International Journal of Research in Orthopaedics
Chaudhary S et al. Int J Res Orthop. 2022 May;8(3):339-344
http://www.ijoro.org

Original Research Article

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20221122

Study of clinical outcome of single intra-articular injection of artificial hyaluronic acid preparation in patients with grade III and grade IV knee osteoarthritis

Sumedh Chaudhary[1], Santosh Ghoti[2]*

[1]Department of Orthopedics, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India
[2]Department of Orthopedics, Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai, Maharashtra, India

Received: 16 February 2022
Accepted: 29 March 2022

***Correspondence:**
Dr. Santosh Ghoti,
E-mail: drsantoshghoti@rediffmail.com

ABSTRACT

Background: Knee osteoarthritis (OA) is problematic in elderlies. Intra-articular injection of hyaluronic acid (HA) has been used with good results in patients with early OA, but evidence to recommend their use in late stages is insufficient. The aim of the study was to analyse whether intra-articular injections of hyaluronic acid preparation can provide relief in patients with grade III and grade IV knee OA.
Methods: This observational study was conducted over 2 years amongst patients with late knee arthritis. On standing radiographs, patients were categorized- group 1 with stage III and group 2 with stage IV knee OA. Standardized technique was employed in all participants for single shot intra-articular hylan-GF-20 injection. Clinical outcomes were evaluated at 3, 6 and 12 months.
Results: Group 1 patients showed significant improvement in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at 3, 6 and 12 months ($p<0.05$). In group 2, improvement was noted in WOMAC score for pain and function at 3 months ($p<0.05$). There was no significant improvement in functional and total WOMAC score at 6 and 12 months ($p>0.05$). Results for the new OA research society international (OARSI) responder criteria measures for proposition D reflected that, 94.87% and 25% patients were responder and 5.13% and 75% of patients were non-responder in group 1 (grade III) and group 2 (grade IV) respectively at the end of 6 months.
Conclusions: In patients with grade III and grade IV knee OA, a single intra-articular injection of HA preparation (Hylan GF-20) showed pain relief for medium and short duration respectively. TKA remains the mainstay of management.

Keywords: Osteoarthritis, Intra-articular, Hyaluronic, Hylan GF-20, Outcome

INTRODUCTION

Life expectancy of Indian populace is increasing, due to better healthcare, amongst other reasons.[1] Prevalence of primary degenerative osteoarthritis (OA), which is mostly related to ageing, is also increasing with increase in the general senility.[2,3] Knee joints are the most common and worst affected and medial compartment is the most common site of OA knee, as medial compartment of knee bears 60-80% of the load during weight bearing.[4]

OA is essentially a dynamic process that may progress periodically in response to the variety of biomechanical, environmental and genetic stresses. Loss of joint movement results from the deprivation of nutrients to chondrocytes due to impairment of flow of synovial fluid. The concentration and molecular weight of synovial fluid

markedly decreases, leading to poor lubrication and load distribution in the joints. Therefore, supplementation of joints with exogenous hyaluronic acid (HA) (a natural complex sugar of glycosaminoglycan family), (visco-supplementation) has been proposed to restore rheological homeostasis of OA joints. Although there is no non-surgical cure for OA, these 'hylan GF-20' injections can relieve pain, reduce inflammation, improve range of motion and overall function.[5,6] Hylan GF-20 has been Food and Drug Administration (FDA) approved since 1997 for the treatment of patient with symptomatic OA knee and, according to current labelling, it can provide pain relief for up to 6 month; but has been shown in some studies to be effective beyond that, delaying total knee replacement for an average of as long as 2.1 years.[7,8] One Cochrane systemic review regarding efficacy data in general concluded that hylan GF-20 was significantly better than placebo for weight bearing pain, night pain, function and patient global assessment, significantly better than steroid and as effective as non-steroidal anti-inflammatory drugs (NSAID).[9] However, most studies have shown efficacy only in early stages of knee OA with arthroplasty being the definitive modality of treatment in advanced OA of the knee.

There is a subset of patients with advanced OA of the knee, which may not be willing for knee arthroplasty either due to familial or socioecomic reasons. NSAIDs remain the only source of pain relief in this subset of patients. There is dearth of locally relevant scientific data regarding the efficacy of intra-articular injection of HA preparation in such patients. The aim of the study was to analyze the efficacy of intra-articular injections of HA preparation in patients with advanced (grade III and grade IV) OA of knee.

METHODS

This was a prospective, observational study conducted between January 2017 and December 2018 (2 years) by the department of orthopaedics at a tertiary care government hospital in central India.

