kg/m^2) with a mean BMI of 25.85 (2.94), supporting the works of the literature suggesting that obesity increases the prevalence of OA.[14,15] Of the 44 subjects who completed the study, 61% were having grade III knee OA and 39% had grade II knee OA. Grade I and grade II of knee OA by KL grading were not included in this study.

The chief complaint of patients enrolled for the study or the main reason for seeking medical attention was pain in the knee, followed by joint stiffness and difficulty in doing daily activities. The VAS score assessed the severity of pain in the subjects, and the mean score calculated at day 0, 8.53 (0.81), showed statistically significant improvement in pain (*P* value .0001) by day 90, 5.97 (0.87). Even though the intensity of pain in study subjects was significantly reduced, it never became zero.

The KOOS score evaluated the knee status of the subjects in different domains and was assessed to determine the response to the treatment. The KOOS pain sub-score of 27.58 (16.45) on day 0 improved to 60.01 (16.33) by day 90 after a single-dose injection of HMW-IAHA with a statistical significance of *P* value <.0001, and this was correlated well with the decrease in pain severity according to VAS. Clinical improvement was seen in the KOOS symptom sub-score, which was statistically significant (*P* value <.0001) with an improvement from a baseline value of 28.74 (17.43) to 62.89 (16.76) by day 90. The effect of visco-supplementation on activities of daily living, sports, recreation function, and quality of life also showed a statistically significant improvement from baseline to follow-up scores on day 90 (*P* value <.0001). The KOOS global score at the baseline, 27.33 (15.18), improved by day 90, 57.26 (14.26), with a statistical significance of *P* value <.0001 at all endpoints. This correlated well with the single-arm clinical trial conducted by Gupta *et al.*[16] to evaluate the efficacy and safety of visco-supplementation where improvement was reflected in all the domains of KOOS at following visits. Our study showed statistically significant

Table 4: Zone-wise changes in synovitis and cartilage and signal morphology from day 0 to day 90

MRI changes	Zones	Day 0 (*n*=44) Mean (SD)	Day 90 (*n*=44) Mean (SD)	*P*
Synovitis	MFTJ	2.3 (1.61)	1.3 (1.3)	<0.0001
	LFTJ	0.16 (0.37)	0.14 (0.35)	0.317
	PFJ	0.34 (0.83)	0.23 (0.64)	0.102
	S region	0.05 (0.3)	0.05 (0.3)	1
	Total synovitis score	2.91 (2.18)	1.77 (1.85)	<0.0001
Cartilage signal and morphology	MFTJ	11.02 (6.26)	10.91 (6.22)	0.317
	LFTJ	9.99 (6.38)	9.99 (6.38)	1
	PFJ	10.35 (4.36)	10.28 (4.39)	0.180
	Total cartilage integrity score	31.2 (13.69)	31.18 (13.7)	0.317

improvement in all the clinical parameters assessed and was consistent with a similar study conducted by Pal *et al.*,[17] where significant improvement from baseline WOMAC score (assessing pain, stiffness, and physical function) was observed. A similar effect was noted by van Tial *et al.*[18] in their study, where KOOS values showed significant improvement from baseline to 14 weeks after visco-supplementation.

A semi-quantitative scoring method, WORMS, was used in our study to assess the morphological changes in the knee joint to get a whole organ evaluation of the knee based on MRI images. We did not observe any radiological change in the subarticular bone marrow abnormality, subarticular cysts, bone attrition, and ligaments in the study population from the baseline scoring. It is well established that the loss of cartilage and derangement in synovial fluid integrity leads to infiltration of cytokines to subchondral bone contributing to the progression of OA. This vicious cycle creates an abnormal mechanical environment in the affected synovial joint, which extends to a stage where subchondral bone recovery is not possible.[19,20] Some improvement was observed in the cartilage signal and morphology in the MFTJ [mean (SD) on day 0: 11.02 (6.26) and day 90: 10.91 (6.22)] and PFJ [mean (SD) on day 0: 10.35 (4.36) and day 90: 10.28 (4.39)] compartments, whereas no changes were evident in the LFTJ compartment. Thus, the change in total cartilage signal and morphology score on day 90 after visco-supplementation was statistically insignificant with a *P* value of 0.317. Statistically insignificant changes were also present in the osteophytes [mean (SD) day 0 16.25 (14.6); day 90 16.41 (14.77)] and menisci [mean (SD) day 0 2.14 (2.21); day 90 2.02 (2.16)] with *P* values of 0.317 and 0.180, respectively. While the above parameters failed to show a significant change, synovitis had a statistically significant improvement from day 0 to day 90 with a *P* value <.0001. Even though the change in synovitis score in LFTJ (*P* value 0.317) and PFJ compartments (0.102) was statistically insignificant, the mean score at the MFTJ compartment was significantly better and improved from 2.3 (1.61) to 1.3 (1.3) on follow-up MRI with a *P* value of <.0001.

