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ORIGINAL ARTICLE

Efficacy of Single-dose Intra-articular Injection of High-molecular-weight Hyaluronic Acid in Patients suffering from Primary Osteoarthritis of Knee

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ABSTRACT

Aim: To find the effectiveness of single-dose intra-articular (IA) injection of high-molecular-weight hyaluronic acid (HMWHA) in patients suffering from primary osteoarthritis (OA) of knee.

Study design: A randomized control trial.

Duration of the study: One-and-a-half years, commencing from October 2014.

Settings: Physical Medicine and Rehabilitation (PMR) Department, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India.

Study population: All patients suffering from OA knee, who fulfilled the American College of Rheumatology (ACR) criteria for classification of idiopathic OA knee and attending the department during the study period.

Materials and methods: Sixty-five patients were randomized to receive either visco-supplementation with single-dose IA injection of HMWHA (study group) or methylprednisolone (control group) and follow-up was done at 1, 3, and 6 months. Outcome measures were done with Western Ontario and McMaster University (WOMAC) and visual analog scale (VAS) for pain.

Results: Both the groups showed significant improvement in both WOMAC and VAS pain score at the end of 3 months. But at the end of 6 months, improvement in terms of WOMAC ($p = 0.09$) and VAS pain ($p = 0.07$) scores in control group was not significant, whereas the study group maintained statistically significant improvement.

Conclusion: A single dose of IA HMWHA is effective in reducing pain and disability in patients with primary OA of knee.

Keywords: Disability, Hyaluronic acid, Primary osteoarthritis of knee, Visco-supplementation, Visual analog scale pain, Western Ontario and McMaster University score.

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INTRODUCTION

Osteoarthritis is a chronic disorder of synovial joints in which there is progressive softening and disintegration of articular cartilage accompanied by new growth of cartilage and bone at the joint margins, cyst formation and sclerosis in the subchondral bone, mild synovitis, and capsular fibrosis. It is the most common joint disease and it can affect any synovial joint in the body but the most common joint is knee. Osteoarthritis is classified into primary and secondary types. Primary or idiopathic is when it develops without any apparent abnormalities. In primary, the degenerative process of "wear-and-tear" occurs with aging.[1]

The pathophysiological mechanism in primary OA is believed to be failure of an otherwise normal joint because of excessive load.[2] Histologically, small tears known as fibrillations and larger tears known as clefts both develop. These defects begin in the superficial zone of cartilage, extend into the transitional zone, and are also propagated by enzymatic breakdown of cartilage, leading to large areas of cartilage loss, thus essentially exposing the underlying subchondral bone. The breakdown of major macromolecules, such as collagen and proteoglycan (PG), is triggered by enzymatic activity in which matrix metalloproteinase (MMP) plays a dominant role. There is alteration in synovial fluid hyaluronic acid (HA), including a decrease in the concentration of normal molecular weight hyaluronate and the production of abnormal hyaluronate, resulting in defective synovial fluid viscosity, elasticity, barrier exclusion, and shielding.[3]

Strengthening of quadriceps and hamstring muscles reduces pain and disability in OA knee.[4] Other physical modalities including transcutaneous electrical nerve stimulation, therapeutic heat, and therapeutic cold can also be used. Pain relief and joint protection can also be achieved through structural support and realignment from the use of orthotic devices.[5] Pharmacological modalities

of treatment include nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 inhibitors, opioids, IA injection of corticosteroid, and HA. In patients with advanced stage or who are not obtaining adequate pain relief or functional improvement from a combination of nonpharmacological and pharmacological treatment, then they should be considered for surgery.[6]

The Osteoarthritis Research Society International recommended visco-supplementation treatment of OA knee with HA.[6] Hyaluronic acid is a high molecular weight biopolysaccharide found in most connective tissues and is particularly concentrated in synovial fluid, the vitreous fluid of eye, umbilical cord, and chicken comb. It is naturally synthesized by a class of integral membrane protein called hyaluronan synthase and degraded by a family of hyaluronidase.[7] Exogenous HA enhances chondrocyte HA and PG synthesis, reduces the production and activity of proinflammatory mediators, MMP, and also alters the behavior of immune cells.[8] In addition to relieving the symptoms, it also modifies the structure of the diseased joint and the rate of OA disease progression.[9]

Hyaluronic acid can be of low-molecular-weight HA with a mass of 0.8 to 8×10^5 Da or HMWHA with mass greater than 1×10^6 Da.[10] Studies show that HMWHA inhibits the expression of proinflammatory cytokines like interleukin-1α, interleukin-6, and tumor necrosis factor-α.[11] It is more effective in blocking the decrease in PG in damaged cartilage and also in terms of restoring PG content in the cartilage. Recent clinical data have demonstrated that the anti-inflammatory and chondroprotective actions of HA visco-supplementation reduce pain, from 4 to 14 weeks after injection, while improving patient function.[12]

This study was conducted to find out the efficacy of single-dose IA injection of HMWHA in patients suffering from primary OA of knee.

