

Original Research Article

Role of viscosupplementation in the management of primary osteoarthritis knee

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ABSTRACT

Background: Viscosupplementation is frequently used as a therapeutic strategy to manage patients with early osteoarthritis of knees. A case series was followed up for a period of one year to study the clinical efficacy of intra-articular hyaluronic acid injections in different Kellegren Lawrence grades of osteoarthritis knee.

Methods: 76 patients with primary osteoarthritis of knee not responding to analgesics, Quadriceps strengthening exercises, superficial and deep heat modalities were recruited after meeting inclusion criteria. They were followed up till the end of one year at an interval of every four months. Seventy patients completed the study and were analyzed for pain, stiffness and physical function using WOMAC osteoarthritis index. WOMAC scores were documented at initial consultation and follow up visits at the end of fourth, eighth and twelfth month.

Results: Patients with Grade 1 and 2 osteoarthritis knee showed improvement in pain, stiffness and physical function following viscosupplementation lasting for one year. Those with Grade 3 osteoarthritis knee initially revealed good pain relief, enhanced function clinically till the second follow up. After that majority of the patients with Grade 3 osteoarthritis demanded for another session of viscosupplementation and expressed worsening of their knee symptoms. In Grade 4 osteoarthritis knee viscosupplementation found to be clinically and statistically ineffective. Adverse reactions following intra-articular hyaluronic acid injections included pain in five patients, pain and swelling in three patients, and injection site erythema in one patient.

Conclusions: Viscosupplementation is a good therapeutic strategy in management of Grade 1-2 osteoarthritis knee. Intra-articular hyaluronic acid injections in Grade 3 osteoarthritis knee helps in delaying surgical intervention. It is ineffective in Grade 4 osteoarthritis knee.

Keywords: Viscosupplementation, Osteoarthritis knee, WOMAC scores

INTRODUCTION

Osteoarthritis is the most common cause of musculoskeletal pain and disability resulting in frequent orthopedic consultations.¹ In the Global burden of disease 2000 study; published in World Health Report 2002, osteoarthritis is the fourth leading cause of years lost due to disease at the global level.² Osteoarthritis prevalence increases with age and accounts for the dependence of elderly individuals for daily activities. Increasing numbers of young and active patients are seeking medical

help for osteoarthritis knee due to highly demanding physical and sporting activities. Decreased quality of life among osteoarthritis sufferers results in loss of around 278 cumulative years per 100,000 persons globally.³ Mild and moderate osteoarthritis of knee, especially in active patients, poses a challenge to manage. A multimodal approach consisting of different non-pharmacologic, pharmacologic and surgical options has been found to be an appropriate regimen for treating osteoarthritis of knee.⁴ Older patients are prone to drug induced adverse reactions owing to their physiological changes.

Viscosupplementation, one of the therapeutic modality in the multimodal approach, reduces the use of NSAIDs and its related complications. It also decreases the frequency of orthopedic consultations. Significant beneficial effects of viscosupplementation in management of osteoarthritis knee have been reported in the literature, while few studies conclude minimal benefits in the long term.⁴

This study is designed to study the effectiveness of viscosupplementation in the management of primary osteoarthritis of knee using WOMAC score in Indian populations.

METHODS

This study was a prospective interventional study without control group from November 2011 to November 2013. Study was conducted at the Department of Orthopedic Surgery, Chalmeda Anada Rao Institute of Medical Sciences. All the patients were followed up every four months till the completion of one year from their date of receipt of first intra-articular hyaluronic acid injection. Out of the seventy-six patients recruited into the study, seventy patients completed the study as per the protocol. Those six patients were excluded from the study. Of them two patients sustained traumatic hemarthrosis and underwent knee aspiration, one patient sustained anterior cruciate ligament injury and has undergone arthroscopic surgery, three patients were lost to follow up.

Before the commencement of the study, a standard injection procedure to perform intra-articular knee injection was clearly laid out. All clinicians performing the intra-articular hyaluronic acid injections were trained accordingly to ensure the uniformity. Prefilled single use hyaluronic acid injection, 2% lidocaine, 0.5% bupivacaine, 21-gauge needle and 5 cc syringe and 5% betadine and sterile gauze are taken.

