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Evaluation of the efficacy for pain relief of intra articular Hyaluronate injections in knee osteoarthritis

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Abstract
Background: Osteoarthritis (OA) is the most common age-related degenerative joint disease in the world. Most current pharmacological options are limited to alleviating pain and improving function. Viscosupplementation with intra-articular sodium hyaluronate offers another approach to the treatment by addressing the degradation of hyaluronic acid (HA) in the synovial fluid by the addition of exogenous HA, resulting in pain reduction and functional improvement. The primary purpose of this study is to evaluate the efficacy of 20mg/2ml Sodium Hyaluronate for relieving the symptoms of knee OA in an Indian setting.
Materials & Methods: Forty five patients with symptomatic osteoarthritis diagnosed as Kellgren-Lawrence Grade I/II not responding to conservative management were administered three intra articular injections of Sodium Hyaluronate at weekly intervals. The subjects were followed up for 28 weeks and assessed by administering Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Modified CRD-Pune version (LK3.1).
Results: We noted a decrease in the Pain subscore of WOMAC from 6.07±1.23 to 2.48±0.63 between Week 0 and Week 28, considered statistically highly significant. Overall, total WOMAC score decreased significantly between Week 0 and Week 28. The commonly encountered adverse effect was injection site pain, seen in 33.3% of patients at Week 1, and 64.4% of patients at Week 2.
Conclusion: We found that viscoelastic supplementation with three intra articular injections of Sodium Hyaluronate at weekly intervals is a simple, safe, effective and minimally invasive modality for conservative treatment of Early Grade (I & II) Osteoarthritis of the knee joint.

Keywords: knee, osteoarthritis, intra-articular, hyaluronic acid, viscosupplementation

1. Introduction
Osteoarthritis (OA) is the most common age-related degenerative joint disease and one of the most important health problems in the world. India has the second largest osteoarthritis patient base, with over 15 million affected. Although OA can affect any synovial joint, OA of the knee joints is the most cumbersome in terms of prevalence and disability [1] and results in disabling symptoms in 10% of the people older than 55 years, a quarter of whom are severely affected [2]. Population surveys have shown that radiographically determined OA of the knee is present in between 15 to 30% of subjects aged over 45 years, and thereafter increases steadily with age [3].
OA is characterized by slow degradation of cartilage, pain, and increasing chronic disability [4] Primary symptoms of the disease are pain and tenderness in the joint [1]. Pathologically, the disease shows joint cartilage degeneration as the central feature associated with concomitant changes in the synovium and subchondral bone metabolism [2]. Subsequently, there is a reduction in the lubricating and viscoelastic properties of the synovial fluid, accompanied by progressive destruction of the cartilage surface, [5] which may alter the transmission of mechanical forces to the cartilage, possibly increasing its susceptibility to mechanical damage, or wear and tear [6].
Most current pharmacological options are limited to alleviating pain and improving functional activity but effective therapeutic alternatives to slow disease progression are also needed [2]. Medical interventions can be directed toward different stages of the disease process: patient education (eg. weight reduction), exercise, analgesics, traditional and cyclooxygenase-2 selective NSAIDs, and eventually orthopaedic surgery, including joint replacement [4]. When simple analgesics, such as acetaminophen prove ineffective, the most common therapy for

treating the signs and symptoms of OA is with Nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have proven efficacy for the relief of pain and inflammation of OA, but their use may be restricted by adverse gastrointestinal effects, including serious occurrences of bleeding [5].

Intra-articular sodium hyaluronate (hyaluronic acid; HA) offers the prospect of another approach to the treatment of OA. Studies have shown that a course of 3-5 injections of HA provides prolonged relief of symptoms in patients with OA of the knee [3]. Hyaluronic acid is present in the synovial fluid and the extra cellular matrix of cartilage, and is responsible for the viscoelasticity and lubricating properties of synovial fluid [4].

Viscosupplementation addresses the degradation of hyaluronic acid in the synovial fluid of patients with knee osteoarthritis by the addition of exogenous HA, or its derivatives, by intra-articular injection [6], and contributes to restoring the elastic and viscous properties of the synovial fluid, resulting in pain reduction and functional improvement. HA also interacts with mediators of inflammation and matrix turnover in joint cells, reduces the apoptosis of chondrocytes, and exerts a biosynthetic chondroprotective effect [2].

