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Efficacy of intra-articular hyaluronic acid in relief of pain in Kellgren and Lawrence grade 2 and 3 osteoarthritis knee

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Abstract
Introduction: Intra-Articular Hyaluronic Acid (IA-HA) supplementation not only improvises the synovial fluid flow dynamics and viscoelasticity but also potentially offers a positive effect on the arthritic disease process by promoting *in vivo* IAHA production and by providing an intra-articular anti-inflammatory effect.
Objective: The primary objective of this study was to compare a single 6ml, intra-articular injection of hylan GF-20 with conservative treatment in patients with symptomatic mild to moderate knee Osteoarthritis (OA).
Methodology: Patients with primary OA knee pain were randomly assigned to arthrocentesis plus a 6ml intra -articular injection of either hylan G-F 20 or conservative methods of treatment in a prospective, single-blinded (evaluator) randomised control study. Results were evaluated at Pre Injection, 3, 8, 16 and 24 weeks post-injection. The primary outcome criterion was change from baseline over 24 weeks in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index and VAS Score.
Results: A total of 70 patients (Kellgren–Lawrence grade II or III) was randomly assigned. Patients receiving hylan G-F 20 experienced statistically significantly greater improvements in WOMAC scores and VAS scores, than patients receiving conservative treatment. No increased risk of local adverse events was observed.
Conclusions: This prospective randomised control study demonstrated that, in patients with knee osteoarthritis, a single 6 ml intra-articular injection of hylan G-F 20 is safe and effective in providing statistically significant, clinically relevant pain relief over 24 weeks, with a modest difference versus conservative treatment.

Keywords: IA-HA, OA Knee, VAS, WOMAC

Introduction
As OA knee advances in its natural course of history it is characterised by loss of articular cartilage, subchondral sclerosis, joint deterioration and osteophyte formation [1]. According to Kellgren-Lawrence classification [2] OA knee is divided into 4 grades. There are different treatment modalities for OA knee amongst which are physiotherapy exercises, medical management with pharmacological drugs and surgical treatment [3]. The need for surgical intervention often arises only when the symptoms of OA are not relieved by conservative means. There is still insufficient evidence available regarding the effectiveness of commonly available methods of conservative treatment [4]. Albeit many frequent and serious side effects of medical management by pharmacological drugs esp. from the category of NSAIDs are known but they are still recommended commonly because they act fast [4].
The normal adult knee joint has around 3.0 mL of synovial fluid (SF), with a hyaluronic acid (HA) concentration of 2.5 to 4.0 mg/Ml [5], which decreases during the initial phase of the OA disease process. Intra-articular type B synoviocytes and fibroblasts synthesize *in vivo* HA, that gets secreted into the joint space. The mean molecular weight of HA in the synovial fluid is 5 to 7x106 Da [6]. With OA, both the concentration as well as molecular weight of HA are decreased by 33% to 50% [7, 8], resulting in further joint breakdown and articular cartilage degeneration. HA acts as the primary protective component of SF for the joint due to its properties of adding viscosity and elastic strength altering the protective barrier as well as flow

dynamics of synovial fluid, which are related directly to HA concentration [9]. Data points towards the fact IAHA supplementation not only improvises the SF flow dynamics and viscoelasticity but also potentially offers a positive effect on the arthritic disease process by promoting *in vivo* IAHA production and by providing an intra-articular anti-inflammatory effect [10,11,12].

Material and Methods

The study was carried out in Department of Orthopaedics, ESIC Model Hospital and PGIMSR, Basaidarapur, New Delhi for a period of 18 months i.e. from October 2017 to March 2019. 70 Patients attending Out Patient Department (OPD) of ESIC Model Hospital and PGIMSR, Basaidarapur, New Delhi with mild to moderate primary osteoarthritis ((*Kellgren & Lawrence* grade 2& 3) between the age of 40-80 years of both male and female gender were included. Patients who had severe OA Knee, inflammatory arthropathies, RA, coagulopathies, Hyperuricemia were excluded from the study. After taking informed consent, the target population was randomized using simple randomisation method into two groups i.e group A and group B of 35 people each with similar baseline characteristics.

a. Group A: Intra-articular hyaluronic acid group/case group.
b. Group B: conservative treatment/ control group.

