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Research Article

Functional Outcome of Intra-Articular Hyaluronic Acid Injection in Osteoarthritis of Knee Joint

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Abstract: Osteoarthritis/Osteoarthrosis (OA) defines an idiopathic, slowly progressive disease of the diarthrodial (synovial) joints. Intra-articular - Hyaluronic acid has been proposed to have many therapeutic mechanisms of action in the OA knee, including shock absorption, joint lubrication, anti-inflammatory effects, chondroprotection, proteoglycan synthesis, and cartilage matrix alterations. Thirty-six patients were selected for the proposed study based on eligibility criteria, study period, and feasibility. Patients with clinical symptoms of osteoarthritis were screened based on inclusion (grades I and 2) and exclusion criteria (previous history of trauma). Patients with grade I or II Osteoarthritis based on Kellegren & Lawrence grading were taken up for the study. After obtaining informed consent, a structured interview schedule was administered to obtain information on their background characteristics and clinical and functional outcome of Osteoarthritis using VAS (Visual Analogue Scale) and WOMAC (The Western Ontario and McMaster Universities Osteoarthritis Index) tools. Following this, the intervention was done. All the patients were given a single injection(6ml) of high molecular weight Hyaluronic acid. This study was done to verify safety and feasibility. Our findings suggest that intra-articular hyaluronic acid is safe for use with knee osteoarthritis. While local and minor adverse events related to hyaluronic acid injection occurred, all symptoms disappeared within 48 hours.

Keywords: Osteoarthritis, Knee, Hyaluronic acid, Effects, Clinical study.

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1. INTRODUCTION

Osteoarthritis/Osteoarthrosis (also called degenerative arthritis, hypertrophic arthritis, or arthritis deformans) is used to define an idiopathic, slowly progressive disease of the diarthrodial (synovial) joints.[1] This disease prefers knees, hips, terminal interphalangeal joints, and the spine. Occurrence in other joints can usually be traced to prior trauma, congenital joint abnormality, underlying systemic disease, or chronic crystalline arthropathy. Osteoarthritis is a chronic, disabling condition affecting 10-15% of adults over 60.[2] Clinical features include joint pain, often described as a deep ache localized to the joint. The pain is aggravated by joint use and relieved by rest, but as the disease progresses, it may become persistent. Articular cartilage is aneural; hence joint pain in osteoarthritis arises from other structures.[3,4] Physical examination of the knee joint in patients with osteoarthritis reveals localized tenderness, bony or soft tissue swelling, bony crepitus, joint effusion, and mobility restriction. Symptomatic osteoarthritis of the knee, which is described as having pain during most days of the month, along with radiologic evidence of arthritis, has a 22-39% prevalence in India. [5,6] There are numerous non-invasive treatment approaches emphasizing pain management, improvement in function, and the potential to modify the disease process and progress of cartilage degeneration.[7,8] Treatment options include analgesic, steroid, non-steroid anti-inflammatory drugs (NSAIDs), glucosamine/chondroitin supplementation, and physical therapy. However, most have either been of short-term success, not addressing the biological pathology or have shown only minor benefits and have many side effects.[9] Strengthening of quadriceps and hamstrings and proper muscle balancing around the knee have been found to reduce the pain and disability of the knee in Osteoarthritis.[10] New experimental studies have begun to target the biomechanical process of Osteoarthritis, focusing on promoting cartilage repair or replacement. Particular attention has been directed towards intra-articular Hyaluronic acid. Intra-articular - Hyaluronic acid has been proposed to have many therapeutic mechanisms of action in the OA knee, including shock absorption, joint lubrication, anti-inflammatory effects, chondroprotection, proteoglycan synthesis, and cartilage matrix alterations.[11] The Primary change in cartilage is a defect in the collagen network of the matrix, and evidence supports the concept that matrix metalloproteinases (MMPs) account for much of the loss of the cartilage matrix in Osteoarthritis. MMPs, plasmin, and cathepsins appear to be involved in the breakdown of articular cartilage in Osteoarthritis. Tissue inhibitors of metalloproteinase (TIMP) and plasminogen activator Inhibitor-I (PAI- I) work to stabilize the system while growth factors such as insulin-like growth factor -I and Transforming growth factor ß are implicated in the repair process, Nitric oxide (NO) plays a significant role in articular cartilage damage in Osteoarthritis. Nitric oxide stimulates the synthesis of MMPs by chondrocytes. Chondrocytes are the major source of NO, the Synthesis of which is stimulated by interleukin-I (IL-I) and tumor necrosis factor (TNF) and by shear stress.[12,13,14] Hyaluronic acid is nearly ubiquitous in the body and is a molecule found intrinsically within the knee joint, providing viscoelastic properties to synovial fluid[9]. As OA progresses, natural Hyaluronic acid concentration and the distribution of Hyaluronic acid within the joint shift towards lower ranges of Hyaluronic acid molecular weight, leading to a degradation of the mechanical/viscoelastic properties of the endogenous synovial fluid.[15,16] Lower ranges of molecular weight distributions have also been shown to be strongly correlated to pain. Intra-articular - Hyaluronic acid administration has aimed to restore this decline in Hyaluronic acid concentration and the average molecular weight distribution within the OA knee.[17] Intra-articular HA therapy provides therapeutic relief through several pathways, including the suppression of pro-inflammatory cytokines and chemokines via inhibitors of the signal transduction pathways from specific cell surface receptors and the promotion of the synthesis of anti-inflammatory mediators.[18] Evidence has shown that HA oligosaccharides and HMWHA polymer chains bind to cell surface receptors such as cluster determinant 44 (CD44), toll-like receptor 2 (TLR-2) and 4 (TLR-4), layilin (LAYN), and intercellular adhesion molecule-I (ICAM-1)The application of biologic treatments such as Intra-articular Hyaluronic acid is growing significantly in osteoarthritis of the knee. Although comparing Hyaluronic acid with other articular and soft tissue injections has led to conflicting results, it seems It has useful effects on the healing and functional improvement of injured tissues. The present study attempted to explore the relationship between occupation (i.e., farmers, which constitute the majority) and knee osteoarthritis in Western Maharashtra. Osteoarthritis is a public health problem, and identifying and monitoring various treatment modalities in high-risk groups is important. The high-risk prevalence of knee osteoarthritis & its impact on physical functioning & quality of life, leading to sometimes loss of precious working hours, means that identifying an approach to prevention should be a public health priority. Due to the lack of studies concerning this topic in India, the present study was done to clinically assess the role of intra-articular Hyaluronic acid injection in patients with symptomatic knee osteoarthritis. Our aim of the study is to **s**tudy the effectiveness of hyaluronic acid injection in knee osteoarthritis. Our objective to achieve this aim is to study the symptomatic improvement in pain and mobility of knee joints and to study complications associated with the procedure

2. MATERIALS AND METHODS

2.1. Study Protocol

This hospital-based prospective observational study entitled 'Functional Outcome of Intra-Articular Hyaluronic Acid Injection in Osteoarthritis of Knee Joint' was conducted in the Department of Orthopaedics, Krishna Institute of Medical Sciences, Karad, during the period 2020-2022. Patients with a clinical-radiological diagnosis of knee osteoarthritis and fulfilling the inclusion and exclusion criteria were selected.

