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Evaluation of efficacy and safety of intra-articular hylan G-F 20 injection in knee osteoarthritis in patients with repeat injection

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Abstract
Objective: To evaluate efficacy and safety of intra-articular hylan G-F 20 injection in patients with knee osteoarthritis.
Material and methods: In this prospective study, pain relief in adult patients with mild to moderate knee osteoarthritis treated with repeat injection of intra-articular hylan G-F 20 (6 ml) was assessed by visual analoge scale (VAS). Difference in pain relief at six months and one year of treatment was measured. Change in the pattern of analgesic use and type of medications used for pain relief were recorded.
Results: Twenty four patients (mean age 56.5 years; 45.83% male) were included. VAS score reduced significantly from 70.42±8.06 at baseline to 22.92±6.24 after six months (p<0.05) and 36.67±8.16 after 12 months (p<0.05). At baseline, 21 (87.50%) patients required two tablets of analgesics daily. After six months of treatment 12 (50%) patients did not require any oral analgesics. After one year of treatment number of patients taking two to three tablets per week were (29.17%). After the mean period of 14.21 (±1.72) years repeat injection was required.
Conclusion: Six ml intraarticular hylan G-F 20 provides effective pain relief in patients with mild to moderate knee osteoarthritis for slightly over one year and reduces requirement of analgesics.

Keywords: Hylan G-F 20, knee osteoarthritis, efficacy

Introduction
Osteoarthritis, the most common type of arthritis is seen in people across the world [1]. The disease is associated burden on the patient and family members because of diability caused by it and direct and indect cost involved in its management [2]. Surgical management is an option for the treatment of osteoarthritis, but only in limited number of patients [2]. Many patients seek non-operative treatment for osteoarthritis and several options are available for the same. Intra-articular injection of hyaluronic acid is one of the non-surgical treatment options for knee osteoarthritis. Hyaluronic acid preparations are generally classified as low molecular weight and high molecular weight formulation [2]. Cross linked formulations in addition to high molecular weight also have better visco-elastic properties and longer retention period in the joints. Hylan G-F 20 is a cross linked high molecular weight viscosupplementation [3] available in India for the treatment of mild to moderate osteoarthritis. Its efficacy and safety for one year has been demonstrated in Indian patients [41]. However, there are limited data on the patients with repeat injection with hylan G-F 20.

Objective
The objective of this study was to evaluate the efficacy and safety of intra-articular hylan G-F 20 injection up to one year in patients with knee osteoarthritis.

Material and methods
In this prospective study, adult patients with knee osteoarthritis (KL grade I to III) who received injection of intra-articular hylan G-F 20 (6 ml) were enrolled. Only those patients who recived the repeat injections were included. Patients with mechanical deformity, other knee abnorbalities and history of knee injury or surgery for knee related problems were

excluded from the study. Intensity of pain was assessed on visual analoge scale (100 mm VAS scale) at baseline, after six months and after one year. The difference in pain intensity at six and 12 months was determined. Grade of knee osteoarthritis was recorded on X rays as per Kellgren and Lawrence system[5] at baseline, six months and 12 months. The change in the pattern of analgesic consumption was evaluated by recording number of analgesic tablets/injections and type of medications used for pain relief. Time interval of repeat injection from baseline was also measured. All the patients were advised standard physiotherapy and modification of daily activities.

Statistical analysis

Categorical data are presented as number and percentages. Continous data are presented as mean and standard deviation. The difference in pain relief was determinined by using paired t test. P value of less than 0.05 was considered as statistically significant.

Results

The study enrolled a total of 28 patients out of which 4 were excluded (2 patients lost in follow up, one patient underwent knee arthroscopy and one patient received intraarticular steroid injection. So we included 24 adult patients with knee osteoarthritis. The mean age of study participants was 56.5 (±7.03) years (range 44-67 years). The number of male and female participants were 11 (45.83%) and 13 (54.17%) respectively. The mean body mass index (BMI) of patients was 24.84 (±1.97) kg/m^2.

A total of 14 (58.33%) patients had osteoarthritis in both knees. Distribution of patients with involvement of left knee, right knee and bilateral knees is given in figure 1.