This study was a single blinded trial as the evaluator was blinded and he didn't know whether the patient is categorised into which group and what was given to the patient. Enrolled patients in IA-HA group received one Hylan G-F 20 6ml; 8mg/ml (Synvisc-One) injection intra-articularly under routine strict aseptic conditions. The approach used for injection of IA-HA was Anterolateral approach also known as Infrapatellar approach or the arthroscopic approach since portals used in knee arthroscopy are analogous to this approach [13, 14]. These approaches are particularly important when the knee cannot be extended or the knee joint has a minimal fluid [15] in it. In this approach the knee is first flexed and then the needle is inserted laterally of the patellar tendon [16] with the direction of the needle towards the femoral notch [17, 18]. This approach passes only through Hoffa's fat pad avoiding major blood vessels and the extensor apparatus. After inserting the needle, SF or any effusion is first aspirated and then IA-HA injected under strict aseptic conditions after painting and draping After giving the injection patients were asked to avoid excessive mobilisation and strenuous or prolonged (greater than 1hr) exercises for the next 2 days along with advice of cold compression. They were informed that they may have temporary swelling or pain. Whereas enrolled patients in conservative treatment group were managed conservatively with physiotherapy, exercises and lifestyle modifications.

Follow-up and assessment

The patients were then followed up at the interval of 3rd week, 8th week, 16th week, and final follow up at 24th week. No NSAIDs was prescribed during follow up period and paracetamol (dosage, 500 mg TDS) was given in case of discomfort. All patients were asked to stop medications 48 hours before follow-up assessment.

Assessment was done by using two scores *viz*. visual analogue score and WOMAC score. Statistical analysis was done with the help of computer using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 22.0 for Windows). A 'p' value less than 0.05 was taken to denote significant difference.

Observations and Results

Following points were drawn from our study

- The study recruited 70 patients, randomised into two Groups, 54.3% of all patients in both subsets were found to be from 51-60 years of age. Mean age of group A and group B was 55.17 ± 10.05 and 55.49 ± 10.45 respectively. 37 males and 33 females were recruited.
- On radiological evaluation, highest number of patients 55.71% were from K/L Grade II. 39(55.71%%) patients had K/L grade II osteoarthritis and 31(44.29%) patient had K/L grade III
- Pain evaluated by the use of VAS score, showed the mean of pain score for HA group as 6.77 pre-injection. From here, the value reduced to 6.23 after 3 weeks. Progressive improvement was noted, at 8 weeks it was at 5.37, at 12 week 4.29 and at 24 week 3.49. For VAS score, HA was efficacious than conservative treatment by a significant margin at 8 week, at 16 week and 24 week ($p< 0.05$).
- Management with IA-HA injections also provided relief in knee pain, stiffness and function as analysed by the WOMAC score in the 2 groups, with differences of significant level. WOMAC for diseased knees was 59.71 before treatment. From here, the values reduced to 54.14 at 3 weeks. Progressive improvement noted with the values being 44.97, 36.91 and 28.43 at 8 weeks, 12 weeks and at 24 weeks respectively. For WOMAC pain, HA was efficacious than conservative treatment by significant margin at 8 weeks, at 16 weeks and at 24 weeks ($p< 0.05$). An advantage of HA in comparison to conservative treatment also was noted for stiffness of the knee ($p< 0.05$) and physical function ($p< 0.05$) at week 8, week 16 and at week 24 IA-HA improvised knee pain and function in the first 3 weeks with insignificant differences between the groups. Significant benefit ($p< 0.05$) were noted with IA-HA at 8 week 8, further improvising at week 16 and continuing upto week 24.
- There were no serious adverse reactions noted during the study in the patients of both the groups.

Discussion

The lesions of articulating cartilage and degenerative changes are tedious to manage and it is a challenging work for the orthopedists around the world because of distinct characteristics of hyaline cartilage and its inherent low healing potential. Pain was the major reason for the patients to seek treatment for their knee problems. The time of presentation of such patients for treatment was variable due to variation in activity related discomfort. The pain threshold in patients is variable, some are able to withstand pain for longer duration than others.