All the patients visiting the orthopaedics out-patient department at the study centre constituted the study population, out of which further selection of patients of knee OA was done as per the American College of Rheumatology (ACR) clinical criteria.

The ACR clinical criteria for diagnosis of OA is presence of knee pain along with at least three of the following six items: age >50 years, morning stiffness <30 min, crepitus on knee motion, bony tenderness, bony enlargement, and no palpable warmth.[10]

All patients clinically diagnosed as having knee OA were subjected to standing, full weight bearing radiographs of the knee joint in both antero-posterior and lateral projections. The Kellgren and Lawrence (KL) radiographic classification of OA knee was employed for staging and classifying severity of OA of knee joints amongst study participants: grade 0- no radiographic feature of OA, grade 1- doubtful joint space narrowing and possible osteophytes lipping, grade 2- definite osteophytes and possible joint space narrowing on antero-posterior weight bearing radiograph, grade 3- multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity, and grade 4- large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity.[11]

By using clinical and radiological criteria as mentioned above, patients with stage III and IV disease were recruited for the study by applying following selection criteria.

Inclusion criteria

Symptomatic knee with confirmed diagnosis on weight bearing radiograph, age more than 50 years, and patients who are reluctant or unable to undergo surgery due to economic or familial reasons or patients who are medically unfit for surgery or patients whose occupational demands preclude them from undergoing arthroplasty.

Exclusion criteria

Patients less than 50 years of age, patients with early (grade I and II) OA of knee, predominantly mechanical symptoms with well-preserved joint, rheumatoid arthritis/inflammatory disease, known history of allergy to any injectable, and patients with post-traumatic arthritis of knee were excluded.

The study was started after taking necessary approval from the institutional ethics committee. Patients with KL grade III and IV primary OA of the knee, who were not willing to undergo TKA were divided into two groups, group 1 consisting of patients with grade III OA and group 2 consisting of patients with grade IV disease. After detailed counseling regarding the procedure, its advantages and potential complications, written informed consent was obtained from each participant before the procedure. Detailed preoperative assessment was done using pre-validated case proforma.

Procedure

The technique for hylan-GF-20 injection followed a standardized method of aseptic no touch technique (Figure 1). The skin was prepared with alcohol and chlorhexidine solution and allowed to air dry. The knee joint was positioned in extension and an 18G needle was introduced from the supero-lateral aspect of the knee. The patello-femoral compartment was followed to allow easier access to the anterior portion of the joint space. Once it was confirmed that the needle had entered into the joint space by aspiration of synovial fluid, readymade prefilled sterile packed syringe was attached to the needle and slowly injected over 5-10 min. Once the hylan GF-20 solution was

pushed inside, the needle was withdrawn slowly and the site was covered with dry dressing. The patients were allowed full mobilization post-procedure and allowed to go home walking on their own. Safety of the procedure was evaluated by the occurrence of any adverse reaction immediately after the injection and or in the post injection period. If the patient had bilateral disease, the second knee was injected after an interval of 1 week.

Figure 1: Clinical photograph of the technique of hylan-GF-20 injection.

Baseline characteristics and diagnostic data was recorded at the initial visit and entered into prospectively collected database for evaluation of clinical outcomes at 3, 6 and 12 months. The baseline data included name, age, sex, side, unilateral or bilateral, weight, BMI, KL grading of OA knee, baseline Western Ontario and McMaster universities (WOMAC) OA score (for pain, stiffness and function) and patient global assessment (PGA) category.[12,13] Then at 3, 6 and 12 months, follow-up assessment with respect to (w. r. t.) WOMAC score, patient global assessment category and OARSI-OMERACT proposition D was undertaken and data recorded and comparisons drawn with baseline values.[12,13]

Data analysis was performed using statistical package for the social sciences (SPSS) (version 18). The continuous variables were handled by calculating the mean and standard deviation. P value>0.05 was considered statistically significant arbitrarily.

RESULTS

A total of 28 patients (23 patients with bilateral involvement and 5 patients with unilateral involvement) were studied as part of the present study. Thus, total '51 study knees' received treatment with hylan-GF-20 as per study protocol after recording baseline scores.

Out of 28 patients, 19 were female and 9 were male. The study group had an average age of 63.64 years, average weight of 63.85 kg, and average BMI index of 25.72. Out of total 51 knees, 25 were right sided and 26 were left sided. According to KL grading, 12 knees belonged to grade IV and remaining 39 knees belonged to grade III. Subsequent analysis was conducted by categorizing data between these 2 KL categories (grade III- group 1 and grade IV- group 2) (Figure 2).