MATERIALS AND METHODS

The study was a randomized control trial conducted at the Department of Physical Medicine and Rehabilitation, RIMS, Imphal, Manipur, India, for a duration of 1 and ½ years commencing October 2014. Patients with primary OA of knee fulfilling the ACR 1986 criteria attending the Department of Physical Medicine and Rehabilitation, RIMS, were included. Exclusion criteria included associated comorbid conditions, such as stroke, heart disease, and vascular diseases, patients with inflammatory disease of joints like rheumatoid arthritis, recent knee trauma patients with body mass index (BMI) > 30, age >70 years, patients with cognitive impairment, Kellgren Lawrence grade IV OA knee (radiological), history of recent knee IA steroid injection within the last 4 weeks, knee pain VAS < 4, and severe malalignment of knee. All the participants were informed about the nature of the study, and those who agreed to participate were asked to sign the informed consent form. The approval of the Institutional Ethics Committee, RIMS, Imphal, was taken before starting the study.

Outcome Measures

The treatment outcome was assessed with WOMAC score and VAS for pain; WOMAC version 3.1 in Likert scale was used, consisting of three subscales: pain (5 items), stiffness (2 items), physical function (17 items). Each item was measured in five-point Likert scale, with minimum WOMAC score 0 and maximum 96.[13] Using a 100 mm line, VAS for pain was assessed with two endpoints representing "no pain" and "worst pain imaginable." Patients are asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The distance along the line from the "no pain" mark is then measured with a ruler giving a pain score out of 100.

Method of Recruitment

After getting informed consent, patients were allocated into two groups: Group I = HMWHA group and group II = steroid (methylprednisolone) group using a block randomization technique.

Group I received IA single dose of 6 mL HMWHA and group II received 80 mg of methylprednisolone in the affected knee of interest. In addition to IA injection, each case received quadriceps and hamstring straightening exercise and oral paracetamol was given as rescue drug.

Procedure

The patient was kept at supine position with the knee extended. Under aseptic and antiseptic condition, the injection site was marked along the superolateral aspect of patella. The needle was angled slightly toward the underside of patella and the desired drug was given. Before giving the injection any knee effusion, if present, was aspirated and after the injection the patient was kept under observation for 30 minutes (Fig. 1).

Baseline assessment and clinical examination of the patients were done at the time of entry and follow-up of the cases were done at 1, 3, and 6 months.

Data Analysis

Data collected from clinical examination, laboratory investigations, X-ray grading, VAS, and WOMAC scale were entered and analyzed using Statistical Package for the Social Sciences Windows version 21. Demographic profiles including age, occupation, duration of symptom, and BMI were analyzed and expressed in their means ±

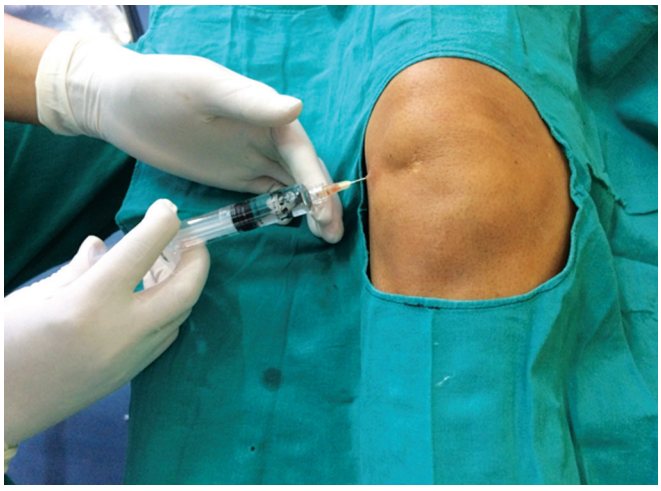


Fig. 1: Administering IA HMWHA to knee

standard deviation (SD). For continuous variables, independent t-test and Mann–Whitney U-test were used. For comparing means among one group, paired t-test and analysis of variance (ANOVA) were used; p-value < 0.05 was taken as significant.