Patients were reviewed in our study at pre-treatment phase and post treatment with either IA-HA or conservative means at 3,8,16 and 24 weeks. The need for this study arose from the fact that because of Indian lifestyle there is wide prevalence of OA in our population and to analyse the efficacy of IA-HA in disease of mild to moderate category which is often managed by conservative means.

Age and sex distribution

In a similar trial conducted by Navarro-Sarabia F *et al*. (2011) [19], of 306 patients having K/L grade 2 and 3 the mean age (SD) of the patients in study and control group were 63 (8.2) and 63.9 (8.9) years respectively. In another trial conducted by Chevalier X *et al*. 2010 [20] randomising 253 patients the mean

age (SD) of the patients in the above 2 groups were 63.6 (9.64) and 62.5 (9.17) respectively. The lower mean age in our study could be explained by the fact that in Indian subcontinent there is early onset of osteoarthritis due to habit of squatting and sitting cross-legged since childhood.

In the trial conducted by Navarro-Sarabia F *et al*. [19] (2011) of 306 patients, 83.7% of patients in both the HA and placebo group were females. Whereas In the trial conducted by Chevalier X *et al*. [20] 2010 randomising 253 patients 74.19% patients were females in IA-HA group and 68.21% patients in placebo group were females. Therefore our findings are not in concordance with these global studies. In our study the overall male group is slightly higher than the females because males working in industries are affected more rapidly from OA in India and due to pain during working they come early for treatment. Also we cater mainly to industrial workplace and the percentage of males are generally higher in Indians.

Radiological grading of oa knee

In the trial conducted by Navarro-Sarabia F *et al*., 2011, 70.6% of patients were from K/L Grade 2 in HA group and 29.6% from K/L Grade 3. In the placebo controlled group 74.5% patients were from K/L grade 2 and 25.5% patients were from K/L grade 3. In this trial overall number of patients were higher in K/L grade 2. In the trial conducted by Chevalier X *et al*. 2010, 51.2% patients were from K/L grade 2 in HA group and 48.8% patients from K/L grade 3.In this study in placebo group 40% patients were from K/L grade 2 and 60% patients were from K/L grade 3. Therefore in this group overall higher number of patients were from K/L Grade 3 by a slight margin. From the above we can draw a conclusion that our study in the aspect of K/L grading was more closer to the study by Navarro-Sarabia F *et al*., [19] 2011 albeit it had more number of patients in K/L grade 2 by a major margin because a higher number of patients might have reported earlier for treatment of knee pain owing to more awareness about disease and better percolation of health facilities in western countries, although this pattern was not noted in the trial conducted by Chevalier X *et al*. [20] 2010. More or less in aspect of K/L grading our sample was similarly distributed in comparison to these trials conducted.

VAS and WOMAC score

Majority of the studies have compared IA-HA with placebo taking generally normal saline as placebo whereas our study compares IA-HA efficacy with conservative methods of treatment. Also the trial period of such studies have been long and owing to time constraints and a smaller sample size it becomes difficult to compare on exact lines our study with previously performed studies. Also there is a significant heterogeneity in the MW of Hyaluronic acid used in these trials along with variation in the number of such injections being repeated from time to time in the course of study. Different trials have used different parameters for assessment of the end results. Nevertheless the studies which are similar to our study in assessment parameters and using HMW Hyaluronic acid are discussed here. The study by Altman *et al*., 2011 [21] assessed VAS and WOMAC (Pain), and showed that patients who were managed with IA-Bio HA maintained achieved improvement from baseline with mean reduction in pain in VAS score of -3.5 mm. Benazzo *et al*. [22], 2016 used biologically derived HMW HA in study and assessed WOMAC (pain) found improvisation in WOMAC A1 pain scores by significant margins. Patients managed with 2 cycles of IAHA sustained relief in knee pain 52 weeks post initiation of treatment. Strand Lim and Takamura [23], 2016 assessed VAS and WOMAC (pain) scores and found statistically significant lowering of pain from baseline over 26 weeks. Mean scores and changes from baseline were significantly different in the between-group analysis ($p < 0.001$). Waddell *et al*. [24], 2005 analysed WOMAC (pain) VAS (pain) and noted that all parameters of pain significantly improved from baseline at week 26 and week 52. In a study conducted by Pal *et al*. [25] 2014 it was found that at 26 weeks, changes from baseline which were statistically significant were noted in all parameters analysing efficacy including the primary efficacy endpoint of WOMAC A1 ($p < 0.0001$). Another study conducted by Strand V *et al*., [26] 2012 analysing a total of 379 patients which was a multicenter randomised controlled trial comparing single IA injection of Gel-200, a new HA cross linked composition to phosphate buffered saline (PBS) for treatment of OA found that by assessing WOMAC pain subscores benefits of Gel-200 were statistically significant at week 13 (p=0.037). In this study in the study group total WOMAC score (100mm) was 69.5(15.99) and control group total WOMAC was 67.8(14.68). In comparison in our study baseline WOMAC in study and control group are 59.71 ± 6.47 and 60.43 ± 5.16 respectively.