Unlike traditional analgesics and NSAIDs, HA is not a rapidly acting agent, but its clinical efficacy on pain shows a carry-over effect that extends the results for a long time after the administration is stopped, identifying it as a symptomatic slow-acting drug for osteoarthritis (SYSADOA).

The efficacy and tolerability of intra-articular injections of sodium hyaluronate have been established in many clinical trials conducted worldwide. Sodium Hyaluronate (Hyalgan®) was approved by the United States Food and Drug Administration in 1997, and was suggested by American College of Rheumatology (ACR) guidelines as a therapeutic choice for pain decrement in knee OA in 2000. This therapeutic agent is now available in over 43 countries worldwide, including India since 2010. However, only one study has been published evaluating its efficacy in an Asian population [5].

2. Materials and Methods

Forty five patients with symptomatic osteoarthritis of one or both knee joints not responding to conservative management who presented during the period of study and gave consent for three intra articular injections of sodium hyaluronate were included as study sample. Patients above 45 years of age with symptomatic osteoarthritis according to American College of Rheumatology and radiographic evidence of osteoarthritis Kellgren-Lawrence Grade I or II were considered. The exclusion criteria included patients with secondary osteoarthritis, clinically apparent tense effusion of the target knee, severe axis deviations of knee; Varus/valgus deformity of knee > 15˚, coagulation or platelet disorders, symptomatic osteoarthritis of either hip, neoplasms, joint prosthesis of lower limbs, recent trauma or open surgery within past 12 months or intra-articular injection of corticosteroid in any joint 3 months before screening. The study was conducted at Sri Siddhartha Medical College Hospital and Research Centre, Tumkur.

2.1 Initial assessment

At the screening visit (visit 1), the patients were assessed for the fulfillment of the entry criteria and demographic characteristics and admitted into the trial. Medical history taking, physical examination and signing of informed consent took place. Subjects were instructed to discontinue or taper off any treatment with NSAIDs, cyclooxygenase-2 inhibitors, or analgesics with the exception of acetaminophen, to ensure a minimum 3-day drug washout period and were scheduled to return to the study center in 7 days for the baseline visit.

At the baseline visit (visit 2), patients were re-examined and assessed by administering the Western Ontario and McMaster University Osteoarthritis Index Modified CRD-Pune version (WOMAC LK3.1).

2.2 Pre Procedural Workup: After selecting the cases on the basis of the above mentioned clinical criteria the patients were subjected to plain radiographs of the affected knee, lateral and antero-posterior views.

Patients were subsequently administered 3 injections of HA at weekly intervals with standard aseptic techniques under sterile conditions by inserting a 21-gauge needle into the patella-femoral joint space. In 23 patients, the injections were administered via infrapatellar route, while in the remaining 22 patients through the suprapatellar approach.

2.3 Materials Required: A pre-set tray with cover, containing the following sterile items was kept ready for use; sterile gloves (size 7.5), sponge-holding forceps and swabs, Betadine, Sterillium/Spirit solution, prefilled syringe of injection Hyalgan 2 ml (10mg/ml), a 21 gauge hypodermic needle (Figure 1).

Hyalgan®, manufactured by Fidia Farmaceutici Spa., Abano Terme, Italy, is a viscous solution consisting of a high molecular weight (500,000-730,000 Da) fraction of purified natural sodium hyaluronate in buffered physiological sodium chloride, having a PH of 6.8-7.5. Hyalgan is supplied as a sterile, non-pyogenic solution in 2 mL pre-filled syringes containing 20 mg of sodium hyaluronate, 17 mg of sodium chloride, 0.1 mg of monobasic sodium phosphate, 1.2 mg of dibasic sodium phosphate, and up to 2cc water for injection.

