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Outcome of Single Intra-Articular Injection of High- Molecular-Weight Hyaluronic Acid in Patients with Knee Osteoarthritis

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Abstract

Background: Osteoarthritis (OA) is the most common type of rheumatic disease and a leading cause of disability. Current treatments aim at alleviating these symptoms by several different methods: non-pharmacological and pharmacological treatments and invasive interventions. Among the regenerative methods, hyaluronic acid (HA) is popular now-a-days where differences exist in concentration, molecular weight, dosage, expected duration of effects and added formulations. Based on HA molecular weight, these products are classified in two groups (high and low). Due to cost effectiveness, low molecular weight HA is commonly used. To find out the outcome of single intra-articular injection of high-molecular- weight HA in patients with knee osteoarthritis. **Material & Methods:** This was a randomized clinical trial conducted among purposively selected 55 patients suffering from Knee OA attending at the Physical Medicine and Rehabilitation outpatient department, DMCH during July 2020 to June 2021. Patients were randomly allocated into two groups; group A received single dose of high molecular weight HA and designed exercise program and group B received same exercise program only. Pre-treatment and 3 weekly post treatment assessment were done up to 12 weeks in each group. In each follow up visit, pain, and functional status were measured in Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) respectively and compared between group A and group B where was considered as significant (p value <0.050. **Results:** The mean age of the participants in group A and group B were 56.8 (±9.8) and 53.3 (±7.4) years respectively where majority of the patients in both groups were female patients with overweight. In group A, VAS and WOMAC significantly decreased from base line to each follow up till 12th weeks after treatment with high-molecular-weight HA (P<0.001). In group B, VAS and WOMAC significantly decreased from base line to each follow up till 12th weeks after treatment with conservative management (P<0.001). After 6 weeks of intervention, the mean VAS scores of the patients became 4.9 ±1.1 and 6.0±1.0 in group A and group B respectively which showed significant statistical difference (P<0.001). At the end of 12 weeks, the VAS score was significantly decreased in group A (2.8±1.3) than group B (4.9±1.7) (P<0.001). After 3 weeks of intervention, the mean WOMAC scores of the patients became 71.2±6.6 and 75.0 ±4.9 in group A and group B respectively which showed significant statistical difference (P<0.001). At the end of 12 weeks, the WOMAC score was significantly decreased in group A (61.9±6.6) than group B (68.1±4.6) (P<0.001).

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Conclusion: Single intra-articular injection of high-molecular-weight Hyaluronic Acid is effective in patients with knee osteoarthritis in reducing pain and improving functional impairment. Long term and large scale research studies are needed to establish the effectiveness and safety of this procedure in patients with knee osteoarthritis.

Keywords:- Osteoarthritis (OA), High-molecular-weight Hyaluronic acid (HMW-HA), Conservative management, Visual Analogue Scale (VAS), and Western Ontario and McMaster Universities (WOMAC).

INTRODUCTION

Osteoarthritis (OA) is by far the most common form of arthritis characterized by focal loss of articular cartilage, remodeling of joint contour with enlargement of affected joints and subchondral osteosclerosis, osteophyte formation at the joint margin.[1] The prevalence of OA rises progressively with age and it has been estimated that 45% of all people develop knee OA at some point during life. There are major ethnic differences in susceptibility; the prevalence of hip OA is lower in Africa, China, Japan and Indian sub-continent than in Europeans countries, and that of knee OA is higher.[1] The incidence of symptomatic knee OA in Bangladesh was 0.9% (0.8% in men and 1.1% in women). The prevalence of knee OA in Bangladesh was more in urban affluent population (11.5%: 6.3% in male and 15.9% in female) than urban slum (9.2%: 10.4% in male and 7.8% in female) and rural population (7.5%: 6.4% in male and 8.5% in female).[2] Patients with knee osteoarthritis tend to increase their physical limitations, pain and functional restrictions with disease progression. Thus, these individuals suffer from progressive increased impact on their activities of daily living, which leads to losses in labor relations, leisure, social life and sleeping quality which leading to decrease in quality of life.[3] The current standard of care for patients with symptomatic OA includes oral anti-inflammatory drugs, physical therapy, topical anti-inflammatory gels, and intraarticular injections.[4,5] Nonsurgical treatments including exercise and weight loss are recommended due to poor symptomatic and functional outcomes with surgical management.[6] However, compliance with nonsurgical treatments is poor, and medications, such as simple analgesics and nonsteroidal anti-inflammatory drugs, are associated with adverse events.[7] Hyaluronic Acid (HA) is a naturally occurring glycosaminoglycan and a component of Synovial Fluid and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize Hyaluronic Acid and secrete into the joint. Hyaluronic Acid enhances viscosity and elastic nature of Synovial Fluid.[8] A Cochrane review and recent systematic review and meta-analysis concluded that HA had beneficial effects on pain, functional improvement.[9,10] Differences exist in concentration, molecular weight, source of HA (biological fermentation-derived HA or avian-derived HA), dosage (number of injections and intervals), expected duration of effects, cross linkage and added formulations.[11] Hyaluronic acids can be of low-molecular-weight HA with a mass of 0.8 to 8 × 105 Da or high-molecular-weight (HMWHA) with mass greater than 1×106 Da.[12] Studies show that HMWHA inhibits the expression of