The index knee is positioned in extension by placing a saline bottle under the distal end of leg to relax the quadriceps muscle. Knee is well exposed all around up to mid-thigh level and painted with 5% Betadine and draped with a sterile hole towel.

Technique

Single needle technique and superolateral entry point were used for injecting viscosupplements in this study. Through superolateral entry local anesthetic is infiltrated into the skin and soft tissues with 21-gauge needle while entering the knee joint. Needle is retained in the joint and the syringe detached. Prefilled hyaluronic acid syringe system is attached to the retained needle and the drug is injected into the knee joint. Three doses of 'Hyruan Plus' injections (2 ml each) were administered once weekly in this study for three consecutive weeks.

Sterile adhesive bandage is applied at the injection site and patients are advised to remove it after two hours.

Patients are also cautioned about the possibility of increased pain and swelling over the next 48 hours following injections, they are advised to apply ice compressive or use analgesics for pain relief. Patients were encouraged to perform their daily routine activities following injection.

Inclusion criteria

Patients with age group 35-65 years, primary osteoarthritis and unilateral symptomatic osteoarthritis knee and active patients were included.

Exclusion criteria

Patients with age group >65 years, bilateral symptomatic osteoarthritis, fixed deformities like varus valgus malalignment, secondary knee osteoarthritis: intra-articular fractures, prior intra-articular steroid or local anesthetic injections, prior surgery on the knee, rheumatoid arthritis, villonodular synovitis, allergic to sodium hyaluronate, active knee joint infection, skin disease at injection site and ligament instabilities.

All the patients recruited into the study underwent clinical and radiographic assessment of knee joint. Details regarding medical comorbidities like diabetes, hypertension, bronchial asthma, personal habits, allergies, previous surgeries, and medication intake were documented. Each patient was explicitly explained about their participation in the study involving intra-articular injection of hyaluronic acid into their knee joint and informed written consent was obtained at initial visit. Clinical and radiographic findings along with WOMAC scores were documented in the study proforma and maintained as separate case record for each patient. Any adverse reaction following intra-articular hyaluronic acid injection was documented in the case record. Follow up data consisting of WOMAC scores were added to the initial case record of each patient. WOMAC questionnaire was administered to each patient at initial visit and follow up visits at the end of fourth, eighth and twelfth month post injection.

A proforma consisting of questions regarding the personal information, occupation, contact address and mobile numbers, medical comorbidities, any surgeries, allergies in the past, physiotherapy details and knee examination details was used at baseline visit for documentation of health status of each patient.

WOMAC questionnaire

Western Ontario and McMaster universities osteoarthritis index is a set of standardized questionnaire used to evaluate the condition of patients with osteoarthritis knee including pain, stiffness, and physical functioning of the joints. WOMAC was developed at Western Ontario and McMaster universities in 1982. The Likert scale version of WOMAC used the following descriptors for all items:

none, mild, moderate, severe, and extreme. These correspond to an ordinal scale of 0-4. Overall the WOMAC performed well with only a small number of DIF (differential item functioning) items identified across the nine grouping factors. The impact of the DIF items rarely influenced the conclusions of group comparisons.⁵

WOMAC index was used to monitor the course of the disease or to determine the effectiveness of treatment using 24 parameters.

Table 1: Interpretation of WOMAC index.

WOMAC score	Parameters	Minimum	Maximum
Total	24	0	96
Pain	5	0	20
Stiffness	2	0	8
Physical function	17	0	68

The WOMAC scale was extensively validated and shown to be a reliable and responsive instrument. Depending on the WOMAC scores, participants were classified as having a mild, moderate, or severe level of symptoms. For WOMAC pain, scores of 0–8, 9–14, and 15–20 correspond to mild, moderate, and severe pain, respectively. For WOMAC functional limitation, scores of 0–22, 23–45, and 46–68 correspond to mild, moderate, and severe functional limitation, respectively.⁶ WOMAC scale is a subjective scale.