Fig 1: Materials Required

2.4 Procedure: All injections were carried out in the Injection Room with dry sterile materials. The patient was made to lie in the supine position with the affected knee placed in 90˚ of flexion to facilitate infiltration. In this position, the anterior portions of the medial and lateral joint lines can easily be palpated as dimples just medial or lateral to the inferior pole of the patella. Often, the lateral joint line is easier to palpate and define, and can be chosen as the site of injection. The actual injection site was marked with a fingernail imprint or the barrel of a pen (Figure 2). Next, sterile preparation with povidone iodine preparation (Betadine) and alcohol was performed (Figure 3).

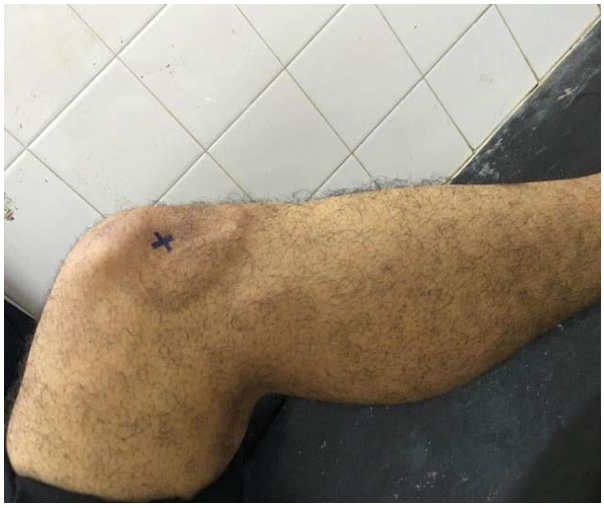


Fig 2: Marking of injection site

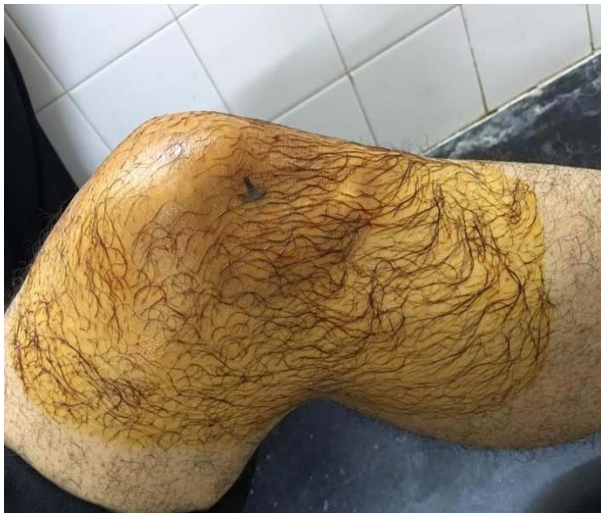


Fig 3: Sterile preparation with povidone iodine (Betadine)

A 21-gauge needle was inserted laterally at the junction of the middle and upper thirds of the patella, midway between the patella and the femoral condyle (Figure 4). Care was taken to minimize trauma to the cartilage of the patella and femoral condyle, by advancing the needle gently between the bone surfaces and redirecting it carefully if bone was encountered before drug could be administered. Following injection of the viscosupplement, the needle was withdrawn and a sterile adhesive bandage was applied.