2.2. Inclusion criteria

1. Age greater than or equal to 40 years
2. Patients with knee pain
3. Osteoarthritis of the knee joint in grades I &II as diagnosed using Kellegren & Lawrence grading.
4. Patients who have consented to the study.

2.3. Exclusion criteria

1. Previous history of trauma around the knee joint
2. Previous history of surgeries around the knee joint
3. Presence of infection at the site
4. Current tobacco use

5. Active cancer patients
6. Endocrine disorders
7. Inflammatory disorders
8. Patients with knee instability
9. Patients with pathological bone disease
10. Patients with non-degenerative arthritis
11. Patients with low-back pain radiating to knees
12. Patients who continued taking painkillers

2.4. Sample size

According to the research article titled 'Intra-articular injections for osteoarthritis of the knee' published in Cleveland Clinic Journal of Medicine, 73% of the patients were found with significant pain relief. Thus, the minimum number of patients required to enroll in the present study is determined below.

$$N=4pq/L^2$$

where p=73%
q=27%
L=15%
$= 4\times73\times27/15^2$
$= 36$

Hence, 36 patients were selected for the study based on eligibility criteria, study period, and feasibility.

2.5. Operational definition

Osteoarthritis (OA) or Degenerative Joint Disease (DJD) is a form of arthritis characterized by the loss of joint smoothness and range of motion without major joint inflammation.[36]

2.6. Ethical consideration

The study was performed as per the declaration by the Ethical Committee of Krishna Institute of Medical Sciences regarding human research ethics. The institutional committee approved the study. All the patients signed the informed consent form.

2.7. Informed Consent

All the participants explained in detail the purpose of the study and the advantages and disadvantages of participating in the study. Informed Consent was obtained before the data collection in the format prescribed by the Indian Council of Medical Research (ICMR).

2.8. Sampling technique

Purposive Sampling

2.9. Clinical Assessment

An initial screening was carried out to assess the grading of osteoarthritis using Kellgren & Lawrence OA grading. There are four grades for the classification of Osteoarthritis:
Grade 0 – no Radiographic features of OA are present
Grade 1 – doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2 – Definite osteophytes and positive JSN on an anterior, posterior weight-bearing radiograph
Grade 3 – multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4 – large osteophytes, marked JSN, severe sclerosis, definite bony deformity.

All the patients that fulfilled the inclusion criteria were given a questionnaire to collect the data in our study. It comprised two components.

1. Questions related to the background characteristics:
This section included questions on age, gender, occupation, and side of the diseased knee joint.
2. Questions related to assessment of clinical and functional outcomes. VAS Score and WOMAC Score were used for the same.

a. Using Visual Analog Scale score

This tool was used as a self-assessment tool for pain, with a score ranging from 0 – 10. Interpretation of the score:
0 - no pain
1-3 – low pain distress score
4-6 – moderate pain distress score
7-10 – high pain distress score.

b. Using Western Ontario and McMaster Universities Arthritis score (WOMAC)

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is widely used to evaluate Hip and Knee Osteoarthritis. It is a self-administered questionnaire consisting of 24 items divided into 3 subscales:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties. The test questions are scored on a scale of 0-4, which correspond to: None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4). The scores for each subscale are summed up, with a possible score range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function. The formula total score/ 96 (in %) calculates the final score. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations. The same investigator made the clinical assessment for each patient before and after intervention at 3 weeks, 3 months, and 6 months.

2.10. Laboratory assessment

Laboratory assessment was performed only once before administering the drug, including routine hematological and blood biochemistry tests.

2.11. Drug administration

The patients enrolling in the study were administered one single injection(6ml) of HALONIX ONE (Sodium Hyaluronate 10mg/ml) intra-articular in the affected knee. Similar interventions were done at 3 weeks, 3 months, and 6 months.

2.12. Data collection

This study was conducted in the Orthopaedics Department of Krishna Institute of Medical Sciences. Patients with clinical symptoms of osteoarthritis were screened based on inclusion and exclusion criteria. Patients with grade I or II Osteoarthritis based on Kellegren & Lawrence grading were taken up for the study. After obtaining informed consent, a structured interview schedule was administered to obtain information on their background characteristics and clinical and functional outcomes of Osteoarthritis using VAS and WOMAC tools.

2.13. Procedure Description[50]

The patient is laid supine on the table. From the lateral side, the synovial cavity was approached (a medial approach also can be used) to drain a synovial fluid effusion if present.

1. The lateral superior border of the patella is detected. The site was marked with a pen, and 1 cm above and 1 cm lateral to this sign, is the site that gives the most accessible pathway to the synovial space.
2. Local anesthetic was applied by 2% lignocaine spray to the skin of the affected knee. The knee was scrubbed with 7.5% Povidone-iodine and chlorhexidine solution and then painted with 10% betadine solution. The knee was then draped with a sterile cloth maintaining asepsis.
3. Then a needle 21-gauge in size, with a 10ml syringe, was attached for synovial fluid for aspiration inserted through stretched skin that helps reduce needle insertion discomfort by Stretching the pain fibers in the skin with the non-dominant hand; the needle should be directed at 45-degree angle distally into the knee, pushing it beneath the patella.
4. Insert the needle to a distance of 1-4 cm, performing an aspiration of synovial fluid to decompress the knee joint cavity and remove as much as possible from the synovial fluid with its catabolite precipitate so it decreases pain. Also, aspiration will prevent dilution of the injected HA.
5. Once the Syringe has filled, it should be evacuated with great care not to injure the articular surface by the needle tip; then, a new syringe containing 6 ml HA will be attached to the same needle inserted, and a gentle injection of the drug is performed.
6. The patient stays in a supine position for a few minutes with the injected joint moved passively in flexion & extension to spread the injected amount of HA across the synovial space to decrease the friction problem
7. Patients were advised to take oral antibiotics and painkillers for 5 days with local ice packs on site of injection to ease the pain of needle puncture.