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pro-inflammatory cytokines like interleukin-1α, interleukin-6, and tumor necrosis factor-α.[13] 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 reduce pain, from 4 to 14 weeks after injection, while improving patient function.[14]

Objectives

General Objective

To find out the outcome of single intra-articular injection of high-molecular-weight Hyaluronic Acid in patients with knee osteoarthritis

Specific Objective

- To determine the effectiveness of single intra-articular injection of high- molecular-weight Hyaluronic Acid regarding pain reduction in patients with knee osteoarthritis
- To measure the effectiveness of single intra-articular injection of high- molecular-weight Hyaluronic Acid regarding functional improvement in patients with knee osteoarthritis
- To compare the effectiveness of single intra-articular injection of high- molecular-weight Hyaluronic Acid over conservative management in reducing pain and improving functional impairment
- To find out the socio-demographic characteristics of the patients

MATERIAL AND METHODS

This was a controlled trial study conducted in the Department of Physical Medicine and Rehabilitation, Dhaka Medical College and Hospital, Dhaka, Bangladesh from July 2020 to June 2021. OPD patients of those who are suffering from Knee OA attending Their age was 40 to 70 in both sex.

Exclusion Criteria

- Those with diabetes mellitus, coagulation disorders, infection, immunosuppressive diseases, malignancy, receiving anticoagulant treatment.
- Tubercular arthritis, Crystalline arthritis, Inflammatory disease,
- Overlying skin infection, patient who had received intra-articular corticosteroid injection or PRP injection over the previous 6 months or viscosupplementation to the target knee.
- Previous joint replacement or arthroplasty on the target knee or any surgical procedure scheduled in the next six months.

Study Procedure

This randomized controlled trial was conducted in the department of Physical Medicine and Rehabilitation, Dhaka Medical College and Hospital (DMCH), Dhaka for one-year duration following approval from the Ethical Review Committee (ERC), DMCH. Patients were randomly allocated in two groups named as group A and group B by lottery. Two small paper marking group A and group B were kept in a jar. Patients were asked to pick up one of the two papers. The picked up marking were patient's group.

Group- A

In this group, patients were allocated with single intra-articular injection of high-molecular-weight Hyaluronic Acid (60 mg / 4

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ml), exercises, ADLs instruction and paracetamol. Patient was placed in a supine position with the knee in full extension. Under aseptic conditions HA, 60 mg / 4 ml preparations were given in supra-patellar pouch through a supra-lateral approach with a pre-filled syringe with 3ml local anesthetic (2% Lidocaine).

Figure 1: Administration of high molecular weight HA

After injection, the patient was sent home and advised to take one day of rest and apply ice to the area. The patients were permitted to carry out tolerable daily activities after the first day. As a pain reliever, paracetamol was recommended.

Group- B

In this group, patients were allocated for conservative management which included Nonsteroidal anti-inflammatory drugs (NSAID), muscle relaxant, therapeutic exercise, knee brace during activity with ADL instructions. Therapeutic exercise included quadriceps strengthening exercise, Vastus Medialis Oblique strengthening exercise, hamstring stretch exercise and hamstring strengthening exercise Quadriceps strengthening exercise was given in the form of extension of knees. For Vastus Medialis Oblique strengthening exercise, patients had to do squat exercises with isometric hip adduction.

For hamstring exercise patients had to be in supine position with a towel. Perform stretch leg rising with one extremity and apply stretch force by pulling on the towel with a dorsiflex position of foot.

Figure 2: Hamstring stretch exercise

For hamstring strengthening exercise patients had to sit on a chair and tighten the muscle by pressing the back of the heel on the front leg of the chair.

Figure 3: Hamstring strengthening exercise

Patients performed each exercise 5-10 repetition per session 2 times daily. While doing each

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exercise, hold the position for 5 seconds and then rest for up to 10 seconds. For all patients, instruction for activity of daily living (ADLs) was prescribed As a pain reliever, . paracetamol was recommended.