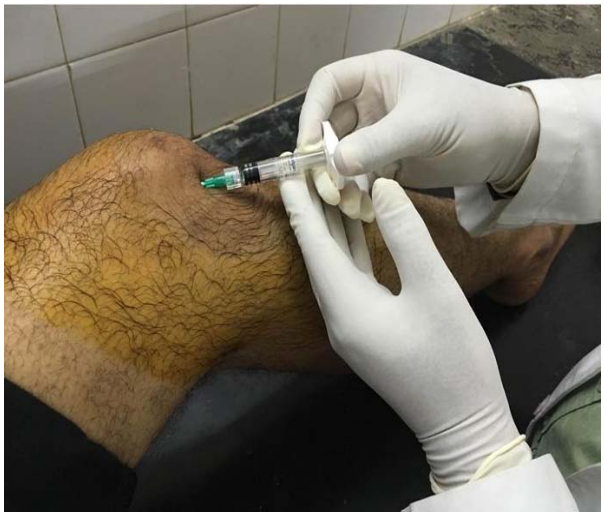


Fig 4: Intra articular administration of viscosupplement

2.5 Post Injection: The patient was asked to spend approximately 10-15 minutes in the supine position. The knee joint was passively flexed and extended through its full range of motion several times to facilitate distribution of the drug. The patients were allowed out of bed 15 minutes after the intra articular injection. All patients were sent home after the injection, with instruction to avoid excessive weight bearing, and strenuous physical activity for 1-2 days following injection, and further recommended to continue mild to moderate level of activities and increase their level gradually as tolerated. All patients were advised to take mild analgesics (Paracetamol 500mg every 8 hours and maximally every 4 hours if pain continued) during the post injection period.

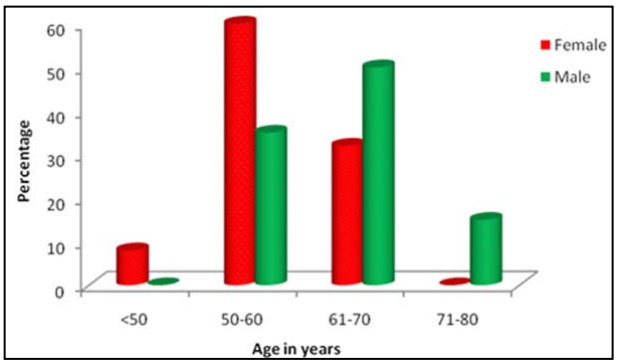
2.6 Follow Up: Clinical assessments were made at baseline, and at weekly visits over 3 weeks. Subsequently, regular follow ups were made 4 weeks after the final injection (Week 8), Week 16, Week 24, and Week 28; i.e at 4, 12, 20 and 24 weeks following the end of treatment. During the treatment phase, the clinical assessments were carried out before each injection. The change in quality of life was evaluated by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Modified CRD-Pune version questionnaire.
The primary outcome measure was a change in the WOMAC LK3.1 score between baseline and final visit, with Last Observation Carried Forward (LOCF) for patients who did not complete the study. Measures of secondary outcome were based on difference in the Pain subscores of WOMAC during the study period.
Treatment safety and tolerability were evaluated based on incidence and type of adverse effects (with special attention to allergic reactions such as skin rash, urtricaria, pruritis, swelling and/or erythema) and the results of physical examinations throughout the duration of the study.

2.7 Statistical Method: Descriptive and inferential statistical analysis was carried out in this study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented as Number (%). Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

3. Results

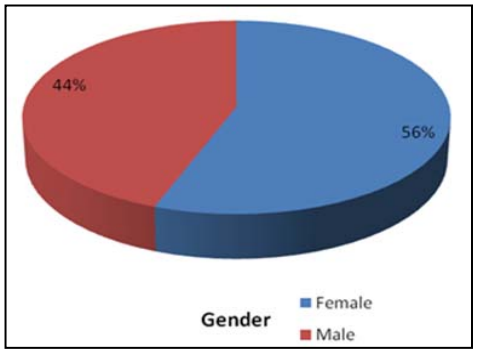
3.1 Observations

Age Distribution: A total of 45 cases were included of which 22 cases were between 50-60 years of age and 18 cases between 61-70 years of age (Graph 1).
The mean age obtained from our study was 60.53±6.59
(Mean ± SD)



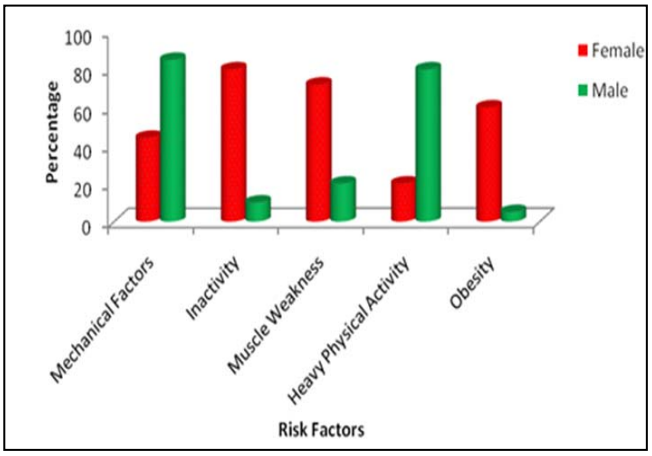
Graph 1: Age group of patients

Gender Distribution: In our study of 45 cases 25 were females and 20 were males. The male to female ratio was 0.8: 1 (Graph 2).