In our study no adverse effects like swelling, painful knee or localised rise of temperature was noted. In our study of the efficacy in the population, statistically significant advantages of treatment relative to the conservative treatment were observed from 3 to 24 weeks. In other studies, comparable findings were noted with the intent to treat population by investigators, who evaluated the role of this IA-HA in OA knee [27, 28]. In our study significant differences statistically were noted in the two groups when VAS and WOMAC scores were analysed. HA reduced knee pain, stiffness and provided better functional mobility. After the IA-HA, the benefit of symptom relief at Week 8 was consistent with the durability of pain relief reported with other hyaluronic acid formulations [29, 30]. In a study by Adams M E *et al*. 1995 which was a Canadian multicenter trial comparing Hylan GF-20 (Synvisc) efficacy given with NSAIDs and with NSAIDs alone using VAS (100 mm scale) scores for analysis of pain in different situations like pain with motion, pain at rest, pain at night, restriction of activity, overall arthritic pain assessment found statistical significant superior results at 26 weeks in GF-20 + NSAIDs group compared to NSAIDs only group. For instance in the 2 above groups at 26 weeks, pain at rest mean VAS (100 mm scale) score (SE) were 11(3) and 22 (3) respectively [29]. These scores were similar to findings of our study. In our study Mean ± St Dev VAS scores at 24 weeks in study and control group were 3.49 ± 1.01 and 6.17 ± 0.98 respectively with a p value between the 2 groups being <.0001. Therefore the findings of our study are consistent with this study in respect of VAS scores. We believe that this treatment resulted in satisfactory outcome and that IA-HA can be an option worth considering for management of OA knee especially in mild to moderate OA who are not worth considering for surgery at this stage or to reduce side effects associated with NSAIDs treatment or allergy to glucosamine products. Though we would also like to emphasize that there is more room for studies on this topic to improve the formula for IA-HA preparation, duration of regimen, and method of administering this injection.