RESULTS

During the study period, a total number of 74 cases were enrolled with 37 in each group. Six cases in the intervention group (HMWHA group) and three cases in the control group were lost in follow-up. Therefore, a total of 65 cases were included in the analysis, with 31 and 34 cases in the study and control group respectively. There were 5 males and 26 females in the intervention group with mean age of 62.06 ± 6.35 years. The control group comprised 6 males and 28 females with mean age of 58.56 ± 8.22 years. The mean duration of complaint was 8.97 ± 7.14 months and 5.41 ± 2.95 months in the HMWHA and control group respectively (Table 1).

Occupations are categorized into housewife, government employees, and self-employed. Among the occupations, housewives are more affected than any other occupation.

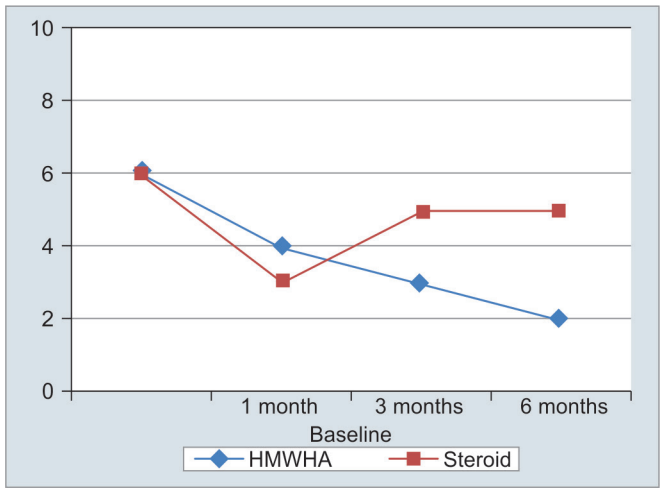
The comparison of VAS between study and control group at the time of enrolment showed no statistically significant difference (p-value > 0.05). But at the end of 1 month postinjection, there was improvement in VAS in both groups. Improvement was seen more in the control group (p-value < 0.05). At the end of 3 and 6 months, the study group maintained the improvement of VAS, which was statistically significant, whereas the control group had worsening of pain indicated by increased VAS. Graph 1 showed the VAS score of both groups at baseline, 1, 3, and 6 months follow-up.

Both the groups showed improvement in WOMAC score at 1 month postinjection, which was statistically significant. As in VAS, the improvement of WOMAC score at the end of 3 and 6 months postinjection was more in the HMWHA group than the control group, which was statistically significant (p-value < 0.05), as shown in Table 2.

Table 3 showed mean scores of outcome measures at 1, 3, and 6 months compared with baseline scores. The improvement in both VAS and WOMAC scores in the HMWHA group was significant till 6 months (p < 0.05). In the control group, the statistically significant improvement was present till 3 months but not at 6 months in both VAS (p > 0.05) and WOMAC score (p > 0.05).

Table 1: Baseline measurements of the HMWHA and steroid group

	HMWHA (n = 31)	*Steroid (n = 34)*	
Characteristics	*n (%)*	*n (%)*	*p-value*
Mean age (years) ± SD	62.06 ± 6.35	58.56 ± 8.22	0.75
Mean BMI, kg/m^2 ± SD	24.32 ± 2.17	24.47 ± 2.01	0.77
Gender			
Male	5 (16.1)	6 (17.6)	0.87
Female	26 (83.9)	28 (82.4)	
Side of affection			
Right	10 (32.3)	16 (47.1)	0.19
Left	15 (48.4)	16 (47.1)	
Both	6 (19.4)	2 (5.9)	
Occupation			
Govt.-employed	5 (16.1)	3 (8.8)	0.62
Self-employed	8 (25.8)	11 (32.4)	
Housewife	18 (58.1)	20 (58.8)	
Mean duration (months) ± (SD)	8.97 ± (7.14)	5.41 ± (2.95)	0.06
Kellgren Lawrence grade			
Grade I	0	4 (11.8)	1.30
Grade II	19 (61.3)	20 (58.8)	
Grade III	12 (38.7)	10 (29.4)	
WOMAC score, mean ± SD	41.81 ± 13.99	37.03 ± 38.50	0.06
VAS score, mean ± SD	62.6 ± 1.26	57.9 ± 1.39	0.18