Graph 2: Gender Distribution

Risk factors: In our study, Mechanical Factors (62.2%) were found to be the most significant risk factor. Inactivity (48.9%), Muscle Weakness (48.9%) and Heavy Physical Activity (46.7%) were the other important precipitating factors encountered (Graph 3).



Graph 3: Risk factors

Symptoms: Transient Morning Stiffness was seen in all the study subjects. Loss of Range of Motion was seen in 88.9% of cases, while 57.8% complained of Painful Crepitus (Table 1).

Table 1: Symptoms

Symptoms	No. of patients (n=45)	%
Transient morning stiffness	45	100.0
Loss of range of motion	40	88.9
Painful Crepitus	26	57.8
Impaired use of joint	10	22.2

Character of Pain: Pain was Localized and Aggravated on Motion/Weight Bearing in all the cases. Rest pain was present in 68.9% of cases.

Discomfort while Walking: In our study, 25 patients exhibited Discomfort while Walking, while the rest were able to walk without discomfort.

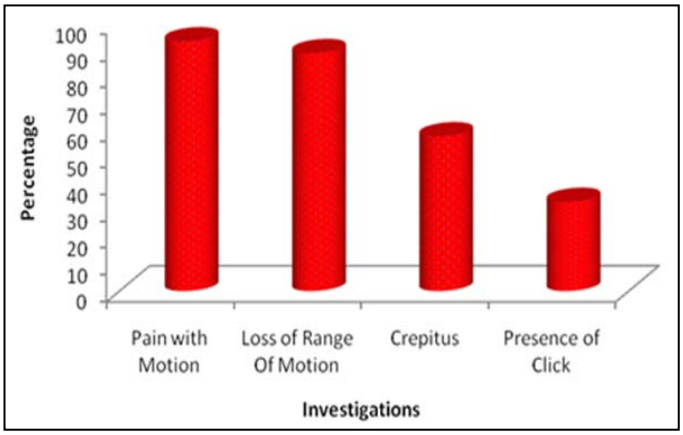
Crepitus: Crepitus was elicited in 26 patients, out of which 14 were male (70%) and 12 were female (48%).

Muscle Wasting: Muscle wasting was seen in 51.1% of cases (n=23), while the remaining 22 patients exhibited no Muscle Wasting.

Affection of Knee Flexion ROM: In our study, 24 patients had Mild Restriction of Knee ROM [>115˚] (53.33%), while 16 patients showed Moderate Restriction [90˚- 115˚] (35.56%).

Grade of Osteoarthritis: In our study, 26 patients (57.8%) were diagnosed with Grade I OA, while 19 patients (42.2%) were diagnosed with Grade II OA, based on the Kellgren-Lawrence radiological scoring.

3.2. Examination: In our series, Pain with Motion was seen in 42 patients (93.3%), while Loss of Range of Motion was seen in 40 patients (88.9%). 26 subjects presented with Crepitus (57.8%) (Graph 4).