Fig 1: Painting of Parts

Fig 2: Drapping of The Knee

The image shows the patient's knee, which is covered with a sterile drape. The drape is held in place with adhesive tape. The patient's leg is extended, and the knee is slightly flexed. The area around the knee is clean and dry. The drape is important for several reasons. First, it helps to keep the area clean and sterile. Second, it helps to prevent the spread of infection. Third, it helps to keep the patient's clothing clean. The drape is placed over the patient's knee in a way that exposes the area where the needle will be inserted. The drape is then held in place with adhesive tape. The adhesive tape is applied in a way that does not interfere with the procedure.

Fig 3: Aspiration of Knee Joint

The image shows the patient's knee joint, with the needle inserted into the suprapatellar pouch. The suprapatellar pouch is a sac of synovial fluid that lies anterior to the knee joint. The needle is connected to a syringe, which is used to aspirate the synovial fluid. The synovial fluid is a clear, yellow fluid that lubricates the joint and helps to cushion the bones. It is also a good source of cells and proteins, which can be analyzed to help diagnose joint disorders.

Fig 4: Administration of Hyaluronic Acid Injection

The image shows the preparation to administer the injection. The patient's knee is exposed and draped with a sterile towel. The area is cleaned with an antiseptic solution. Then, Syringe filled with hyaluronic acid is inserted into the knee joint. The injection is usually done under local anesthesia, so the patient should feel only a small amount of pain. The injection may take a few minutes to complete.

3. OBSERVATIONS AND RESULTS

1) Bar diagram showing age and gender-wise distribution of study sample.

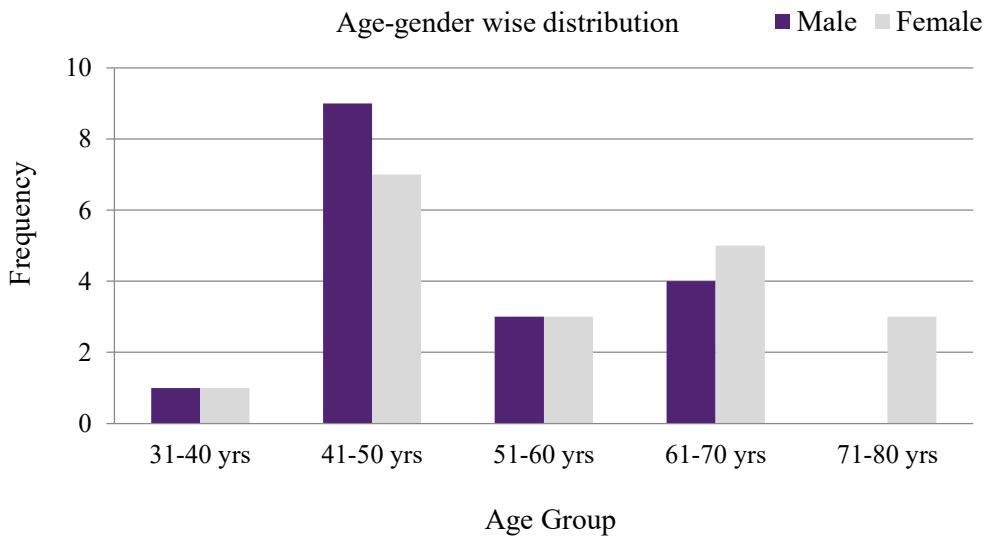

Fig 5: Age-Gender Wise Distribution

Table 1: Statistics related to age in years	
Age (years) Statistics	
N	36
Mean	54.25
Std. Error of Mean	1.873
Std. Deviation	11.236
Range	38
Minimum	40
Maximum	77

The table provides statistics related to age in years. There were a total of 36 individuals included in the data. The mean age is 54.25 years, with a standard error of the mean at 1.873. The standard deviation, representing the dispersion of the data, is 11.236. The range of ages spans 38 years, from a minimum of 40 to a maximum of 77. These statistics provide an overview of the age distribution within the dataset, indicating the average age and the spread of ages among the individuals.

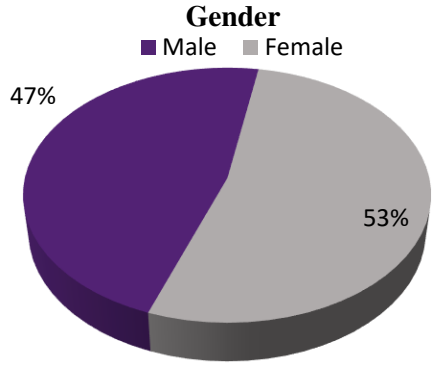

Fig 6: Gender Wise Distribution

The mean age of the 36 study samples was 54.25 years (standard deviation – 11.24 years), with the lowest at 40 years and the highest at 77 years. There were 17 (47%) male and 19 (53%) female in the study, while 16 (44.44%) samples were from the 41-50 years age group, followed by 9 (25%) subjects in the 61-70 years age group.

2) Pie chart showing knee side affected among the study sample.

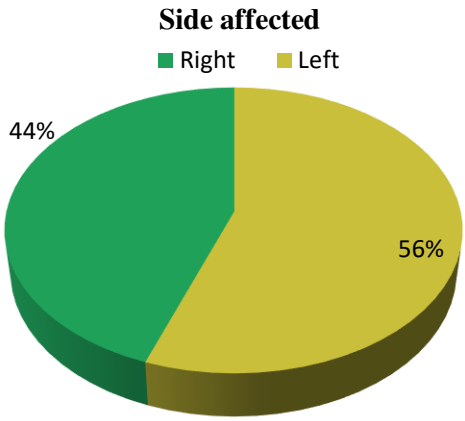

Fig 7: Knee Side Affected Among Study Sample

The above pie chart shows that 20 (56%) of the subjects had left knee affected while the remaining 16 (44%) with right knee affected and were given intervention. The chart reveals that out of the 36 subjects, 20 (56%) had their left knees affected, while the remaining 16 (44%) experienced issues with their right knees. These individuals were then given appropriate interventions or treatments based on their knee conditions. The pie chart visually represents the proportion of subjects affected by left and right knee issues, highlighting this dataset's higher prevalence of left knee afflictions.

3) Pie chart showing grades of osteoarthritis among the study sample.