Full weight bearing anteroposterior X-rays of knee joint obtained in standing position were studied and graded using Kellegran Lawrence grading scale by resident doctors and confirmed by one of the senior orthopedic surgeon. In case of discrepancy, the highest grade given by the clinicians was taken into consideration after obtaining a consensus.

Data were entered Microsoft excel spreadsheet and analyzed using SPSS 17.0 version. The effectiveness of viscosupplementation was evaluated by comparing WOMAC scores at each follow up visit with baseline scores for each Kellegran Lawrence grade of osteoarthritis knee using paired samples t-test.

The primary end point measured the decrease in pain and overall improvement following injection of hyaluronic acid in different grades of osteoarthritis knee using WOMAC pain subscale and WOMAC composite score respectively. Secondary outcome measures included the improvement in stiffness and physical function.

RESULTS

Sixty percent of the patients were between 46-55 years in this study. About 17 percent of patients in this study were less than 45 years of age raising a concern for increased

incidence of osteoarthritis among younger patients. In this population osteoarthritis was distributed similarly among both males and females. No side specific predilection for osteoarthritis knee was noticed in this study. Out of the seventy patients in this study fifteen had Grade 1 osteoarthritis, thirty-one had Grade 2, nineteen had Grade 3 and five had Grade 4 osteoarthritis knee (Table 2).

Table 2: Demographic details.

Variable	Number (70)	Percentage (%)
Age distribution		
35-45	12	17.14
46-55	43	61.42
55-65	15	21.42
Sex distribution		
Female	37	52.85
Male	33	47.14
Side distribution		
Right side	34	48.57
Left side	36	51.43
Kellegran Lawrence grade distribution		
Grade I	15	21.42
Grade II	31	44.28
Grade III	19	27.14
Grade IV	5	7.14

WOMAC composite score consisting of physical function subscale showed a decrease following intra-articular injections in all grades of osteoarthritis knee on the first, second and third follow up visits when compared to baseline. However, there was a rise the duration from the index intra-articular injection increased as shown in.

Mean differences of 21.33, 15.6, and 15.2 were noted with WOMAC composite score in Grade 1 osteoarthritis between the baseline value and the first, second and third follow up visits respectively. And these particular differences were statistically significant [MD 21.33, 15.6, 95%, CI 13.95-28.72, 6.86-24.34, 6.09-24.30, p value 0.000, 0.002, and 0.003 respectively]. Similarly clinical and significant reduction in WOMAC composite score was found in Grade 2 and 3 osteoarthritis after intra-articular hyaluronic acid injection. However, statistically significant difference was not found between the baseline and each follow up visits composite WOMAC score in Grade 4 osteoarthritis knees as shown in Table 3.

WOMAC pain scores showed a decline in all grades of osteoarthritis knee following intra-articular hyaluronic acid injection when compared with the baseline values. There was an increase in the WOMAC pain scores as the duration of the follow up visit increased. Grade 1 and 2 osteoarthritic knees maintained low WOMAC pain scores till the last follow up visit while Grade 3 knees maintained it till the second follow up visit. Grade 4

osteoarthritic knees showed persistently high scores from first follow up visit itself.

The mean WOMAC stiffness scores decreased in all grades of osteoarthritis knee following viscosupple-

mentation but the scores were high as the grade of osteoarthritis increased. Increase in the stiffness scores when compared to the previous follow up visit were noted after intra-articular hyaluronic acid supplementation.

Table 3: Mean differences in WOMAC composite scores after viscosupplementation in different grades of osteoarthritis knee.