Graph 4: Examination

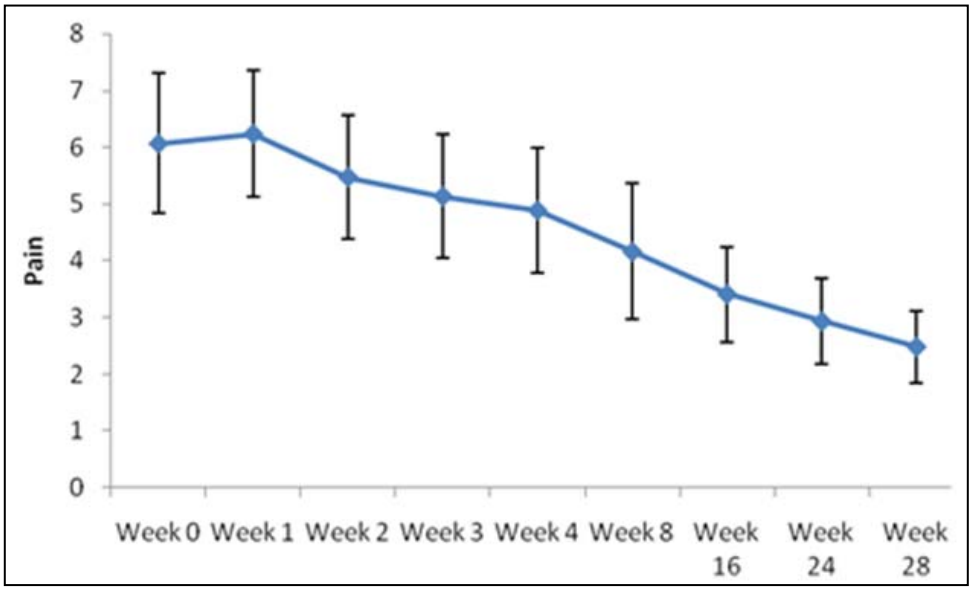
3.3 Pain: An Assessment from Week 0 to Week 28

There was a decrease in the Pain subscore of WOMAC between Week 0 and Week 28 (Table 2, Graph 5). While the score at Week 1 (6.24±1.11) decreased with moderate significance (p=0.031), the pain relief from Week 2 to Week 28 was statistically highly significant (p<0.001).

Table 2: Pain: An Assessment from Week 0 to Week 28

Pain	Min-Max	Mean±SD	Difference[+]	t value[+]	P value[+]
Week 0	3.00-9.00	6.07±1.23	-	-	-
Week 1	4.00-9.00	6.24±1.11	-0.178	-2.231	0.031*
Week 2	3.00-9.00	5.48±1.09	0.523	4.378	<0.001**
Week 3	3.00-8.00	5.14±1.09	0.864	7.802	<0.001**
Week 4	3.00-8.00	4.89±1.10	1.114	10.716	<0.001**
Week 8	2.00-8.00	4.16±1.20	1.841	15.163	<0.001**
Week 16	2.00-6.00	3.41±0.84	2.591	17.259	<0.001**
Week 24	2.00-5.00	2.93±0.76	3.068	19.509	<0.001**
Week 28	2.00-4.00	2.48±0.63	3.523	21.895	<0.001**

[+]computed from Week 0



Graph 5: Pain: An Assessment from Week 0 to Week 28

3.4 WOMAC: An Assessment from Week 0 to Week 28

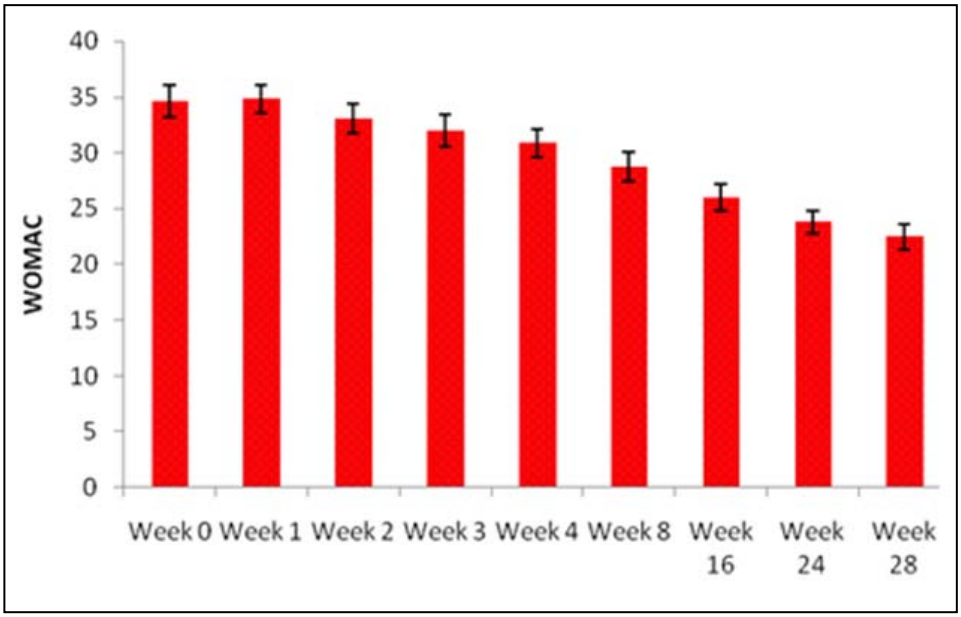
There was a decrease in the total score of WOMAC between Week 0 and Week 28.