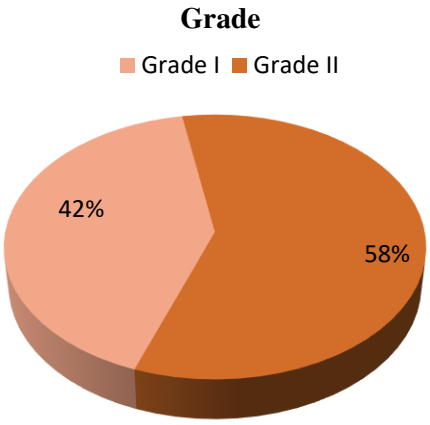

Fig 8: Grades of Osteoarthritis Among Study Sample

The above pie chart shows that 21 (58%) subjects had grade II osteoarthritis while the remaining 15 (42%) had grade I osteoarthritis.

4) Line diagram showing WOMAC score according to gender

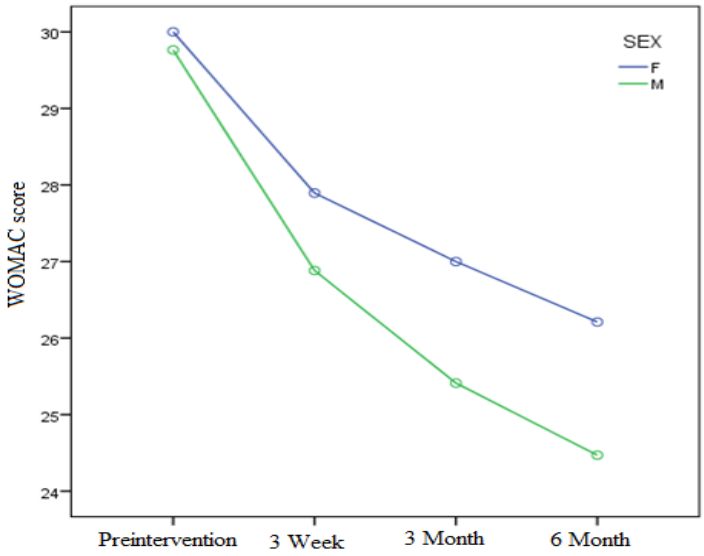

Fig 9: Womac Score According to Gender

Descriptive Statistics

Table 2: Womac Score According to Gender

Variable	SEX	Mean	Std. Deviation	N
WOMAC preintervention	F	30.00	2.357	19
	M	29.76	1.751	17
	Total	29.89	2.067	36
WOMAC 3W Post-intervention	F	27.89	1.997	19
	M	26.88	2.497	17
	Total	27.42	2.273	36
WOMAC 3M Post-intervention	F	27.00	2.427	19
	M	25.41	2.373	17
	Total	26.25	2.500	36
WOMAC 6M Post-intervention	F	26.21	2.992	19
	M	24.47	2.348	17
	Total	**25.39**	**2.811**	**36**

Table 3: Tests of Between-Subjects Effects						
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**	**Partial Eta Squared**
Intercept	106241.994	1	106241.994	7167.031	**.000**	.995
SEX	46.966	1	46.966	3.168	**.084**	.085
Error	504.006	34	14.824			

On application of repeated measures of ANOVA, there was a significant decline in WOMAC score among study subjects after intervention (p=0.000). At the same time, there was no significant difference in WOMAC scores between both genders (p=0.084). It means hyaluronic acid injection in joints reduces WOMAC scores in all subjects and reduces scores equally in both genders.

5) Line diagram showing WOMAC score according to the side affected

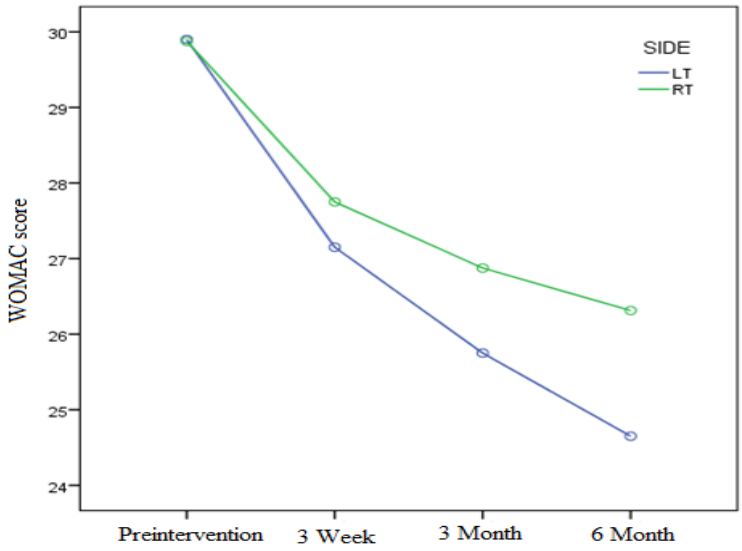

Fig 10: Womac Score According to Side Affected

Descriptive Statistics

Table 4: Womac Score According to Side Affected				
Variable	SIDE	Mean	Std. Deviation	N
WOMAC preintervention	LT	29.90	1.944	20
	RT	29.88	2.277	16
	Total	29.89	2.067	36
WOMAC 3W Post-intervention	LT	27.15	2.390	20
	RT	27.75	2.145	16
	Total	27.42	2.273	36
WOMAC 3M Post-intervention	LT	25.75	2.049	20
	RT	26.88	2.918	16
	Total	26.25	2.500	36
WOMAC 6M Post-intervention	LT	24.65	1.899	20
	RT	26.31	3.497	16
	Total	25.39	2.811	36

Table 5: Tests of Between-Subjects Effects						
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**	**Partial Eta Squared**
Intercept	105863.375	1	105863.375	6844.872	.000	.995
SIDE	25.125	1	25.125	1.625	.211	.046
Error	525.847	34	15.466			

On application of repeated measures of ANOVA, there was a significant decline in WOMAC score among study subjects after intervention (p=0.000). At the same time, there was no significant difference in WOMAC score between the two sides of the knee (p=0.211). It means hyaluronic acid injection in joints reduces WOMAC score in all subjects and reduces score equally on both sides of the knee.