WOMAC score for pain and function as assessed at baseline, at 3 months, 6 months and 12 months has been summarized in Table 1. Average baseline scores for pain, function and total WOMAC score of group-1 patients are 8.33, 27.05 and 36.07 respectively; and for group-2 scores are 12.08, 41.16 and 54.41 respectively. The WOMAC scores significantly improved after the intervention in the form of treatment with hylan-GF-20 in all patients of Group 1 (grade III) at 3 and 6 months ($p<0.05$), did slid slightly at 12 months but the improvement still remained significant vis-à-vis baseline ($p<0.05$).

In group 2 (grade IV OA knee), patients showed some improvement in WOMAC score for pain and function as compared to baseline score at the end of 3 month ($p<0.05$). However, this improvement deteriorated over time and by the end of 6 months patients were only slightly better in terms of pain ($p<0.05$) and by 12 months the WOMAC score for pain was higher in comparison to baseline. There was no significant improvement in functional and total WOMAC score at the end of 6 months and 12 months ($p>0.05$).

PGA grade/scale of 51 knees is as given below in Table 2. Out of 51 knees, the baseline score was fair in 7, poor in 36 knees and very poor in 8 knees on PGA scale, with no patients belonging to very good or good categories. The proportion of patients belonging to higher categories improved significantly after receiving hylan GF-20, although some patients belonging to grade IV did deteriorate again at 12 months w. r. t. PGA scores.

The overall result for the new OARSI responder criteria measures for proposition D are summarized in Table 3. An improvement >20% in pain or function is defined as responder in proposition D as per OARSI-OMERACT criteria. In our study we found in group 1 (grade III) OA knee, 94.87% of patients were responder and rest of 5.13%

were non-responder. In group 2 (grade IV) OA knee, 25% patients were responder and rest of 75% of patients were non-responder at the end of 6 months. At end of 12 months, 71.79% and 0% patients were responder, 28.21% and 100% patients were non-responder in grade III and grade IV OA knees respectively. This indicates no effect of hylan GF-20 Injection in grade IV OA knees at the end of 12 month. Out of the total 51 study knees, 5 (12.82%) of the 39 from group-1 (grade-III) and 8 (66.67%) of the 12 from group-2 (grade-IV) underwent arthroplasty by the end of one year.

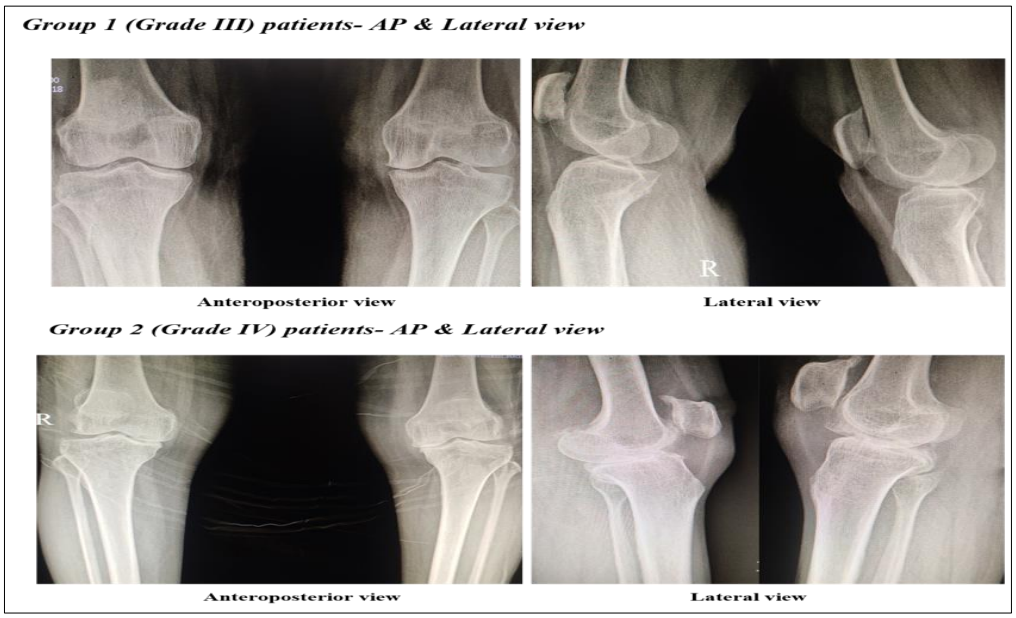

Figure 2: Radiological images- group 1 (grade III) and group 2 (grade IV).

Table 1: WOMAC scores amongst study participants at baseline, 3 months, 6 months and 12 months.