While the score at Week 1 (34.84±1.24) decreased insignificantly (p=0.107), the decrease in the total WOMAC score from Week 2 (33.05±1.29) to Week 28 (22.45±1.09) was statistically highly significant (p<0.001) (Table 3, Graph 6).

Table 3: WOMAC: An Assessment from Week 0 to Week 28

WOMAC	Min-Max	Mean ± SD	Difference[+]	t value[+]	P value[+]
Week 0	32.00-37.00	34.64±1.43	-	-	-
Week 1	33.00-37.00	34.84±1.24	-0.200	-1.647	0.107
Week 2	31.00-35.00	33.05±1.29	1.636	10.708	<0.001**
Week 3	30.00-36.00	32.02±1.42	2.659	15.472	<0.001**
Week 4	29.00-34.00	30.84±1.29	3.841	24.143	<0.001**
Week 8	27.00-32.00	28.75±1.37	5.932	31.108	<0.001**
Week 16	24.00-28.00	26.02±1.21	8.659	41.123	<0.001**
Week 24	22.00-26.00	23.82±1.02	10.864	53.787	<0.001**
Week 28	21.00-25.00	22.45±1.09	12.227	58.831	<0.001**

[+]computed from week 0

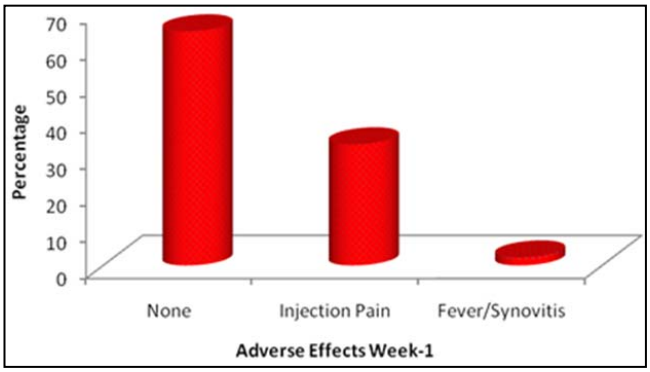


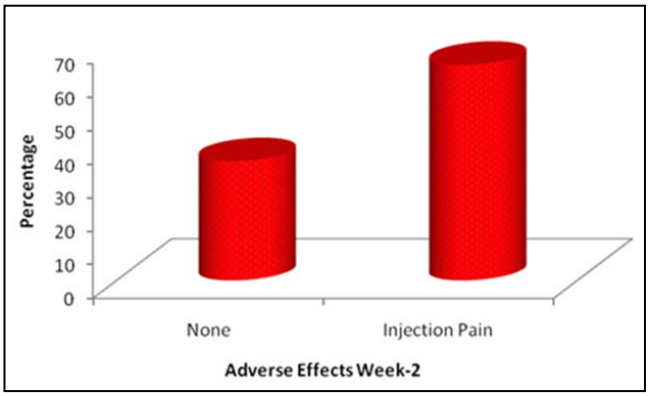
Graph 6: WOMAC: An Assessment from Week 0 to Week 28