6) Line diagram showing WOMAC score according to grades of osteoarthritis

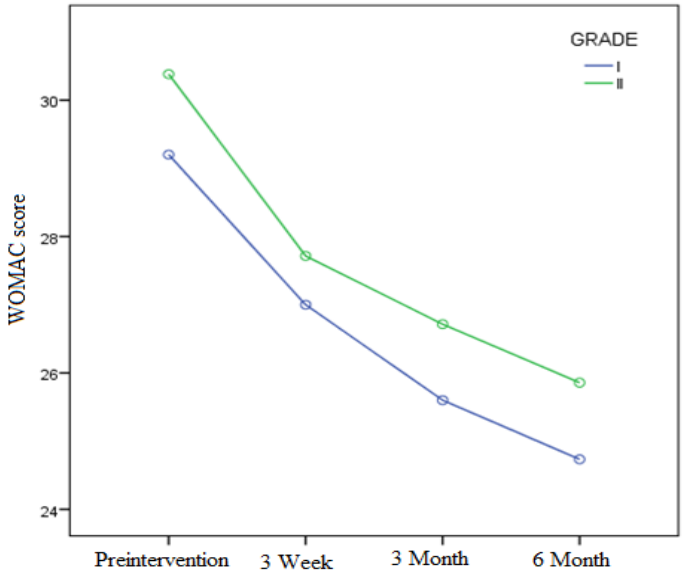

Fig 11: Womac Score According to Grades of Osteoarthritis

Descriptive Statistics

Table 6: Womac Score According to Grades of Osteoarthritis

Variable	GRADE	Mean	Std. Deviation	N
WOMAC preintervention	I	29.20	1.859	15
	II	30.38	2.109	21
	Total	29.89	2.067	36
WOMAC 3W Post-intervention	I	27.00	2.035	15
	II	27.71	2.432	21
	Total	27.42	2.273	36
WOMAC 3M Post-intervention	I	25.60	2.165	15
	II	26.71	2.667	21
	Total	26.25	2.500	36
WOMAC 6M Post-intervention	I	24.73	1.981	15
	II	25.86	3.245	21
	Total	25.39	2.811	36

Table 7: Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	103197.150	1	103197.150	6831.587	**.000**	.995
GRADE	37.372	1	37.372	2.474	**.125**	.068
Error	513.600	34	15.106			

On application of repeated measures of ANOVA, there was a significant decline in WOMAC score among study subjects after intervention (p=0.000). At the same time, there was no significant difference in WOMAC score between the two grades of osteoarthritis (p=0.125). It means hyaluronic acid injection in joints reduces WOMAC score in all subjects, and it reduces score equally in both grades of osteoarthritis.

7) *Line diagram showing VAS score according to gender*

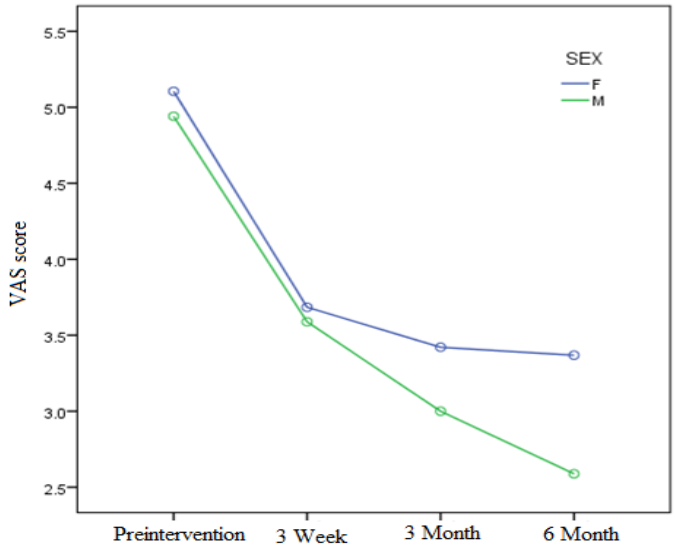

Fig 12: Vas Score According to Gender

Descriptive Statistics

Table 8: Vas Score According to Gender

	SEX	Mean	Std. Deviation	N
VAS preintervention	F	5.11	.658	19
	M	4.94	.659	17
	Total	5.03	.654	36
VAS 3W Post-intervention	F	3.68	1.108	19
	M	3.59	1.004	17
	Total	3.64	1.046	36
VAS 3M Post-intervention	F	3.42	.961	19
	M	3.00	.866	17
	Total	3.22	.929	36
VAS 6M Post-intervention	F	3.37	1.065	19
	M	2.59	.795	17
	Total	3.00	1.014	36

Table 9: Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1978.123	1	1978.123	889.643	**.000**	.963
SEX	4.790	1	4.790	2.154	**.151**	.060
Error	75.599	34	2.224			

On application of repeated measures of ANOVA, there was a significant decline in VAS score among study subjects after intervention (p=0.000). At the same time, there was no significant difference in VAS scores between both genders (p=0.151). It means hyaluronic acid injection in joints reduces VAS scores in all subjects and reduces scores equally in both genders.

8) Line diagram showing VAS score according to the side affected

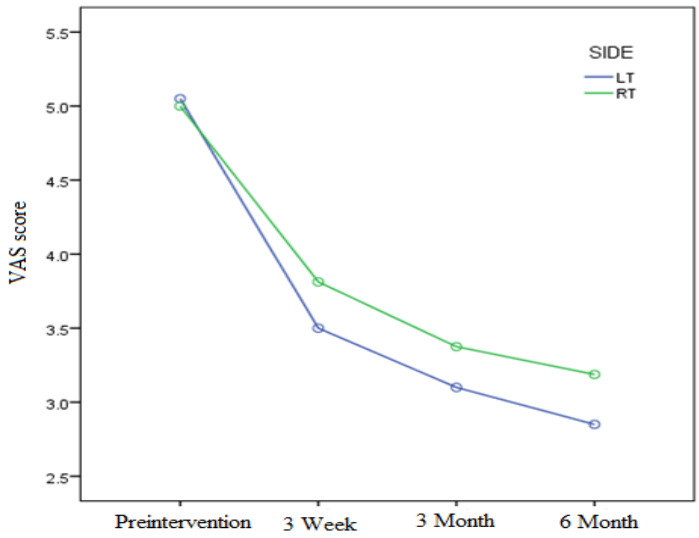

Fig 13: Vas Score According to Side Affected

Descriptive Statistics

Table 10: Vas Score According To Side Affected

	SIDE	Mean	Std. Deviation	N
VAS preintervention	LT	5.05	.605	20
	RT	5.00	.730	16
	Total	5.03	.654	36
VAS 3W Post-intervention	LT	3.50	.946	20
	RT	3.81	1.167	16
	Total	3.64	1.046	36
VAS 3M Post-intervention	LT	3.10	.912	20
	RT	3.37	.957	16
	Total	3.22	.929	36
VAS 6M Post-intervention	LT	2.85	.813	20
	RT	3.19	1.223	16
	Total	3.00	1.014	36

Table 11: Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1983.368	1	1983.368	856.991	**.000**	.962
SIDE	1.701	1	1.701	.735	**.397**	.021
Error	78.688	34	2.314			

On application of repeated measures of ANOVA, there was a significant decline in VAS score among study subjects after intervention (p=0.000). At the same time, there was no significant difference in VAS score between the two sides of the knee (p=0.397). It means hyaluronic acid injection in joints reduces VAS score in all subjects and reduces score equally on both sides of the knee.