In our study, the total WORMS score, which gives an overall analysis of the knee joint structural morphology, showed significant improvement (*P* value <.0001) between the day 0, 66.57 (36.06), and day 90, 65.14 (35.62), values. This corroborated well with the findings ofNandi *et al.*,[21] where the total WORMS score improved from baseline at MFTJ and PFJ after weekly injections of HMW hyaluronic acid for 3 weeks on 6 months follow-up.

Our study observed that even if there is no evident regrowth of cartilage post visco-supplementation, hyaluronic acid's chondroprotective effects reduced the cartilage destruction rate. Despite being a single-arm, short-term study, the therapeutic effects of our study were consistent throughout the study period.

The literature suggests that the cartilage lacks vasculature and innervation and therefore is not capable of producing pain and inflammation. Thus, it was formulated that the source of pain in degenerative diseases is non-cartilaginous structures like synovium, capsule, subchondral bone, and periarticular muscles.[11] The structural changes were seen in the advanced cases second to these findings. A pilot study conducted by Vincent *et al.*[22] measured the synovial fluid biomarkers for inflammatory and oxidative stress following visco-supplementation and showed improvement in synovial fluid viscosity and inflammation. Another study conducted by Henrotin *et al.*[10] also showed a significant decrease in WORMS synovitis score post visco-supplementation along with an improvement in global KOOS score and subscales. In our study, there was a statistically significant improvement in synovitis, following visco-supplementation, which emphasizes the anti-inflammatory property of exogenous HA.[23]

This was a single-arm study with no control arm as this was a proof-of-concept study. The results of this study, despite its limitation in time, sample size, and the lack of a control arm, do warrant the safety and efficacy of visco-supplementation in the treatment of knee OA, and we hope that the scope of research can be further expanded and larger studies can be conducted with greater effort. In our study, no adverse events were reported, except for the injection site pain in 33 study subjects for about 3 days, which was controlled with acetaminophen.

It may be concluded from our study that a single dose of intra-articular injection with high-molecular-weight hyaluronic acid produces statistically significant improvement in the pain, stiffness, activities of daily living, and knee-related quality of life as well as is effective in maintaining the articular cartilage integrity and reducing synovial inflammation at least for 3 months, although it fails to increase the cartilage thickness. The outcomes derived

from our study were in conjunction with the literature supporting the chondroprotective and anti-inflammatory effects of exogenous hyaluronic acid supplementation, thus suggesting the safe and effective use of visco-supplementation without any severe adverse effects or adverse drug reactions. Visco-supplementation should therefore continue to be part of the array of treatment options available for the management of knee OA.

List of abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
LFTJ	Lateral femorotibial joint
MFTJ	Medial femorotibial joint
PDFS	Proton density fat saturation
PFJ	Patellofemoral joint

Declaration of patient consent

The study conducted after getting informed consent from the subject in the language which he/she understand and no images of patients were used in the study.

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Name	Role
Dr. Shweta Jain	Concept design
Dr. Anjuna R	Radiological evaluation
Dr. Ayush Khandelwal	Radiological evaluation
Dr. Joyutpal Biswas	Radiological evaluation

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Nil.

Conflicts of interest

There are no conflicts of interest.

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