Data analysis

The data collected from the patients were analyzed. The statistical analysis was conducted using SPSS version 25 statistical software. Associations of categorical data were assessed using Chi square test while associations of continuous data were assessed using Student's t test and paired sample t test.

Ethical Consideration

Ethical clearance was taken from the Ethical Review Committee (ERC) of DMCH. After the approval of research protocol by the committee, permission for the study was taken from the Department of Physical Medicine and Rehabilitation, DMCH. Informed written consent was taken from all patients after adequate explanation of the purpose of the study. They were assured of protection of their autonomy, privacy and confidentiality.

RESULTS

[Table 1] showed that in group A, 9(31.0%) patients were from ≤50 year's age group and another 9(31.0%) patients were from 51-60 year's age group while in group B, 10(38.5%) patients were from ≤50 year's age group and 12(46.2%) patients were from 51- 60 year's age group. There was no statistical difference regarding age between two groups as the P value was 0.166. The mean ages of the patients were 56.8 ±9.8 and 53.3 ±7.4 years in group A and group B respectively (P=0.148).

[Table 2] showed that in group A, 23(79.3%) patients were female while in group B, 15(57.7%) patients were female. There was no statistical difference regarding gender between two groups as the P value was 0.083.

[Table 3] showed that 28(96.6%) and 24(92.3%) patients had grade 2 OA knee according to Kellgren-Lawrence grade in group A and group B respectively. There was no statistical difference regarding Kellgren-Lawrence grade between two groups as the P value was 0.598 (obtained by Fisher Exact test).

[Table 4] showed that 13(44.8%) patients in group A and 17(65.4%) patients in group B had over weight. There was no statistical difference regarding BMI between two groups as the P value was 0.311.

[Table 5] showed that 14(48.3%) and 17(65.4%) patients had knee OA on right side in group A and group B respectively. There was no statistical difference regarding side involvement between two groups as the P value was 0.201.

[Table 6] showed that in group A, VAS significantly decreased from base line (8.3±0.7) to 3 weeks (6.3±0.9) after treatment with high molecular weight HA. The VAS score further decreased in each follow up. Finally, at 12th week, it decreased to 2.8±1.3 which was statistically significantly different to baseline VAS scores. Therefore, it could conclude that high molecular weight HA (at 12th week follow up) elicits a statistically significant decrease in VAS scores.

[Table 7] showed that in group B, VAS significantly decreased from base line (8.0±0.5) to 3 weeks (6.9±0.8) after treatment with conservative management (P <0.001). The VAS score further decreased in each follow up. Finally, at 12th week, it decreased to 4.9±1.7

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which was statistically significantly different to baseline VAS scores.

[Table 8] showed that in group A, WOMAC scores significantly decreased from base line (78.1±6.3) to 3 weeks (71.2±6.6) after treatment with high molecular weight HA (P <0.001). The WOMAC score further decreased in each follow up. Finally, at 12th week, it decreased to 61.9 ±6.6 which was statistically significantly different to baseline WOMAC score. Therefore, it could conclude that high molecular weight HA (at 12th week follow up) elicits a statistically significant decrease in WOMAC scores.

[Table 9] showed that in group B, WOMAC significantly decreased from base line (80.1±6.1) to 3 weeks (75.0 ±4.9) after treatment with conservative management. The WOMAC score further decreased in each follow up. Finally, at 12th week, it decreased to 68.1±4.6 which was statistically significantly different to baseline WOMAC scores.

[Table 10] showed that the mean Visual Analogue Scale (VAS) scores of the patients were 8.3±0.7 and 8.0±0.5 at baseline in group A and group B respectively. There was no statistical difference regarding VAS scores between two groups as the P value was 0.110 (obtained by Student-t test). After 6 weeks of intervention, the mean VAS scores of the patients became 4.9±1.1 and 6.0 ±1.0 which showed significant statistical difference. At the end of 12 weeks, the VAS score was significantly decreased in group A (2.8±1.3) than group B (4.9±1.7).

[Table 11] showed that the mean WOMAC scores of the patients were 78.1 ±6.3 and 80.1±6.1 at baseline in group A and group B respectively. There was no statistical difference regarding WOMAC scores between two groups as the P value was 0.304 (obtained by Student-t test). After 3 weeks of intervention, the mean WOMAC scores of the patients became 71.2±6.6 and 75.0 ±4.9 which showed significant statistical difference. At the end of 12 weeks, the WOMAC score was significantly decreased in group A (61.9 ±6.6) than group B (68.1±4.6).