Grade	Visit	Mean	Mean difference	95% Confidence intervals		Sig (2- tailed)
				Lower limit	Upper limit	P value
	IV	39.8				
1 (N =15)	FU 1	18.4667	21.33333	13.94892	28.71775	0
	FU2	24.2	15.6	6.86198	24.33802	0.002
	FU3	24.6	15.2	6.09515	24.30485	0.003
	IV	50.2903				
2 (N =31)	FU 1	17.2903	33	27.03339	38.96661	0
	FU2	21.4839	28.80645	22.25006	35.36284	0
	FU3	27.3871	22.90323	16.5244	29.28205	0
	IV	59				
3 (N =19)	FU 1	22.3684	36.63158	31.00106	42.2621	0
	FU2	30.4737	28.52632	19.96234	37.0903	0
	FU3	39.5789	19.42105	11.00154	27.84057	0
	IV	57				
4 (N =5)	FU 1	30.2	26.8	2.41465	51.18535	0.038
	FU2	35.2	21.8	-3.90874	47.50874	0.078
	FU3	42.6	14.4	-9.8935	38.6935	0.175

Table 4: Mean differences in WOMAC pain scores following viscosupplementation in different grades of osteoarthritis knee.

Grade	Visit	Mean	Mean difference	95% Confidence intervals		Sig (2- tailed)
				Lower limit	Upper limit	P value
	IV	8.4				
1 (N =15)	FU 1	2.73	5.667	4.206	7.127	0
	FU2	4.47	3.933	2.067	5.799	0
	FU3	4.6	3.8	1.486	6.114	0.003
	IV	9.65				
2 (N =31)	FU 1	2.61	7.032	5.725	8.339	0
	FU2	3.58	6.065	4.488	7.641	0
	FU3	5.1	4.548	3.06	6.036	0
	IV	10.47				
3 (N =19)	FU 1	4.32	6.158	4.773	7.542	0
	FU2	5.42	5.053	3.657	6.448	0
	FU3	7.21	3.263	1.99	4.537	0
	IV	10.6				
4 (N =5)	FU 1	5.6	5	0.789	9.211	0.03
	FU2	6.6	4	-2.019	10.019	0.139
	FU3	8	2.6	-3.063	8.263	0.271

The mean differences of WOMAC stiffness scores between baseline and each follow visit after intraarticular hyaluronic acid administration noted in this study were of 2.13, 1.60, and 1.53 respectively. These differences were statistically significant at first and second follow up visits only [MD 2.13, 1.60, 1.53, CI 1.27-2.99, 0.60-2.6, 0.33-

2.73, p value 0.000, 0.004, 0.016 respectively for first second and third follow up visits]. Grade 2 patients showed statistically significant mean differences in stiffness scores till the end of the last follow up visit. Grade 3 osteoarthritic knees showed statistically significant difference like Grade 1 patients. Grade 4 WOMAC stiffness scores at any follow up visit did not

show statistically significant mean difference when compared to the baseline value.

Average WOMAC physical function scores decreased after the administration of hyaluronic acid injections in

all grades of osteoarthritis of knee. Grade 1 and 2 osteoarthritic knees maintained low scores throughout the study period following viscosupplementation. Grade 3 and 4 osteoarthritic knees showed elevated scores as the duration increased from the index injection.

Table 5: Mean differences in WOMAC stiffness scores after viscosupplementation in different grades of osteoarthritis knee.

Grade	Visit	Mean	Mean difference	95% confidence intervals		Sig (2- tailed)
				Lower limit	Upper limit	P value
	IV	3.6				
1 (N =15)	FU 1	1.47	2.133	1.274	2.993	0
	FU2	2	1.6	0.601	2.599	0.004
	FU3	2.07	1.53	0.333	2.733	0.016
	IV	3.87				
2 (N =31)	FU 1	1.35	2.516	1.802	3.23	0
	FU2	1.55	2.323	1.522	3.123	0
	FU3	1.87	2	1.219	2.781	0
	IV	4.37				
3 (N =19)	FU 1	2	2.368	1.594	3.142	0
	FU2	2.26	2.105	1.053	3.158	0.001
	FU3	2.84	1.526	0.397	2.655	0.011
	IV	5.2				
4 (N =5)	FU 1	2.2	3	0.366	5.634	0.03
	FU2	2.6	2.6	0.025	5.175	0.139
	FU3	3	2.2	-0.345	4.745	0.271

Table 6: Mean differences in WOMAC physical function scores following viscosupplementation in different grades of osteoarthritis knee.