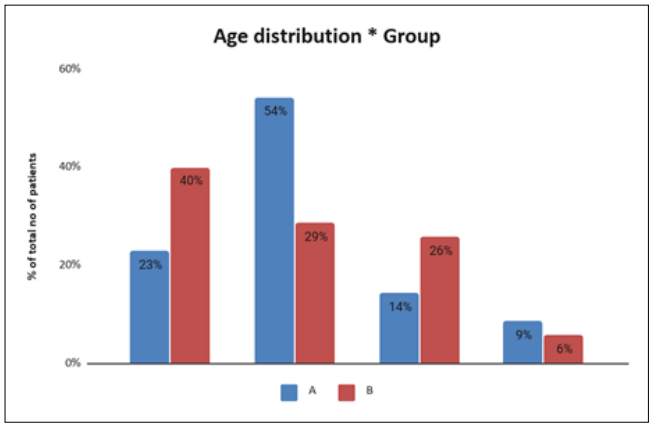

Fig 1: KL grading

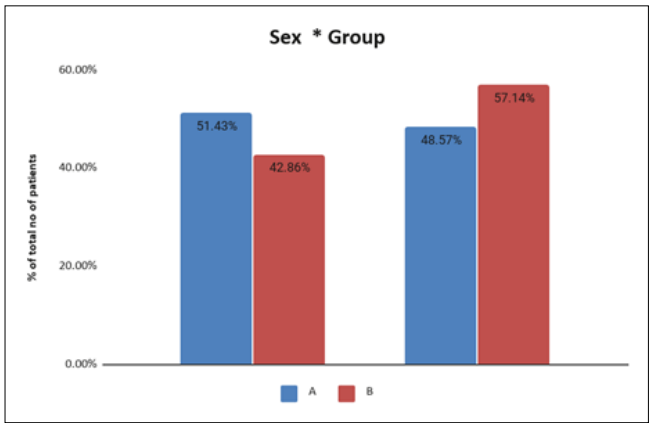

Fig 2: Sex Group

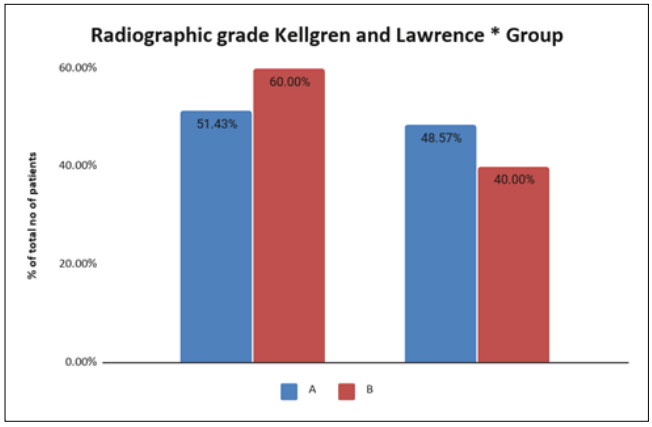

Fig 3: Age distribution

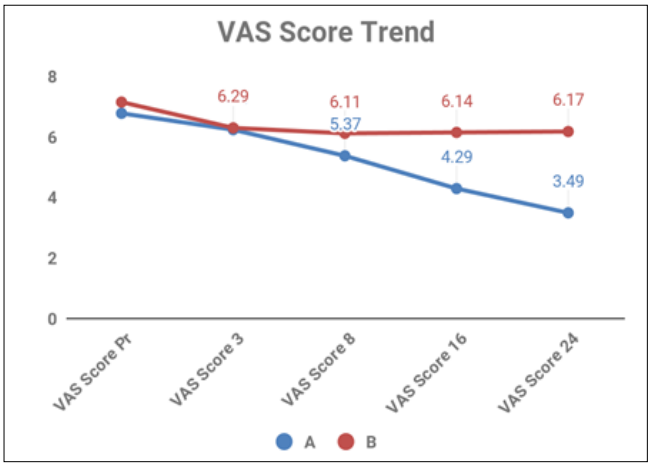

Fig 4: VAS score

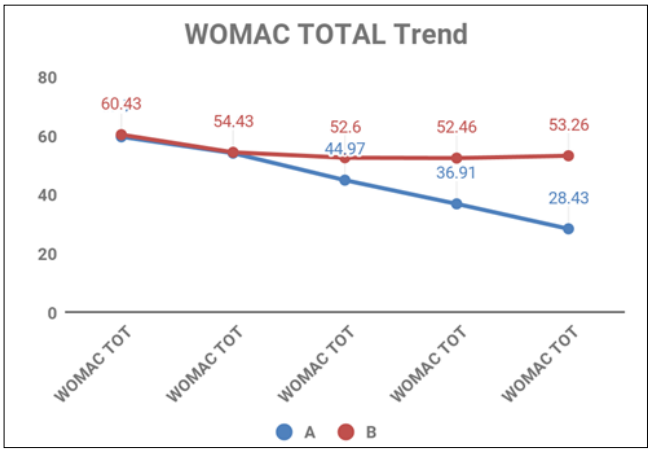

Fig 5: WOMAC score

References

1. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet. 2005; 365:965-973.
2. Rutjes AW, Juni P, da Costa BR *et al*., Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med. 2012; 157:180-191.
3. Carr AJ, Robertsson O, Graves S *et al*., Knee replacement. Lancet. 2012; 379:1331-1340.
4. Zhang W, Nuki G, Moskowitz RW *et al*. OARSI recommendations for the management of hip and knee osteoarthritis part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010; 18:476-499.
5. Watterson JR, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. J Am. Acad. Orthop. Surg. 2000; 8:277Y84.
6. Gibbs DA, Merrill EW, Smith KA *et al*. Rheology of hyaluronic acid. Biopolymers. 1968; 6:777Y91.
7. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res. Ther. 2003; 5:54Y67.
8. Bressan E, Favero V, Gardin C *et al*. Biopolymers for hard and soft engineered tissues: application in Odontoiatric and plastic surgery field. Polymers. 2011; 3:509Y26.
9. Brockmeier SF, Shaffer BS. Viscosupplementation therapy for osteoarthritis. Sports Med Arthrosc. 2006; 14(3):155-162.
10. Zhang W, Nuki G, Moskowitz RW *et al*. OARSI recommendations for the management of hip and knee osteoarthritis part III: Changes in evidence following systematic cumulative update of research published through. Osteoarthritis Cartilage. 2009-2010; 18:476-499.
11. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and Hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res. Ther. 2003; 5:54Y67.
12. Goldberg VM. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. Osteoarthritis Cartilage. 2005; 13:216-224.
13. Zurlo JV, Towers JD, Golla S. Anterior approach for knee arthrography. Skeletal Radiol. 2001; 30:354-356.
14. Moser T, Moussaoui A, Dupuis M *et al*., Anterior approach for knee arthrography: tolerance evaluation and comparison of two routes. Radiology. 2008; 246:193-197.
15. Neustadt DH. Intra-articular injections for osteoarthritis of

the knee. Cleve Clin J Med. 2006; 73(10):897-8, 901-4, 906-11.
16. Zuber TJ. Knee joint aspiration and injection. Am Fam Physician. 2002; 66(8):1497-500, 1503-4, 1507.
17. Esenyel C, Demirhan M, Esenyel M *et al*., Comparison of four different intra-articular injection sites in the knee: a cadaver study. Knee Surg Sports Traumatol Arthrosc. 2007; 15(5):573-7.