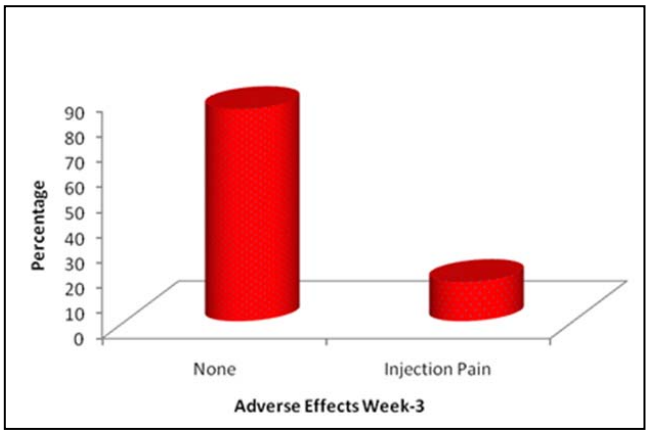
3.5 Adverse Effects: At Week 1, 64.4% of the patients suffered no Adverse Effects, while 33.3% complained of injection site pain. One patient discontinued the treatment due to fever and synovitis. At Week 2, injection site pain was the only Adverse Effect, seen in 29 patients. At Week 3, majority of the patients (84.4%) suffered no Adverse Effects (Table 4), (Graph 7, 8 & 9).

Table 4: Adverse Effects

Adverse Effects	No. of patients (n=45)	%
Week 1		
None	29	64.4
Injection Pain	15	33.3
Fever/Synovitis	1	2.2
Week 2		
None	16	35.6
Injection Pain	29	64.4
Week 3		
None	38	84.4
Injection Pain	7	15.6







Graph 7, 8, 9: Adverse Effects

4. Discussion

Our present study showed 26 patients diagnosed with Grade I OA (57.78%), while Grade II OA was seen in 19 patients (42.22%). This was comparable with the series by Huang *et al*. with 51% of Grade I OA and 49% of Grade II OA, and that of Berenbaum *et al.* [7] with 54% and 46% respectively.

In this series, there was a decrease in the Pain subscore of WOMAC from 6.07±1.23 to 2.48±0.63 between Week 0 and Week 28 ($p<0.001$). This was similar to the results obtained by Huang *et al.* [5] wherein the sodium hyaluronate group revealed significant change from baseline to Week 25 in WOMAC pain scores (29.28±1.92) than the placebo group ($p=0.0050$). In the series by Berenbaum *et al.* [7] patients improved markedly during the first month after treatment and the effect was maintained for the duration of the study. After 6 months from the end of treatment (ie, Week 26), patients who had received Hyalgan had decreased their WOMAC pain score by 18.4±1.5 within the ITT population. Rayegani *et al.* [8] found that the WOMAC mean pain parameter was decreased meaningfully in the Hyalgan group from 6.91±3.82 to 5.08±3.71 after 52 weeks of follow-up. In the study by Ucar *et al.* [1], in the middle-aged group, WOMAC pain values post injection (3.7±1.9) were found to be statistically lower when compared with preinjection values (4.9±1.7).

This study noted an improvement in the total score of WOMAC between Week 0 (34.64±1.43) and Week 28 (22.45±1.09). This was comparable to the results shown by Rayegani *et al.* [8] who noted a change from 28.69±16.69 at baseline to 27.46±16.36 at Week 52 with regard to the total WOMAC score.

Our series reported a favourable safety profile with minimal adverse effects. Most patients tolerated the treatment well. The most commonly encountered adverse effect was injection site pain, seen in 33.3% of patients at Week 1, and 64.4% of patients at Week 2. One patient discontinued the treatment due to fever and synovitis. This was similar to the series by Berenbaum *et al.*, [7] wherein the proportion of patients reporting any adverse effect in the safety population was 75 out of 213 (35.2%) with Hyalgan, most adverse effects being unrelated to treatment. The proportion of patients reporting local adverse effect was 3.8% with Hyalgan. No case of acute pseudoseptic arthritis was observed.

5. Conclusion

This study highlights the benefits of viscosupplementation for the treatment of OA of the knee which provides good efficacy for pain relief and improved functional outcome.

Thus, based on the results obtained, viscoelastic supplementation with three intra articular injections of Sodium Hyaluronate (Hyalgan) at weekly intervals was found to be a viable conservative treatment option for Early Grade (I & II) Osteoarthritis of the knee joint.

6. Acknowledgements

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