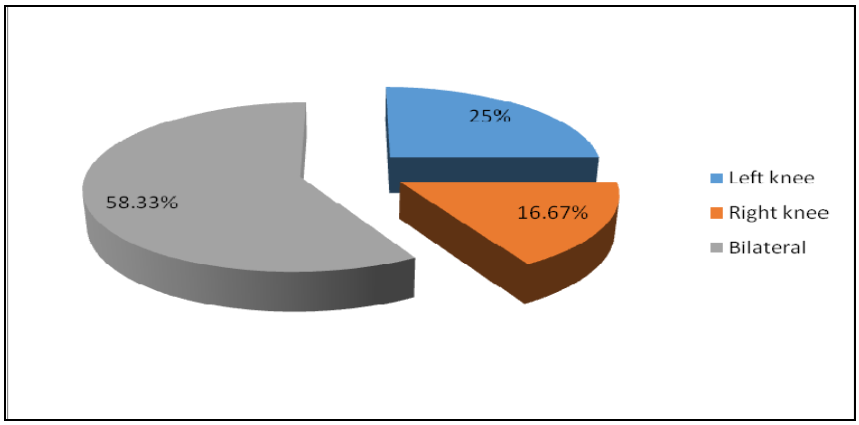

Fig 1: Distribution of knee osteoarthritis

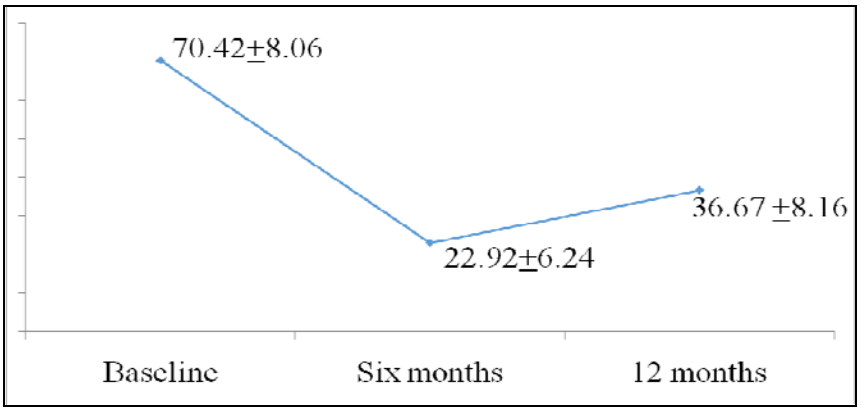

Fig 2: Pain according to VAS score at different visits

Pain score on the VAS scale reduced from 70.42±8.06 at baseline to 22.92±6.24 after six months and 36.67±8.16 after 12 months (figure 2). Reduction in VAS scale from baseline to six month was 67.45% whereas from baseline to 12 months it was 47.93%. The difference from baseline to six months and 12 months was statistically significant (p<0.05). Pain score increased from 22.92±6.24 to 36.67±8.16 (60% increase; figure 2). The difference in pain score from six months to 12 months was also statistically significant (p<0.05).

Number and percentages of patients with different grades of osteoarthritis are given in table 1. At baseline, number of patients with grade I, II and III were 3 (12.50%), 17 (70.83%) and 4 (16.67%) respectively. After six months and 12 months number of III patients did not change. However, one patient from grade I progressed to grade II osteoarthritis (table 1).

Table 1: Grade of osteoarthritis

	Pre-injection N (%)	Six months N (%)	One year N (%)
Grade I	3 (12.50%)	3 (12.50%)	2 (8.33%)
Grade II	17 (70.83%)	17 (70.83%)	18 (75%)
Grade III	4 (16.67%)	4 (16.67%)	4 (16.67%)

At baseline, 21 (87.50%) patients required two tablets of analgesics daily whereas two (8.33%) patients needed one tablet daily. One patient was receiving two tablets of analegsics daily in addition to two to three injections per week. After six months of treatment 12 (50%) patients did not require any oral analgesics whereas seven (29.17%) and five (20.83%) patients required one to two tablets daily and two to three tablets daily respectively (table 2). After one year of treatment number of patients taking two to three tablets per week were (29.17%).

Table 2: Need of oral analgesics in study participants

	Baseline N (%)	Six months N (%)	One year N (%)
Nil	--	12 (50%)	1 (4.17%)
Daily 1 tablet	2 (8.33%)	--	--
1-2 tablets per week	--	7 (29.17%)	7 (29.17%)
Daily 2 tablets	21(87.50%)	--	--
2-3 tablets per week	--	5 (20.83%)	12 (40%)
3-4 tablets per week	--	--	3 (12.5%)
4-5 tablets per week	--	--	1 (4.2%)
Daily 2 tablets + 2-3 injections per week	1(4.17%)	--	--

Table 3: Types of oral analgesics used in the study participants

	Baseline N (%)	Six months N (%)	One year N (%)
Nil	--	11 (45.83%)	1 (4.17%)
Aceclofenac	7 (29.17%)	3 (12.50%)	8 (33.33%)
Diclofenac	9 (37.50%)	4 (16.67%)	10 (41.67%)
Ibuprofen plus paracetamol	5 (20.83%)	3 (12.50%)	2 (8.33%)
Tramadol plus paracetamol	3 (12.50%)	2 (8.33%)	3 (12.5%)
Missing data	--	1 (4.17%)	--