Table 1: Comparison of age between two groups. (N=55)

Age (in years)	Group A (n=29)	Group B (n=26)	P value
≤50 yrs.	9(31.0%)	10(38.5%)	0.166
51-60	9(31.0%)	12(46.2%)	
61-70	11(37.9%)	4(15.4%)	
Mean ±SD	56.8 ±9.8	53.3 ±7.4	

Table 2: Comparison of gender between two groups. (N=55)

Gender	Group A (n=29)	Group B (n=26)	P value
Male	6(20.7%)	11(42.3%)	0.083
Female	23(79.3%)	15(57.7%)	

Table 3: Comparison of Kellgren-Lawrence grade between two groups. (N=55)

Kellgren-Lawrence	Group A (n=29)	Group B (n=26)	P value
Grade			
2	28(96.6%)	24(92.3%)	0.598
3	1(3.4%)	2(7.7%)	

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Table 4: Comparison of Body Mass Index (BMI) between two groups. (N=55)

BMI	Group A (n=29)	Group B (n=26)	P value
Normal	9(31.0%)	6(23.1%)	0.311
Overweight	13(44.8%)	17(65.4%)	
Obese	7(24.1%)	3(11.5%)	

Table 5: Comparison of side involvement between two groups. (N=55)

Side involvement	Group A (n=29)	Group B (n=26)	P value
Right	14(48.3%)	17(65.4%)	0.201
Left	15(51.7%)	9(34.6%)	

Table 6: Comparison of pain by Visual Analog Scale (VAS) score in group A (n=29)

Visual Analog Scale (VAS) score	Mean ± SD	P value
Week 0 vs Week 3		
Week 0	8.3±0.7	<0.001
Week 3	6.3±0.9	
Week 0 vs Week 6		
Week 0	8.3±0.7	<0.001
Week 6	4.9 ±1.1	
Week 0 vs Week 9		
Week 0	8.3±0.7	<0.001
Week 9	4.1±1.2	
Week 0 vs Week 12		
Week 0	8.3±0.7	<0.001
Week 12	2.8±1.3	

Table 7: Comparison of pain by Visual Analog Scale (VAS) score in group B (n=26)

Visual Analog Scale (VAS) score	Mean ± SD	P value
Week 0 vs Week 3		
Week 0	8.0±0.5	<0.001
Week 3	6.9±0.8	
Week 0 vs Week 6		
Week 0	8.0±0.5	<0.001
Week 6	6.0 ±1.0	
Week 0 vs Week 9		
Week 0	8.0±0.5	<0.001
Week 9	5.5±1.4	
Week 0 vs Week 12		
Week 0	8.0±0.5	<0.001
Week 12	4.9±1.7	

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Table 8: Comparison of WOMAC score in group A (n=29)

WOMAC score	Mean ± SD	P
Week 0 vs Week 3		
Week 0	78.1 ±6.3	<0.001
Week 3	71.2 ±6.6	
Week 0 vs Week 6		
Week 0	78.1 ±6.3	<0.001
Week 6	69.4 ±7.1	
Week 0 vs Week 9		
Week 0	78.1 ±6.3	<0.001
Week 9	66.0 ±7.2	
Week 0 vs Week 12		
Week 0	78.1 ±6.3	<0.001
Week 12	61.9 ±6.6	

Table 9: Comparison of pain by WOMAC score in group B (n=26)

WOMAC score	Mean ± SD	P value
Week 0 vs Week 3		
Week 0	80.1 ±6.1	<0.001
Week 3	75.0 ±4.9	
Week 0 vs Week 6		
Week 0	80.1 ±6.1	<0.001
Week 6	72.7 ±5.0	
Week 0 vs Week 9		
Week 0	80.1 ±6.1	<0.001
Week 9	70.1 ±4.8	
Week 0 vs Week 12		
Week 0	80.1 ±6.1	<0.001
Week 12	68.1 ±4.6	

Table 10: Comparison of VAS score between two groups. (N=55)

VAS score	Group A	Group B	P value
	Mean ±SD	Mean ±SD	
Week 0	8.3±0.7	8.0±0.5	0.110
Week 3	6.3±0.9	6.9±0.8	0.028
Week 6	4.9 ±1.1	6.0 ±1.0	<0.001
Week 9	4.1±1.2	5.5±1.4	<0.001
Week 12	2.8±1.3	4.9±1.7	<0.001

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Table 11: Comparison of WOMAC scores between two groups at baseline. (N=22)