Grade	Visit	Mean	Mean difference	95% Confidence intervals		Sig (2-tailed)
				Lower limit	Upper limit	P value
	IV	27.8				
1 (N =15)	FU 1	14.27	13.533	7.566	19.501	0
	FU2	17.73	10.067	3.479	16.654	0.006
	FU3	17.93	9.87	2.96	16.773	0.008
	IV	36.77				
2 (N =31)	FU 1	13.32	23.452	18.736	28.167	0
	FU2	16.35	20.419	15.623	25.216	0
	FU3	20.42	16.355	11.584	21.126	0
	IV	44.16				
3 (N =19)	FU 1	15.95	28.211	23.91	32.511	0
	FU2	22.79	21.368	14.689	28.047	0
	FU3	29.53	14.632	7.974	21.289	0
	IV	41.2				
4 (N =5)	FU 1	20.4	20.8	2.905	38.695	0.032
	FU2	26	15.2	-2.63	33.03	0.077
	FU3	31.6	9.6	-7.188	26.388	0.188

There was a mean difference of 13.53, 10.07 and 9.87 noted in WOMAC physical function score between baseline and the first, second and third follow up visits respectively in patients with Grade 1 osteoarthritis knee after viscosupplementation. These differences were

statistically significant (MD 13.53, 10.07, 9.87, CI 7.57-19.50, 3.48-16.65, 2.96-16.77, and p-value 0.000, 0.006, 0.008 respectively). Statistically significant mean differences of WOMAC physical function scores were found in grade 2 and 3 osteoarthritis knee. Statistical

significance was not achieved in Grade 4 osteoarthritis knee as shown in Table 6.

Adverse reactions

Increased pain and swelling developed in three patients following intra-articular hyaluronic acid injection. These patients were managed with NSAIDs and topical ice compressive. Increased pain alone developed in five patients and was managed with analgesics. Extrusion of hyaluronic acid into the extra-articular tissues due to faulty injection technique might have caused the pain and swelling.

Injection site erythema developed in one patient and subsided spontaneously after few days. Second dose of the injection was given slightly away from the erythematous region. Third dose was given at the standard superolateral entry point as the redness got completely disappeared. No systemic or serious adverse reactions were encountered in this study (Table 7).

Table 7: Data of adverse reactions in patients.

Adverse reaction	Number	Percentage
Erythema	1	11%
Pain and swelling	3	33%
Pain	5	56%

DISCUSSION

Therapeutic use of viscosupplementation in osteoarthritis of knee was first reported by Rydell and Balazs.⁵ The frequency of the use of viscosupplementation as a therapeutic strategy to manage primary osteoarthritis knee is increasing day by day, especially in young active patients presenting with symptoms of osteoarthritis knee.

Viscosupplementation might help in relieving pain to some extent in elderly patients who cannot undergo operative management in view of their medical comorbidities.

The mean age of the participants in this study is 51 years ranging from 35 to 65 years.

There is almost equal recruitment of male and female patients despite more prevalence of primary osteoarthritis knee among females. This can be attributed for majority of railway employees being manual laborers and are males. Eight out of seventy patients developed local adverse reactions in this series accounting for a complication rate of 12.85% which is in conformity with the reported literature. No serious adverse events were observed in this series.

Wang et al reported decrease in osteoarthritis knee symptoms following intra-articular hyaluronic acid injections.⁶ Aggarwal et al in their meta-analysis showed

that viscosupplementation is a good therapeutic choice in osteoarthritis knee patients not responding to non-operative measures.⁷ In this study, beneficial effects were found after viscosupplementation as shown by the decreased composite WOMAC scores at the end of fourth, eighth and twelfth month follow up visit when compared with initial visit WOMAC scores.