At baseline, number of patients taking aceclofenac, diclofenac, ibuprofen plus paracetamol and tramadol plus paracetamol were seven (29.17%), nine (37.50%), five (20.83%) and three (12.50%) respectively. After six months of treatment, no analgesic was required in 11 (45.83%). The number of patients taking different analgesics after six months is given in table 3. After 12 months of treatment, aceclofenac and diclofenac was required in eight (33.33%) and ten (41.67%) respectively. After the mean period of 14.21 ($\pm$1.72) years repeat injection was required in the study participants. Hylan G-F 20 intra-articular injection, both initial and repeat therapy was very tolerated without serious adverse events.

Discussion

Knee osteoarthritis is a common clinical problem in orthopaedic clinic practice. Traditionally known as a disease of old age, is seen even in young individuals [1]. In our study, the mean age of study participants was 56.5 years, but more than half (54.17%) patients were less than the mean age, suggesting early occurance of knee osteoarthritis.

Female gender is one of the significant risk factors for knee osteoarthritis.[6] In our study, females outnumbered, but male population was also high i.e. 45.83%. Obesity is also a known risk factor for knee osteoarthritis [6]. The mean BMI of patients in our study was 24.84 kg/m^2. There were only 9(37.5%) patients with BMI of 25 kg/m^2 or more. Although our main objective was not to examine the risk factors for knee OA, these observations suggest that knee OA is common in males as well as those with normal BMI. Another an observation worth reporting is high occurance of bilateral osteoarthritis.

Worldwide many studies have demonstrated efficacy and safety of hylan G-F 20 in patients with knee osteoarthritis [7, 11]. The long term efficacy up to one year is also been demonsarted in several trials [4, 8, 12]. There are limited data from Indian patients especially those who have received repeat injection of hylan G-F 20. Our study is important from that perspective. We observed efficacy of hylan G-F 20 in providing pain relief for one year. The reduction in pain can be attributed to analgesic activity of Hylan G-F 20 [2].

Shortly after one year, all of the study participants required second injection of hylan G-F 20. The VAS score after 12 months of initial injection was still significantly lower compared to baseline, but was higher than that after six months.

Although, a study has shown that knee replacement can be delayed with hylan G-F 20 when given in patients with patients with severe osteoarthritis of knee joint [13], this is not an ideal patient population for injection. The ideal patient population for the use of viscosupplementation is not known. However, the evidence suggests that the benefit of viscosupplementation is more likely in younger patients and those with earlier grades of the disease [2]. Similar to a published study [4] from India, we also included patient up to grade III knee osteoarthritis. In our study, all except three patients had greade II-III osteoarthritis. There were only three patients with grade I knee osteoarthritis. In these three patients hylan G-F 20 was injected because of severe pain in the knee disproportionate to findings on X ray.

Intraarticular injection of hylan G-F 20 with appropriate care results in better response compared to only appropriate care [14]. Judicious use of analgesics, exercise and lifestyle modification are the components of appropriate care. Analgesic consumption is known to be associated with several complications including gastrointestinal, renal and cardiovascular adverse events [2]. Physicians as well as patients seek therapuetic options which can reduce requirement of analgesics in osteoarthritis. Hylan G-F 20 injection in patients with knee osteoarthritis has been shown to reduce the intake of analgesics [15]. Reduction in analgesic consumption after hylan G-F 20 intraarticular injection was evidence in this study, both at six and 12 months after initial therapy. This is important from the point that, in countries like India, over the counter consumption of non-steroidal anti-inflammatory agents (NSIADs) is common. Patients may not be aware about serious complication of self consumption of NSAIDs without healthcare profesional's advice. Hylan G-F 20 administation both initial and repeat injection was well tolerated without any serious adverse events.

Overall, we found efficacy of hylan G-F 20 for slightly over one year with reduction in requirement of analgesic agents. Our study has some limitations. Possibility of over the counter medications by some can not be excluded. We did not capture the use of over the counter medications and local analgesic applications used by the patients during one year after initial injection of hylan G-F 20. Single group study design, single center data and small sample size limit generalization of findings to entire universe of patients with knee osteoarthritis. Nevertheless, this study provides significant insights for the use of intra-articular injection of hylan G-F 20 in Indian patients.

Conclusion

Hylan G-F 20 intraarticular injection is effective for slightly over one year in providing pain relief in patients with knee osteoarthritis. Initial as well as repeat injection is well tolerated without serious adverse events. Analgesic requirement in knee osteoarethritis is reduced after hylan G-F administration.

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