9) Line diagram showing VAS score according to grades of osteoarthritis

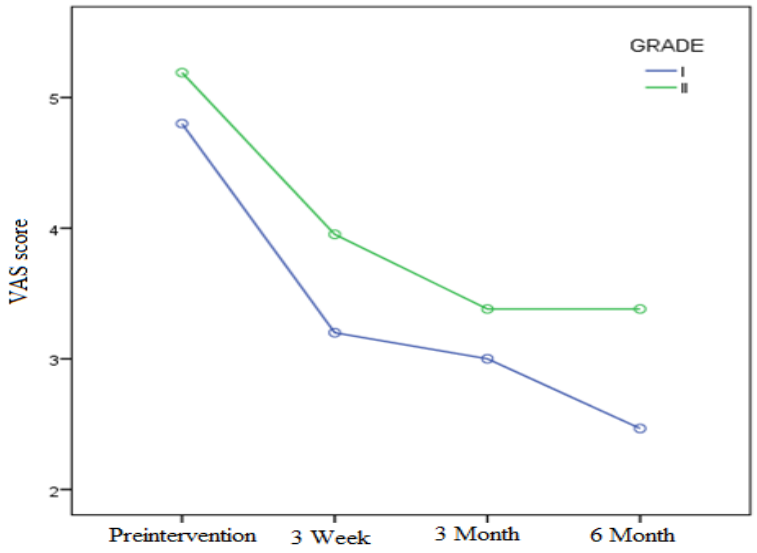

Fig 14: Vas Score According to Grades of Osteoarthritis

Descriptive Statistics

Table 12: Vas Score According to Grades of Osteoarthritis

	GRADE	Mean	Std. Deviation	N
VAS preintervention	I	4.80	.676	15
	II	5.19	.602	21
	Total	5.03	.654	36
VAS 3W Post-intervention	I	3.20	.676	15
	II	3.95	1.161	21
	Total	3.64	1.046	36
VAS 3M Post-intervention	I	3.00	.845	15
	II	3.38	.973	21
	Total	3.22	.929	36
VAS 6M Post-intervention	I	2.47	.516	15
	II	3.38	1.117	21
	Total	3.00	1.014	36

Table 13: Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1887.114	1	1887.114	952.159	**.000**	.966
GRADE	13.003	1	13.003	6.561	**.015**	.162
Error	67.386	34	1.982			

On application of repeated measures of ANOVA, there was a significant decline in VAS score among study subjects after intervention (p=0.000). At the same time, there was a significant difference in VAS scores between the two grades of osteoarthritis (p=0.015). It means hyaluronic acid injection in joints reduces the VAS score in all subjects, and the VAS score was less in grade I than in grade II osteoarthritis after 6 months of intervention.

10) Line diagram showing WOMAC score according to occupation

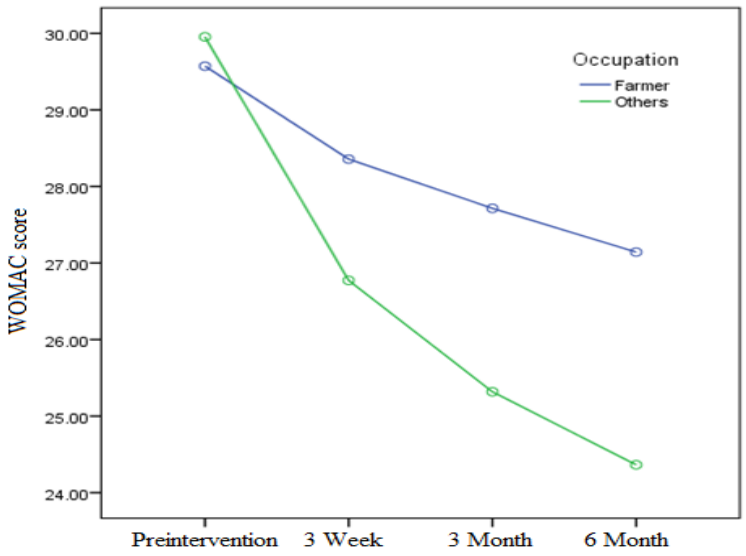

Fig015: Womac Score According to Occupation

Descriptive Statistics

Table 14: Womac Score According to Occupation

Variable	Occupation	Mean	Std. Deviation	N
WOMAC preintervention	Farmer	29.57	2.310	14
	Others	29.95	1.963	22
	Total	29.89	2.067	36
WOMAC 3W Post-intervention	Farmer	28.35	1.392	14
	Others	26.77	2.505	22
	Total	27.42	2.273	36
WOMAC 3M Post-intervention	Farmer	27.71	2.301	14
	Others	25.31	2.190	22
	Total	26.25	2.500	36
WOMAC 6M Post-intervention	Farmer	27.14	2.797	14
	Others	24.36	2.300	22
	Total	25.39	2.811	36

Table 15: Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	102765.831	1	102765.831	7564.182	**.000**	.996
Occupation	86.970	1	86.970	6.402	**.016**	.158
Error	461.919	34	13.586			

On application of repeated measures of ANOVA, there was a significant decline in WOMAC score among study subjects after intervention (p=0.000), and there was a significant difference in WOMAC score between farmers & other occupation subjects (p=0.016). It means hyaluronic acid injection in joints reduces WOMAC score in all subjects, and it reduces score more other occupation subjects than farmers.