Graph 1: Visual analog scale score of study participants at baseline and 1, 3, and 6 months follow-up (n = 65)

Table 2: WOMAC scores of study participants at baseline, 1, 3, and 6 months follow-up (n = 65)

	Groups		
Parameters	*Study (n = 31)*	*Control (n = 34)*	
WOMAC	*Mean (SD)*		*p-value**
Baseline	41.81 ± 13.99	37.03 ± 13.47	0.06
1 month	30.06 ± 10.63	18.68 ± 9.64	0.00
3 months	20.71 ± 7.57	30.29 ± 3.74	
6 months	18.16 ± 6.89	32.82 ± 14.32	

*Two-way mixed ANOVA

DISCUSSION

The current study showed that the mean age of the study population was 62.06 ± 6.35 and 58.56 ± 8.22 years in the intervention (HMWHA group) and control (steroid) group respectively. There were 5 males and 26 females in the HMWHA group, whereas the steroid group consisted of 6 males and 28 females. It was observed that females (83%) were more affected than males (16.9%). Similar finding was observed in the study conducted by Strand et al[14] in which 59% of the study population was female. The reason for the difference between females and males may be multifactorial and related to less cartilage volume and greater cartilage wear, overall differences in mechanical alignment, and other gender and social factors.[15]

Physical activities involving repetitive motions and high forces, such as kneeling/squatting, climbing, and heavy lifting are important risk factors for knee OA. Mechanical loading and its related structural damage are thus considered the main mechanisms of knee OA. Martin et al[16] observed occupational activities involving kneeling, squatting, lifting, climbing, sitting as risk factors for developing OA of knee. Zonunsanga et al[17] also found that time spent for knee activities, such as squatting and kneeling or knee bending activities in a day are risk factors for development of higher disability on OA knee patients. In our study, housewives were more affected than other occupations, probably because of household activities that involved squatting, bending, kneeling, lifting, etc.

Excessive loading of the joint is the most important means by which obesity causes OA. It is in the weight-bearing joints of the knee and to a lesser extent the hips that obese individuals are most at risk of developing OA. Because of the way the knee joint works, the effect of excess weight can be four or five times greater in key parts of the joint so that even modest weight gain speed up the breakdown of cartilage and increases susceptibility to OA. High BMI as a risk factor for developing OA of knee was observed by Blagojevic et al.[18] In our study, 63.1% of the study population fall under normal BMI; moreover, the present study had a small sample size. Hence, probably we could not observe the relationship of BMI and OA severity because of these reasons.

Improvement in WOMAC score after IA injection of steroid was also found in the study conducted by Leopold et al.[19] In their study, 100 patients with knee OA were randomized to receive IA injection of either Hylan G-F 20 or the corticosteroid, and they were followed for 6 months. Both the groups demonstrated improvements in baseline WOMAC scores. The scores on the VAS improved for patients receiving Hylan G-F 20 (median 70–52 mm; $p < 0.01$) but not for the patients who received the corticosteroid (median 64–52 mm; $p = 0.28$). Similar findings were observed in our study too. At the end of 6 months, HA group has significant improvement in both WOMAC and VAS ($p < 0.05$), but the improvement in control group was not significant in both WOMAC ($p = 0.09$) and VAS ($p = 0.07$) scores.

Bellamy et al[20] reviewed a Cochrane database on IA corticosteroid for treatment of OA of the knee and found that corticosteroid products provide opportunity to treat OA in individual knee joints. Their analyses supported the contention that the IA corticosteroid class is superior to placebo, though they could not confirm the long-term benefit.