WOMAC	Group A	Group B	P value
	Mean ±SD	Mean ±SD	
Week 0	78.1 ±6.3	80.1 ±6.1	0.304
Week 3	71.2 ±6.6	75.0 ±4.9	0.018
Week 6	69.4 ±7.1	72.7 ±5.0	0.053
Week 9	66.0 ±7.2	70.1 ±4.8	0.015
Week 12	61.9 ±6.6	68.1 ±4.6	<0.001

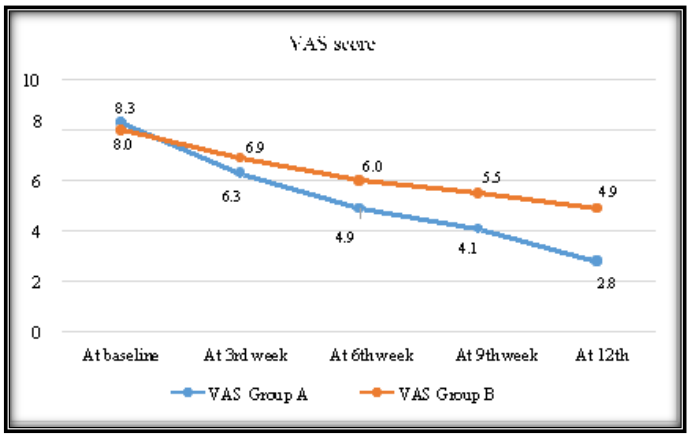

Figure 4: VAS scores of patients(N=55)

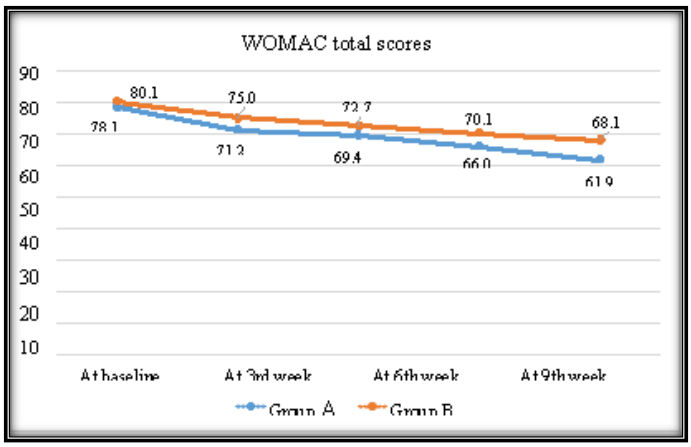

Figure 5: WOMAC total scores of group A and group B (N=55)

DISCUSSION

Osteoarthritis is a degenerative joint disease that occurs primarily in older individuals, characterized by erosion of the articular cartilage, morphologic alterations of the synovial membrane, hypertrophy of bone at the margins, subchondral sclerosis, a range of biochemical and and joint capsule.[15] The present randomized clinical trial had been conducted among 55 patients with knee OA to find out the outcome of single intra-articular injection of high-molecular-weight Hyaluronic Acid in patients with knee osteoarthritis. At the end of 12 weeks follow up, it was found that high-molecular-weight Hyaluronic Acid significantly reduced pain and improved functional impairment compared to conservative management. Age is the most potent risk factor for OA.[16] In table 1, it was shown that in group A, 9 (31.0%) patients were from ≤50 year's age group and another 9 (31.0%) patients were from 51-60 year's age group while in group B, 10(38.5%) patients were from ≤50 year's age group and 12 (46.2%) patients were from 51-60 year's age group. The mean age of the patients was more than 50 years which matched the Bangladeshi study of Moniruzzaman, et al. (2018),[17] where they also found that the mean age of the patients was more than 50 years. In other studies, similar finding was also reported.[18,19,20,21] In table III, it was presented that majority of the patients were found female which matched other studies.[22] As likely as men to develop OA women are about twice. Overall differences in mechanical