11) Line diagram showing VAS score according to occupation

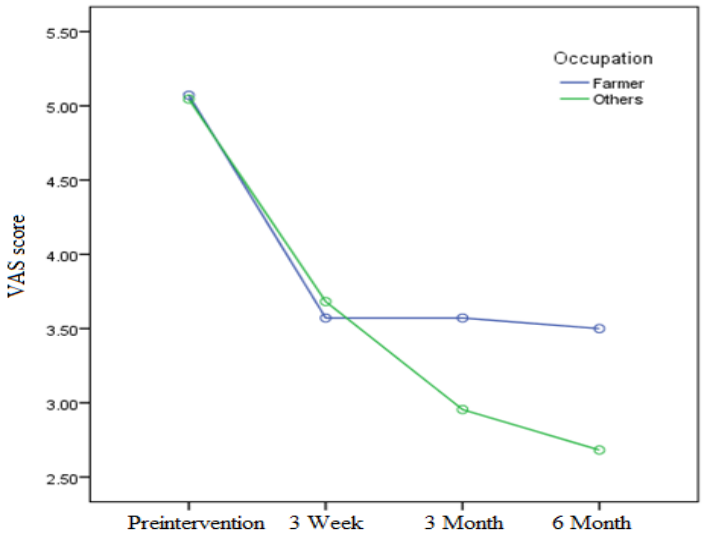

Fig 16: Vas Score According to Occupation

Descriptive Statistics

Table 16: Score According to Occupation

	Occupation	Mean	Std. Deviation	N
VAS preintervention	Farmer	5.07	.73005	14
	Others	5.04	.57547	22
	Total	5.03	.62994	36
VAS 3W Post-intervention	Farmer	3.57	1.15787	14
	Others	3.68	.99457	22
	Total	3.64	1.04616	36
VAS 3M Post-intervention	Farmer	3.57	.85163	14
	Others	2.95	.95005	22
	Total	3.22	.95077	36
VAS 6M Post-intervention	Farmer	3.50	.94054	14
	Others	2.68	.94548	22
	Total	3.00	1.01419	36

Table 17: Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1935.013	1	1935.013	860.152	**.000**	.962
Occupation	3.902	1	3.902	1.734	**.197**	.049
Error	76.487	34	2.250			

On application of repeated measures of ANOVA, there was a significant decline in VAS score among study subjects after intervention (p=0.000). At the same time, there was no significant difference in VAS score between farmers & other occupations (p=0.197). It means hyaluronic acid injection in joints reduces VAS score in all subjects and reduces score equally in all occupations.

4. DISCUSSION

Osteoarthritis (OA) is the commonest joint disease in the world, with age- increase in both incidence and prevalence. OA is one of the leading causes of disability worldwide, with more than 10% of the elderly population having symptomatic disease. In osteoarthritis of the knees, the microscopic degenerative debris is a constant cause of chemical and mechanical irritation during walking and knee movement, resulting in aggravation of pain. By mediating chondroprotective action, Hyaluronic acid therapies can delay joint deterioration by interfering with the early catabolic and inflammatory events and promoting anabolic responses, subsequently reducing OA pain.[1] The pathogenesis of knee osteoarthritis is complex and driven by inflammatory mediators within the affected joint. Joint changes such as synovitis, subchondral bone remodeling (thickening, bone collapse, bone cysts), degeneration of ligaments and menisci, and hypertrophy of the joint capsule are involved in the pathogenesis of Osteoarthritis. The underlying pathophysiology of osteoarthritis remains largely unknown; it has been proposed that the glycosaminoglycan-proteoglycan matrix plays a major role. Therefore, HA (HA), a large viscoelastic glycosaminoglycan, has recently been used for therapeutic management. It is said to possess several protective properties, which include shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface, and lubrication. HA injections have

brought about a reduction in the perception of pain by inhibiting inflammatory mediators and acting by decreasing cartilage degeneration and promoting cartilage matrix synthesis.[11-14] This study demonstrated the feasibility and safety of administering hyaluronic acid for knee osteoarthritis. This therapy significantly improves pain scores, health utility, patient satisfaction, and goal-orientated outcomes.

4.1. Age

The mean age of the study population was 54.25(standard deviation – 11.24 years), with the majority belonging to the 41-50 age group, followed by 61-70 years. The youngest patient in the study had an age of 40 years, and the oldest had an age of 77 years. It was by the Pushpa S. Patil et al. 37 study, with maximum patients in the 5th and 6th decade. A similar trend was seen in Lawrence RC et al. 38 series while estimating the prevalence of arthritis and selected musculoskeletal disorders. The incidence increases with age; by age 65, approximately 80% have radiographic evidence of OA. An individual's peak performance is considered to be around the age of 30 years, and after that, physical decline starts gradually. Around 50 years, the decline becomes fast, and as such, the degenerative changes start appearing symptomatically. In females, because of hormonal changes due to menopause, the degenerative changes start appearing early.

4.2. Gender

In this study, 17 (47%) males and 19 (53%) females were affected by osteoarthritis, which was by the research by Cole et al. [39] in which there were 53 males and 58 females, and Goyal et al. 40; there were 71 females and 29 male patients.
This difference is possibly due to more squatting, moving ahead while squatting, and a higher prevalence of obesity among women. Similar trends were also observed by Iqbal MN et al. 41, which had 74% women and 26% men, and Sharma MK et al. 42, which had 70.1% women and 29.9% men.