KL grade	WOMAC	Baseline			3 months			6 months			12 months		
		Score	Max	Min	Score	Max	Min	Score	Max	Min	Score	Max	Min
Grade III (group 1)	Pain	8.33	13	4	3.25	11	1	3.48	12	1	4.1	12	1
	Function	27.05	38	14	12.25	31	3	14.41	33	4	17.02	38	2
	Total	36.07	53	20	15.66	42	9	17.74	43	5	21.26	50	3
Grade IV (group 2)	Pain	12.08	13	11	9.95	13	6	10.83	13	7	12.17	14	10
	Function	41.16	48	31	30.86	39	15	37.33	47	19	42.36	30	48
	Total	54.41	62	45	43.7	54	21	48.75	60	26	55.27	64	42

Table 2: PGA grade amongst study participants at baseline 6 months and 12 months.

PGA	Baseline	6 months	12 months
Very good	-	-	3
Good	-	21	23
Fair	7	19	3
Poor	36	6	15
Very poor	8	5	7
Total	51	51	51

Table 3: OARSI responder criteria measures for proposition D during follow-ups.

OARSI	Baseline	6 months	Percentage	12 months	Percentage
Grade III (group 1) (n=39)					
Responder	-	37	94.87	28	71.79
Non-responder	-	2	5.13	11	28.21

Continued.

OARSI	Baseline	6 months	Percentage	12 months	Percentage
Grade IV (group 2) (n=12)					
Responder	-	3	25	0	0
Non-responder	-	9	75	12	100

Note: *-Responder >20% pain/function improvement, one shift improvement on PGA scale, and non-responder <20% pain/function improvement, no improvement on PGA scale

DISCUSSION

The pain-relieving mechanism of intra-articular injection of hyaluronic preparation, such as hylan GF-20, is yet to be completely elucidated. It has been suggested that the injections may stimulate the synthesis of endogenous HA and act as scavenger, reducing the amount of inflammatory degradation products in the joint.[14] It is further hypothesized that the viscoelastic and anti-inflammatory function of synovial fluid may be improved by the treatment.[14] The present study constituted a detailed clinical outcome analysis of consecutive patients of late knee OA treated by single hylan GF-20 intra-articular injection.

The subject of HA injection in the treatment of OA has been vastly studied. Within the literature a large number of clinical trials, systematic reviews and meta-analysis had sought to answer the questions of HA injection efficacy and how it compares to other treatment modalities. Wang et al conducted a meta-analysis of randomized controlled trials, which confirmed the therapeutic efficacy and safety of intra-articular injection of HA for the treatment of OA knee.[15] The effect of intra-articular injections of hyaluronic preparation (hylan GF-20) was further substantiated in the present study, as it demonstrates significant improvement in pain for medium term in grade III and for very short term in patients with grade IV OA of knee.

Majority of the patients with grade III OA did not require arthroplasty by the end of 1 year, a finding closely comparable to the study conducted by Tarek et al.[16] Most of the grade III OA knees showed significant improvement in pain, functional outcome at the end of 3 and 6 months, which echoes result of often quoted systematic analysis conducted by Bellamy et al.[17] One recently conducted randomized clinical trial compared hylan GF-20 single shot injection with corticosteroid injection and reported both group as having similar improvement in pain, knee function at the time of 6 months follow-up.[18]

Chevalier et al had reported single intra-articular injection of hylan GF-20 injection to be safe and effective in providing statistically significant, clinically relevant pain relief, as measured by WOMAC pain over 26 weeks, with modest difference with placebo, a finding corroborative with observations of the present study wherein WOMAC pain score significantly improved in most of the grade III patients and in some of grade IV OA knee at 6 months.[19]

Various criteria have been used to define patients as "responders" or "non-responders" to intervention by evaluating both constant and intermittent pain and taking into account pain intensity as well as distress and the impact of OA knee pain on quality of life.

Among them, OARSI responder criteria A, B and outcome measures in arthritis clinical trials (OMERACT-OARSI) proposition D have been validated in various studies to be able to detect clinically important statistically detectable differences between treatment groups.[17] In our study we found that among grade III OA knee patients, 94.87% of patients were responder at 6 months and 71.79% were responder at 12 months. In the group of grade IV OA patients, responders were 25% at 6 months and none of them were responder at 12 months. This indicates that hylan GF-20 injection have good efficacy in grade III OA patients and very poor efficacy in grade IV OA knees at the end of 12 month.

The principle limitation of the present study was the lack of accounting for possible confounding factor, which could influence the result of treatment. It is often difficult to translate evidence extracted from very tightly regulated environment of randomized controlled studies and apply it to the realism of everyday practice. This is very true for knee OA, a condition with complex natural history. The efficacy parameters reported above may have been heavily influenced by external factors. Another shortcoming of the present study is the lack of a comparative group. Also, we have studied the response of a single injection of HA. It would be interesting to see whether repeated injections of HA preparation at 6 monthly or 12 monthly intervals in selected patients with advanced OA of knee can provide pain relief for few years.