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alignment, and other gender and social factors, the reason for the difference between females and males may be multifactorial and related to less cartilage volume and greater cartilage wear.[23] Systematic review reported that physical work activities (especially kneeling, squatting, lifting, and climbing) can cause and/or aggravate knee OA.[24] In table II, it was found that housewives were more affected than patients involved in other occupations, probably because of household activities that involved squatting, bending, kneeling, lifting, etc. Moniruzzaman, et al (2018),[17] was observed 60.0% of their study participants were housewife, followed by sedentary worker (33.3%). Other study also had same observation.[19] [Table 3] showed that 28 (96.6%) and 24(92.3%) patients had grade 2 OA knee according to Kellgren-Lawrence grade in group A and group B respectively. Others belonged to grade 3 OA knee according to Kellgren-Lawrence grade. Other studies had patients with grade 1 OA knee according to Kellgren-Lawrence grade which the present study missed due to the purposive selection criteria of patients.[25] Excessive loading of the joint is the most important means by which obesity causes OA. Table IV showed that majority of the patients were over weighted and obese which matched other studies.[18,19,20,21] [Table 5] showed that 14(48.3%) and 17(65.4%) patients had knee OA on right side in group A and group B respectively and there was no statistical difference regarding side involvement between two groups. The insignificant p value of independent variables indicated that both groups were identical which further justify our randomization process. [Table 6] showed that in group A, VAS significantly decreased from base line (8.3±0.7) to 3 weeks (6.3±0.9) after treatment with high molecular weight HA. The VAS score further decreased in each follow up. Finally, at 12th week, it decreased to 2.8±1.3 which was statistically significantly different to baseline VAS scores. Therefore, it could conclude that high molecular weight HA (at 12th week follow up) elicits a statistically significant decrease in VAS scores. The content of synovial fluid, in the presence of osteoarthritis, has a decreased concentration and molecular weight of hyaluronic acid. The rationale for the intraarticular injection of hyaluronic acid is to restore the viscoelasticity of synovial fluid by providing exogenous HA thus helping to augment the flow of synovial fluid, normalize the synthesis and inhibit the degradation of endogenous hyaluronic acid, and relieve joint pain.[26] [Table 8] showed that in group B, VAS significantly decreased from base line (8.0±0.5) to 3 weeks (6.9±0.8) after treatment with conservative management. The VAS score further decreased in each follow up. Finally, at 12th week, it decreased to 4.9±1.7 which was statistically significantly different to baseline VAS scores. The study of Anwer & Alghadir (2014),[18] demonstrated that isometric quadriceps exercises brought significant gains in strength of the quadriceps muscle after training program. By spreading the forces out over a greater area, strong muscles stabilize the joints in a proper alignment, attenuate shocks that are transmitted to the joints and minimize the effect of impact. So it may be hypothesized that improvement in muscle strength is one of the main causes of reduced pain and disability. [Table 9] shows that in group A, WOMAC scores significantly decreased from base line (78.1±6.3) to 3 weeks (71.2±6.6) after treatment with high molecular weight HA. The WOMAC score further decreased in each follow up.

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Finally, at 12th week, it decreased to 61.9 ±6.6 which was statistically significantly different to baseline WOMAC scores. Studies showed that high molecular weight hyaluronic acid inhibits the expression of proinflammatory cytokines like interleukin-1α, interleukin-6, and tumor necrosis factor-α. It is more effective in blocking the decrease in PG in damaged cartilage and also in terms of restoring PG content in the cartilage. After injection recent clinical data have demonstrated that the anti-inflammatory and chondroprotective actions of HA visco-supplementation reduce pain, from 4 to 14 weeks, while improving patient function.[14] [Table 10] shows that in group B, WOMAC significantly decreased from base line (80.1±6.1) to 3 weeks (75.0±4.9) after treatment with conservative management. The WOMAC score further decreased in each follow up. Finally, at 12th week, it decreased to 68.1 ±4.6 which was statistically significantly different to baseline WOMAC scores. The prospective study of Hafez, et al. (2013),[27] reported that strengthening the hamstring muscles in addition to strengthening the quadriceps muscles proved to be beneficial for perceived knee pain, range of motion, and decreasing the limitation of functional performance of patients with knee OA. [Table 11] and figure I shows that there was no statistical difference regarding VAS scores between two groups. After 6 weeks of intervention, the mean VAS scores of the patients became 4.9±1.1 and 6.0±1.0 in group A and group B respectively which showed significant statistical difference. At the end of 12 weeks, the VAS score was significantly decreased in group A (2.8±1.3) than group B (4.9±1.7). The prospective, randomized, placebo-controlled trial of Dougados, et al. (1993),[28] suggested that intra-articular injections of the high molecular weight hyaluronic acid may improve clinical condition and have a long-term beneficial effect in patients with osteoarthritis of the knee. Yengkhom, et al (2017),[19] also observed that the VAS scores significantly reduced after administration of high-molecular-weight Hyaluronic Acid. [Table 11] and figure II showed that the mean WOMAC scores of the patients were 78.1±6.3 and 80.1±6.1 at baseline in group A and group B respectively. There was no statistical difference regarding WOMAC scores between two groups as the P value was 0.304. After 3 weeks of intervention, the mean WOMAC scores of the patients became 71.2±6.6 and 75.0±4.9 in group A and group B respectively which showed significant statistical difference. At the end of 12 weeks, the WOMAC score was significantly decreased in group A (61.9±6.6) than group B (68.1±4.6). This greater efficacy of high-molecular-weight Hyaluronic Acid might be due to the fact that it restores normal biochemical properties/ characteristics in various joint structures, resulting in improved pain control and function. On the other hand, though exercise has proven benefit in reduction of pain and improvement of functional status, it was difficult for patients to adhere with exercise program especially when majority of the patients were housewives. Moreover, on the exercise group, one fourth of the patients were day laborer for whom low educational status might be a matter of obstacle to understand and follow the instructions properly. The study of Hermans, et al (2019),[20] observed that adding intra-articular injections with a high-molecular-weight Hyaluronic Acid derivative to usual care treatment in an everyday clinical setting resulted in statistically significant more