In a study conducted by Huskisson and Donnelly[21] on safety and efficacy of IA HA, 100 patients with OA knee were given five doses of HA weekly. Primary efficacy criteria were pain on walking measured with VAS and Lequesne Index. At the end of 5 weeks, there was significant difference in favor of HA against placebo ($p = 0.087$). Wobig et al[22] conducted a study on the efficacy and safety of visco-supplementation with Hylan G-F 20 in a multicenter, double-masked clinical study in patients with chronic idiopathic OA of the knee. Three doses of IA injections of 2 mL Hylan G-F 20 were administered 1 week apart to 57 knees. The control group (60 knees) received 2 mL of physiologic buffered saline solution at the same intervals. Using a VAS, patients were assessed for pain during weight-bearing, pain at rest during the night,

Table 3: Comparison of mean score of outcome measures at baseline and 1, 3, and 6 months

	Group	*Baseline*	*1 month*	*3 months*	*6 months*
VAS	HMWHA	62.6 ± 12.6	41.6 ± 12.4 ($p < 0.00$)	28.4 ± 10.0 ($p < 0.00$)	24.8 ± 10.6 ($p < 0.00$)
	Steroid	57.9 ± 13.9	30.3 ± 23.80 ($p < 0.00$)	45.9 ± 13.7 ($p < 0.00$)	50.6 ± 15.7 ($p = 0.07$)
WOMAC	HMWHA	41.81 ± 13.99	30.06 ± 10.63 ($p < 0.00$)	20.71 ± 7.568 ($p < 0.00$)	20.71 ± 7.568 ($p < 0.00$)
	Steroid	37.03 ± 13.46	18.68 ± 9.64 ($p < 0.00$)	30.29 ± 13.74 ($p < 0.00$)	32.87 ± 14.32 ($p = 0.09$)

reduction of pain during the most painful movement of the knee, and treatment success. There was improvement in all six variables with Hylan G-F 20 beginning after the first injection and the improvement continued through the study endpoints. In a prospective trial conducted by Miltner et al,[23] 43 patients with osteoarthritic had changes of both knees by HA. The injected knee represented the treatment group, while the contralateral knee served as the control. The VAS value at rest was reduced from 3.83 ± 1.72 to 1.36 ± 1.42 cm and during weight-bearing from 7.57 ± 1.34 to 3.75 ± 1.32 cm in the treatment group ($p < 0.01$).

In our study too, the HMWHA group had observed improvements in both VAS and WOMAC scores from the baseline to the end of 1 month (p-value = 0.00). The improvements in VAS and WOMAC scores were maintained at the end of 3 and 6 months (p-value = 0.00). Similar findings were also observed by Leopold et al.[19] But the improvement of VAS and WOMAC scores in the control group was not significant at the end of 6 months ($p < 0.05$).

Moreland[8] studied the mechanism of IA HA and Hylans for the treatment of pain associated with knee OA, and clinical studies demonstrate various physiological effects of exogenous HA. Hyaluronic acid can reduce nerve impulses and nerve sensitivity associated with the pain of OA. In experimental OA, they found out that this glycosaminoglycan has protective effects on cartilage, which may be mediated by its molecular and cellular effects. Exogenous HA enhances chondrocyte HA and PG synthesis, reduces the production and activity of proinflammatory mediators and MMPs, and alters the behavior of immune cells. They concluded that many of the physiological effects of exogenous HA may be a function of its molecular weight. Several physiological effects probably contribute to the mechanisms by which HA and Hylans exert their clinical effects in knee OA. In our study, 8 mg of sodium hyaluronate with its molecular weight of 1.2 to 1.8 million Da which comes under HMWHA was used.

The most common acute adverse effects following IA HA include pain, warmth, and swelling. Allergic reaction and aseptic arthritis can develop within hours of injection. Bernardeau et al[24] reported two cases of acute aseptic arthritis developed after IA injection of HA. Both cases were managed with NSAID and aspiration of the effusion and recovered within 7 days.

There were no major adverse effects following IA injection of HMWHA. But majority of the cases (22 in 31) had mild increase in pain after injection of HMWHA, which were managed with paracetamol and ice pack. No infections or systemic adverse reactions were noted in the current study.

The limitations of the study are nonimage guidance injection technique, nonblinding of the study, and shorter follow-up.

With this study, it was possible to demonstrate the effectiveness of IA administration of HMWHA with regards to pain and function in patients suffering from OA. The low incidence of side effects and the safety of HA will make it suitable for the treatment of OA in elderly patients who cannot tolerate NSAIDs or for whom they are contraindicated. To evaluate the long-term effects of HA, studies with longer follow-up periods are suggested.

CONCLUSION

From the current study, it was found that single dose of IA HMWHA is effective in reducing pain and disability in patients with primary OA of knee up to 6 months. A larger sample size with longer period of follow-up will be necessary to see if the improvement is maintained for longer term.

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