18. Waddell D, Estey D, DeWayne C *et al*., Viscosupplementation under fluoroscopic control. Am J Med Sports. 2001; 3:237-241.
19. Navarro-Sarabia F, Coronel P, Collantes E *et al*. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intraarticular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis. 2011; 70(11):1957-1962.
20. Chevalier X, Jerosch J, Goupille P *et al*. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis. 2010; 69(1):113-119.
21. Altman RD, Rosen JE, Bloch DA *et al*. Safety and efficacy of re treatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX Trial. Osteoarthr Cartil. 2011; 19:1169-75.
22. Benazzo F, Perticarini L, Padolino A *et al*. A multi-centre, open label, long-term followup study to evaluate the benefits of a new viscoelastic hydrogel (Hymovis®) in the treatment of knee osteoarthritis. Eur Rev Med Pharmacol Sci. 2016; 20:959-68.
23. Strand V, Lim S, Takamura J. Evidence for safety of retreatment with a Singleintra articular injection of Gel-200 for treatment of osteoarthritis of the knee from the double-blind pivotal and open-label retreatment clinical trials. BMC Musculoskelet Disord. 2016; 17:240.
24. Waddell DD, Cefalu CA, Bricker DC. A second course of hylan G-F 20 for the treatment of osteoarthritic knee pain: 12-month patient follow-up. J Knee Surg. 2005; 18:7-15.
25. Pal S, Thuppal S, Reddy KJ *et al*. Long-term (1-year) safety and efficacy of asingle 6-ml injection of Hylan G-F 20 in indian patients with symptomatic knee osteoarthritis. Open Rheumatol J. 2014; 20:54-68.
26. Strand V, Baraf HS, Lavin PT *et al*., A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteoarthritis Cartilage. 2012a; 20(5):350-356.
27. Kalay S. The Effectiveness of Intraarticular Hyaluronic Acid Treatment in Primary Gonarthrosis. MD Thesis. Ankara, Turkey, Ankara Numune Hospital, Physical Therapy and Rehabilitation Clinic, 1997.
28. Tekeoglu I, Adak B, Goksoy T *et al*. Effects of intra-articular injections of sodium hyaluronate (Orthovisc) and betamethasone on osteoarthritis of the knee. J Rheumatol Med Rehabil. 1998; 9:220-224.
29. Adams ME, Atkinson MH, Lussier AJ *et al*. The role of Viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicentre trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage. 1995; 3:213-225.
30. Frizziero L, Govoni E, Bacchini P. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: Clinical and morphological study. Clin Exp Rheumatol. 1998; 16:441-449.