4.3. Womac Score

In the current study, the mean WOMAC score decreased significantly from baseline to 3rd week to 3rd month to 6th month. It coincided with the study done by Brandt KD and colleagues[43], which showed significant improvement in WOMAC score at Weeks 0, 1, 2, 3, 7, 11, 15, 21, and 27 in knee osteoarthritis patients who received hyaluronic acid injections. Similarly, Day R and colleagues[44] reported that patients with osteoarthritis knee treated with hyaluronic acid followed for up to 13 weeks after the last injection revealed that a regimen of 5 weekly IA injections of HA is both productive, in terms of pain and stiffness, and safe. A secondary outcome measure confirmed these results by the Lequesne Index. An improvement in flexion and extension of the knee supported these findings. The patients treated with HA demonstrated benefits up to 13 weeks after the last injection. This study was powered to detect differences based on previous estimates from OA trials using the WOMAC instrument. E.C. Huskisson et al. [45] revealed that patients diagnosed with osteoarthritis knee who received 5 weekly doses of hyaluronic acid showed superior results to placebo regarding the functional outcome, pain scores, and Lequesne index. Cole et al. studied patients with symptomatic and unilateral knee OA in a double-masked, randomized clinical trial comparing LP-PRP injections and HA injections under ultrasound guidance and measured outcomes including WOMAC, IKDC, VAS, and Lysholm knee scores for 1 year. No difference was seen between the groups regarding the WOMAC pain score, but there was an improvement in the IKDC score and VAS score in LP-PRP compared with HA. They also found that patients with mild OA and lower body mass index had statistically significant improvement compared with other patients.[53] Additionally, analysis of intra-articular biochemical markers approached statistical significance with a decrease in proinflammatory markers, IL-1ß, and TNF-a. In the present study, we treated patients with a single injection(6ml) of hyaluronic acid, and our results were similar to the findings of T. Conrozier and colleagues et al., who studied the effectiveness of a single dose(6ml) of hyaluronic acid vs three doses of 2ml.[45] In summary, the risk/benefit ratio of a single 6 mL injection appears to be good, and this regimen could be developed as an alternative to the currently approved 3 x 2 mL regimen for treating symptomatic knee OA. There is indeed a need for effective and safe single-injection products since repeated intra-articular injections can be a limiting factor for viscosupplementation treatment. A 6 mL single injection could be particularly useful for patients undergoing concomitant anti-thrombotic therapy (i.e.vitamin K antagonists, aspirin, clopidogrel). A single-dose treatment regimen may improve patient compliance in patients with active and busy lifestyles or traveling challenges due to distance or schedule. A single-dose regimen would also reduce the risk of procedure-related local AE's, particularly infectious arthritis, and offer medico-economic benefits. Furthermore, not only a single injection allows major compliance from the patients and reduces risks connected to intra-articular injection, but also has its importance in pharmaco-economics: a minor number of injections shortens medical costs connected to hospital visits, medications, work time of physicians and nurses and patients' absenteeism. The present study's findings are in keeping with other experimental studies of this nature; however, there is heterogeneity across studies about the severity of the OA populations included and the frequency, dose, and duration of hyaluronic acid interventions. In addition, the long-term outcomes of this form of therapy have yet to be established. The duration of the expected benefit of hyaluronic acid injections remains unclear, as most other studies investigate the persistence of the desirable effects up to 12 months' post interventions. Still, only a few studies have a follow-up period beyond that. Wei-Wei He[47] et al. compared the results of intra-articular corticosteroid vs. hyaluronic acid. They found no significant difference in WOMAC score for the two groups at 3 months ($p = 0.29$). However, HA shows a greater relative effect than CS at 6 months ($p = 0.005$). Intraarticular CS is more effective in pain relief than intraarticular HA in the short term (up to 1 month), while HA is more effective in the long term (up to 6 months). The current research supports the main advantage of using hyaluronic acid: its more productive function in restoring articular function than NSAIDs, corticosteroid injections, and prolotherapy.

4.4. Vas Score

The current study's mean VAS score has decreased significantly from baseline to 3rd week to 3rd month and 6th month. This is by the studies investigating the clinical efficacy of intra-articular hyaluronic acid injections in osteoarthritis

knees. In their studies, R. Altman et al. [48] found that patients receiving hyaluronic acid showed a significant reduction in VAS score continuously for up to 26 weeks. At 26 weeks, patients treated with hyaluronic acid had slight pain or were pain-free compared to placebo-treated or naproxen-treated patients. FANG WANG *et al.* [49] performed a meta-analysis of trials comparing HA with CS for the treatment of OA. The VAS score remained the same for the two drugs in the short term (1 month), but hyaluronic acid had a better VAS score than corticosteroids after ≥ 3 months. It is also reflected in the present study, where the VAS score decreased up to at least 6 months. Initial pain relief is because of the viscosupplementation effect of hyaluronic acid, and as time passes, the chondroprotective and chondro-regeneration effect starts; hence pain relief at a later period is better.

4.5. Occupation

In the present study, the WOMAC and VAS scores decreased post-intervention in both groups until 6 months, but a noticeable change was noted regarding farmers. The early changes, i.e., when measured in the 3rd week, showed no difference in the patient's occupation, but in the 3rd month and 6th month, the farmer group showed meagre improvement in scores compared to the non-farmers. It can be attributed to the patient's (farmers) noncompliance to avoid squatting, frequent bending, or joint loading activities. A study done by Cooper et al. [50] found that occupational knee bending is a positive risk factor for the development of osteoarthritis knee. The odds of getting osteoarthritis knee with increased Occupational knee bending were significantly higher than those with no knee bending. The odds ratio varied from 1.2 to 6.9 for different types of knee bending. Similar findings were observed by Sandmark H et al., and the odds for different positions varied from 2.2 to 3.0.

4.6. Complications

In the current study, only 3 patients had pain and redness at the injection site. The side effects related to the injection of hyaluronic acid are considered uncommon and, when present, usually manifest in mild and self-limited form. The risk of adverse events in hyaluronic acid-treated participants was not significantly increased compared to other knee osteoarthritis treatment options. These findings are consistent with Dennis Y. Wen et el[51] published research involving hyaluronic acid as an intervention in knee OA. In most of the trials of hyaluronic acid, rates of adverse reactions have been low (generally zero to 3 percent).[52] No systemic reactions were attributed to hyaluronic acid. Most reported adverse reactions consisted of minor localized pain or effusion, almost always resolved within one to three days. Case reports of induced pseudogout exist. It is unclear whether the hyaluronic acid or the injection procedure caused these local reactions. No long-term side effects have been reported. No major complications occurred among study subjects, such as deep infection, muscle atrophy, deep vein thrombosis, fever, hematoma, tissue hypertrophy, or other major adverse events. The present study has several limitations. First, this was an open-label study, so no comparison with a control group was performed. Second, the follow-up period was relatively short as a clinical trial to verify the efficacy in the long term.

5. CONCLUSION

This study was done to verify safety and feasibility. Our findings suggest that intra-articular hyaluronic acid is safe for use with knee osteoarthritis. While local and minor adverse events related to hyaluronic acid injection occurred, all symptoms disappeared within 48 hours. The current data support using hyaluronic acid in early OA to minimize symptoms and possibly prevent or slow progression to more advanced OA. However, more research needs to be conducted into the long-term benefits of hyaluronic acid injection in early OA. Future studies to be conducted include standardization and optimization of hyaluronic acid concentration, dosage, and frequency for use in different grades of OA and different joints throughout the body. The primary imperatives of hyaluronic acid therapy remain the control of symptoms; because pain is the most pressing problem in OA, we evaluated only clinical parameters using the WOMAC and VAS scoring systems. Radiographic follow-up investigation methods such as magnetic resonance imaging may be considered for evaluating cartilage regeneration (if any) in subsequent research efforts.

6. AUTHORS CONTRIBUTION STATEMENT

Dr. Parthiv Shah conceptualized and designed the study and assisted Dr. Umang Sachapara in data collection. Dr. Nitin Patil analyzed the data and provided valuable inputs toward designing the manuscript. All authors read and approved the final manuscript. The authors whose names are listed certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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