CONCLUSION

In conclusion, it can be said that in patients with grade-III OA of knee, hylan GF-20 injection can provide satisfactory pain relief with improvement lasting even up to 1 year. Hence hylan GF-20 injection can be used as a satisfactory treatment modality in patients with grade III OA knee. Although the results in grade IV patients are poor, they may be tried for very short-term relief in the exceptional circumstances when the patient wants to postpone their knee arthroplasty surgery for few months because of socioeconomic factors or familial reasons. Instead of becoming single therapeutic answer, the result presently reported can become an addition in the armamentarium of orthopedic surgeon when discussing treatment options with their patients.

Funding: No funding sources
Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. RGI. Sample Registration System Statistical Report 2011, 2013. Available at: https://censusindia.gov.in/Vital_Statistics/SRS/Sample_Registration_System.aspx. Accessed on 12 November 2021.
2. Silman AJ, Hochberg MC. Epidemiology of the Rheumatic Diseases. 2nd ed. Oxford: Oxford University Press. 2001;42-6.
3. Pal CP, Singh P, Chaturvedi S, Pruthi KK, Vij A, Epidemiology of knee osteoarthritis in India and related factors. Indian J Orthop. 2016;50:518-22.
4. Haq I, Murphy E, Dacre J. Osteoarthritis. Postgrad Med J. 2003;79:377-83.
5. Yang ZY, Chen W, Li CX, Wang J, Shao DC, Hou ZY, et al. Medial compartment decompression by fibular osteotomy to treat medial compartment knee osteoarthritis: a pilot study. Orthopedics. 2015;38(12):e1110-4.
6. Balazs EA, Denlinger JL. Visco-supplementation: a new concept in the treatment of osteoarthritis. The J Rheumatol. 1993;39:3-9.
7. Ng HY, Lee KA, Shen YF. Articular cartilage: structure, composition, injuries and repair. JSM Bone Joint Dis. 2017;1(2):1010.
8. Farrokhi S, Voycheck CA, Tashman S, Fitzgerald GK. A biomechanical perspective on physical therapy management of knee osteoarthritis. J Orthop Sports Physical Therapy. 2013;43(9):600-19.
9. Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino AJ, Mont MA. Knee osteoarthritis: a primer. Permanente J. 2017;21.
10. Wu CW, Morrell MR, Heinze E, Concoff AL, Wollaston SJ, Arnold EL, et al. Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. Semin Arthritis Rheumatism. 2005;35(3):197-201.
11. Menkes CJ. Radiographic criteria for classification of osteoarthritis. J Rheumatol. 1991;27:13-5.
12. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: international knee documentation committee (IKDC) subjective knee evaluation form, knee injury and osteoarthritis outcome score (KOOS), knee injury and osteoarthritis outcome score physical function short form (KOOS-PS), knee outcome survey activities of daily living scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res. 2011;63(11):208-28.
13. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure–an OARSI/OMERACT initiative. Osteoarthritis and Cartilage. 2008;16(4):409-14.
14. Wen DY. Intra-articular hyaluronic acid injections for knee osteoarthritis. Am Fam Physician. 2000;62(3):565.
15. Boutefnouchet T, Puranik G, Holmes E, Bell KM. Hylan GF-20 visco-supplementation in the treatment of symptomatic osteoarthritis of the knee: clinical effect survivorship at 5 years. Knee Surg Relat Res. 2017;29(2):129.
16. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee: a meta-analysis of randomized controlled trials. JBJS. 2004;86(3):538-45.
17. Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Visco-supplementation for the treatment of osteoarthritis of the knee. Cochrane database of systematic reviews. 2006;2.
18. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-articular, single-shot hylan GF-20 hyaluronic acid injection compared with corticosteroid in knee osteoarthritis: a double-blind, randomized controlled trial. J Bone Joint Surg Am. 2016;98:885-92.
19. Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, Bailleul F, Pavelka K. Single, intra-articular treatment with 6 ml hylan GF 20 in patients with symptomatic primary osteoarthritis of the knee: a randomized, multi-centre, double-blind, placebo-controlled trial. Ann Rheumat Dis. 2010;69(01):113-9.

Cite this article as: Chaudhary S, Ghoti S. Study of clinical outcome of single intra-articular injection of artificial hyaluronic acid preparation in patients with grade III and grade IV knee osteoarthritis. Int J Res Orthop 2022;8:339-44.