Some studies suggest that the beneficial effects of viscosupplementation are less likely to be seen in elderly patients and those with advanced radiographico-osteoarthritis of knee joint.^{8,9} Few studies suggested favourable response to intra-articular injection of hyaluronic acid in older population with advanced osteoarthritis knee, attributing it to increased sensitivity to the analgesic effect in this group of patients.¹⁰ In this study, it is observed that the WOMAC scores in Kellegren Lawrence Grade IV patients decreased in terms of pain, stiffness and physical function but statistical significance was not being achieved. Decrease in scores can be explained by the increased sensitivity to detect analgesic effects by these patients and statistical insignificance points towards unfavorable response to intraarticular hyaluronic acid in advanced osteoarthritis knee. This study has only five patients in middle age group with a mean age of 60 years with Grade IV osteoarthritis changes.

Studies have reported significant improvement in WOMAC pain and physical function following viscosupplementation for osteoarthritis knee.¹¹ This study showed improved pain, stiffness and physical function following intra-articular hyaluronic acid injections in patients with Kellegren Lawrence grade 1-3 osteoarthritis knees.

Clinically and statistically significant beneficial effects were observed in Kellegren Lawrence grade 1 and 2 osteoarthritis at the end of one year. Majority of patients in grade 3 either complained of increased symptoms by the end of second follow up visit or demanded for another dose of viscosupplementation. Though there is significant improvement in pain and physical function, the response is sustained for short term only in Grade 3 osteoarthritis of knee.

Despite of the statistically significant improvements in all the WOMAC subscales following viscosupplementation for grade 1-3 osteoarthritis knee, the scores in patients with greater radiological grade are higher as shown in the results of this study. And also, there is an increased trend in each WOMAC subscale score when compared with the prior follow up visit score after viscosupplementation. Increased trends of the WOMAC composite score, pain, stiffness and physical function scores with each consecutive follow up visit in this study suggests that the effect of intra-articular injection of hyaluronic acid wanes over time requiring repeat doses of viscosupplementation.

Arrich et al reported that there is no proven clinical benefit after viscosupplementation in osteoarthritis knee.¹² In their meta-analysis majority of the studies were low powered (<30 patients), the mean age of the populations in some of the included studies were above 65 years and there is no mention about the severity of the osteoarthritis. Randomized controlled trial by Lundsgaard et al demonstrated no significant difference in treatment outcomes between the hyaluran and saline injection groups indicating a high placebo response to intra-articular injections.¹³ This trial mentioned about the severity of osteoarthritis knee using Kellegren Lawrence grading in its population but did not do the subgroup analysis when computing the differences in outcomes. The revised AAOS 2013 osteoarthritis knee treatment clinical practice guidelines could not recommend viscosupplementation in the management of osteoarthritis of knee joints based on the lack of minimum clinically important improvement (MCII) in the three-high quality and eleven moderate quality research studies included in this analysis. Several reviewers have criticized the use of minimum clinically important improvement as a metric in view of its inherent faults in determining the clinically significant differences in treatment outcomes.¹⁴ In this study, clinically and statistically significant differences in WOMAC pain, stiffness and physical function following viscosupplementation were demonstrated in K-L Grade 1 and 2 osteoarthritis knee contradicting the results of the above-mentioned trials and guidelines. However, the findings in Grade 4 osteoarthritis knee of this study are in agreement with them.

CONCLUSION

Viscosupplementation with three consecutive doses of once weekly intra-articular hyaluronic acid injections following Kellegren Lawrence grade 1 and 2 osteoarthritis knee have shown clinically and statistically significant beneficial effects in terms of pain and function lasting till the end of one year in this series. In Kellegren Lawrence grade 3 osteoarthritis knees, viscosupplementation has shown good improvements in pain and physical function initially but the response did not sustain till the end of one year in majority of the patients as suggested by the increased scores in the last follow up visit in this series. Intra-articular hyaluronic acid injections are not useful in

Kellegren Lawrence grade 4 osteoarthritis knees as shown by the persistently high WOMAC scores in this group of patients in this study. Only local adverse reactions like increased pain, swelling and erythema occurred in this series in eight patients. All of them were managed with ice compressive and acetaminophen successfully.

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