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responders to therapy. However, Chevalier, et al. (2010),[22] did not find any difference between high molecular weight hyaluronic acid and placebo regarding WOMAC function though they stated that there was a modest superiority of high molecular weight hyaluronic acid over the placebo for pain at 26 weeks. The study of Chevalier, et al (2010),[22] included older patients with Kellgren–Lawrence grade I, II and III while the patients of the present study was younger than that study and most of the patients had Kellgren–Lawrence grade II. Chevalier, et al. (2010),[22] recommended that in daily practice, the favorable benefit/risk profile of a single injection of 6 ml hylan G-F 20 has the major advantage of decreasing the number of injections from three to five to only one. There were no major adverse effects following injection of high molecular weight hyaluronic acid. However, three patients complained of mild pain after injection which were managed with paracetamol and ice pack. No infections or systemic adverse reactions were noted in the current study. This randomized controlled trial demonstrated that significant pain reduction and functional improvement were achieved in both groups. Group A showed significant improvement over group B in pain reduction (VAS) and functional status (WOMAC).

Limitations of the Study

Some limitations were perceived while planning and conducting the study, Likes-Long term follow up could not be done, single center study & lack of ultrasonography guided injection facilities.

CONCLUSIONS

It is concluded that single intra-articular injection of high-molecular-weight Hyaluronic Acid is effective in patients with knee osteoarthritis in reducing pain and improving functional impairment. High molecular weight hyaluronic acid would be an effective treatment for patients with OA knee in low resources setting hospitals. Long term and large scale research studies are needed to establish the effectiveness and safety of this procedure in patients with OA knee. Long term follow up could not be done.

REFERENCES

1. Joshi VL, Chopra A. Is there an urban-rural divide? Population surveys of rheumatic musculoskeletal disorders in the Pune region of India using the COPCORD Bhigwan model. J Rheumatol. 2009;36(3):614-22. doi: 10.3899/jrheum.080675.
2. Haq SA, Davatchi F. Osteoarthritis of the knees in the COPCORD world. Int J Rheum Dis. 2011;14(2):122-9. doi: 10.1111/j.1756-185X.2011.01615.x.
3. Sutbeyaz ST, Sezer N, Koseoglu BF, Ibrahimoglu F, Tekin D. Influence of knee osteoarthritis on exercise capacity and quality of life in obese adults. Obesity (Silver Spring). 2007;15(8):2071-6. doi: 10.1038/oby.2007.246.
4. Pham T, Maillefert JF, Hudry C, Kieffert P, Bourgeois P, Lechevalier D, et al. Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis. A two-year prospective randomized controlled study. Osteoarthritis Cartilage. 2004;12(1):46-55. doi: 10.1016/j.joca.2003.08.011.
5. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008;16(2):137-62. doi: 10.1016/j.joca.2007.12.013.
6. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin

Annals of International Medical and Dental Research
E-ISSN: 2395-2822 | P-ISSN: 2395-2814
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Orthop Relat Res. 2010;468(1):57-63. doi: 10.1007/s11999-009-1119-9.
7. Harvey WF, Hunter DJ. The role of analgesics and intra-articular injections in disease management. Med Clin North Am. 2009;93(1):201-11, xii. doi: 10.1016/j.mcna.2008.07.010.
8. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop. 2014;5(3):351-61. doi: 10.5312/wjo.v5.i3.351.
9. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006;2006(2):CD005321. doi: 10.1002/14651858.CD005321.pub2.
10. Miller LE, Block JE. US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials. Clin Med Insights Arthritis Musculoskelet Disord. 2013;6:57-63. doi: 10.4137/CMAMD.S12743.
11. Migliore A, Bizzi E, De Lucia O, Delle Sedie A, Bentivegna M, Mahmoud A, et al. Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from In Vitro and Animal Studies and Instructions for Use. Clin Med Insights Arthritis Musculoskelet Disord. 2016;9:89-101. doi: 10.4137/CMAMD.S38857.
12. Maharjan AS, Pilling D, Gomer RH. High and low molecular weight hyaluronic acid differentially regulate human fibrocyte differentiation. PLoS One. 2011;6(10):e26078. doi: 10.1371/journal.pone.0026078.
13. Neumann A, Schinzel R, Palm D, Riederer P, Münch G. High molecular weight hyaluronic acid inhibits advanced glycation endproduct-induced NF-kappaB activation and cytokine expression. FEBS Lett. 1999;453(3):283-7. doi: 10.1016/s0014-5793(99)00731-0.
14. Roque V, Agre M, Barroso J, Brito I. Managing knee ostheoarthritis: efficacy of hyaluronic acid injections. Acta Reumatol Port. 2013;38(3):154-61.
15. Man GS, Mologhianu G. Osteoarthritis pathogenesis - a complex process that involves the entire joint. J Med Life. 2014;7(1):37-41.
16. Martel-Pelletier J, Pelletier JP. Is osteoarthritis a disease involving only cartilage or other articular tissues? Eklem Hastalik Cerrahisi. 2010;21(1):2-14.
17. Al-Mahmood MR, Uddin MT, Islam MT, Fuad SM, Rahman Shah T. Correlation between goniometric measurements of range of motion and radiographic scores in osteoarthritis knee: An observational study among females. Medicine (Baltimore). 2022;101(32):e29995. doi: 10.1097/MD.0000000000029995.
18. Anwer S, Alghadir A. Effect of isometric quadriceps exercise on muscle strength, pain, and function in patients with knee osteoarthritis: a randomized controlled study. J Phys Ther Sci. 2014;26(5):745-8. doi: 10.1589/jpts.26.745.
19. Vincent P. Intra-Articular Hyaluronic Acid in the Symptomatic Treatment of Knee Osteoarthritis: A Meta-Analysis of Single-Injection Products. Curr Ther Res Clin Exp. 2019;90:39-51. doi: 10.1016/j.curtheres.2019.02.003.
20. Hermans J, Bierma-Zeinstra SMA, Bos PK, Niesten DD, Verhaar JAN, Reijman M. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: a randomised controlled trial. BMC Musculoskelet Disord. 2019;20(1):196. doi: 10.1186/s12891-019-2546-8.
21. Bahrami MH, Raeissadat SA, Cheraghi M, Rahimi-Dehgolan S, Ebrahimpour A. Efficacy of single high-molecular-weight versus triple low-molecular-weight hyaluronic acid intra-articular injection among knee osteoarthritis patients. BMC Musculoskelet Disord. 2020;21(1):550. doi: 10.1186/s12891-020-03577-8.
22. Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis. 2010;69(1):113-9. doi: 10.1136/ard.2008.094623.
23. Palmer KT. Occupational activities and osteoarthritis of the knee. Br Med Bull. 2012;102:147-70. doi: 10.1093/bmb/lds012.
24. Baron D, Flin C, Porterie J, Despaux J, Vincent P. Hyaluronic Acid Single Intra-Articular Injection in Knee Osteoarthritis: A Multicenter Open Prospective Study (ART-ONE 75) with Placebo Post Hoc Comparison. Curr Ther Res Clin Exp. 2018;88:35-46. doi: 10.1016/j.curtheres.2018.04.001.
25. Medical Advisory Secretariat. Intra-articular viscosupplementation with hylan g-f 20 to treat osteoarthritis of the knee: an evidence-based analysis. Ont Health Technol Assess Ser. 2005;5(10):1-66.

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Vol-8, Issue-6 | November- December 2022
DOI: 10.53339/aimdr.2022.8.6.18
Page no- 140-153 | Section- Research Article (Physical Medicine and Rehabilitation)

26. Hafez AR, Al-Johani AH, Zakaria AR, Al-Ahaideb A, Buragadda S, Melam GR, et al. Treatment of knee osteoarthritis in relation to hamstring and quadriceps strength. J Phys Ther Sci. 2013;25(11):1401-5. doi: 10.1589/jpts.25.1401.
27. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther. 2003;5(2):54-67. doi: 10.1186/ar623.
28. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC Musculoskelet Disord. 2015;16:321. doi: 10.1186/s12891-015-0775-z.

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