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A comparative study of the results of conservative therapy, intra-articular steroid injection therapy and intra-articular hyaluronic acid injection therapy in primary osteoarthritis of knee: A prospective study in eastern Indian population

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Abstract

Background: To compare the results of intra articular steroid, intra articular hyaluronic acid and conservative therapy, in primary osteoarthritis of knee. There are many literature comparing the efficacy between hyaluronic acid and steroids, however to compare the three variables we are not aware of any studies available.

Materials & Methods: 45 patients attending were selected and randomized 15 each in each group (A, B and C). The patients treated with hyaluronic acid (A) received one course of three weekly injections. The patients treated with the steroid (B) received one injection at the time of enrollment in the study. In group C, physical therapy in the form of heat and physiotherapy were taught to patients. Western Ontario and McMaster University Osteoarthritis Index and Lequesne were used to assessed the patients.

Results: All the three groups were followed at 2, 4, and 6 months. In group A on first visit WOMAC average score is 70.8 which improves to 68, 61.06 and then to 64 (p- 0.00001). In group B average score before injection is 71.2; the follow up average score 60.4, 66.93, 73.86(p-0.00001). In group C patients WOMAC score in first visit is 72; the follow up average score 68.53, 74.8, 79 (p <0.00001). No significance difference were found with the lequesne score. The best effect can be seen around 4 months with steep decrease in WOMAC score in group A. In group B it is seen that at 6 months the effect of corticosteroids has weaned away. In group C the improvement is slow and deteriorates with further follow up.

Conclusions: Methylprednisolone has a short term benefit as compare to hyaluronic acid group. In case of patients undergoing conservative therapy no significance improvement. Awareness of this pattern is useful to formulate a therapeutic plan for patients with knee Osteoarthritis.

Keywords: Results, conservative therapy, intra-articular steroid injection therapy, intra-articular hyaluronic acid injection therapy

Introduction

Osteoarthritis (OA) is a public health concern, and is the leading osteoarticular pathology in developed countries. It has been estimated that 69.9 and 100 million people are affected by osteoarthritis in the US and Europe, respectively [1, 2]. In India about 5-6% of the population has joint and related diseases [3].

The increased prevalence of osteoarthritis with aging, coupled with the demographics of aging populations, makes osteoarthritis a high priority health care problem. Osteoarthritis of the knee can cause symptoms ranging from mild to disabling. Initial management of most patients should be nonoperative and may include physical therapy, bracing, orthosis, ambulatory aids, glucosamine, chondroitin, intra-articular injections of steroid or hyaluronic acid, and analgesics. Many procedures have been described for treatment of the osteoarthritic knee, including arthroscopic debridement, osteochondral or chondrocyte transplantation, high tibial osteotomy, distal femoral osteotomy, arthroplasty, and arthrodesis. The choice of procedure depends on the patient's age and activity expectations, the severity of the disease, and the number of knee compartments involved [4].

We report the results of a prospective institutional based, randomized study comparing the efficacy of intra-articular injections of the steroid (methyl prednisolone 80 mg), Hyaluronic acid (Hyalgan molecular weight 500,000 – 730,000 daltons) and conservative therapy (physiotherapy and NSAIDs) in 45 patients with primary osteoarthritis of the knee.

Materials and Methods

This was a randomized, double blinded, prospective study. After approval of institutional ethics committee, the patient suffering from knee OA who satisfied the inclusion criteria were offered enrolment. Total of forty five patients were enrolled between from February 2013 to March 2014. Fifteen patients each for conservative treatment, intra articular steroid injections and intra articular hyaluronic acid injections.

Inclusion criteria were patient above 40 years with primary osteoarthritis of knee both male and female, along with radiographic OA grade II–III (According to Kellgren and Lawrence (KL) grading scale (Kellgren and Lawrence 1957) [5]. Exclusion criteria age below 40 years, post traumatic knee, local infections in and around knee joint, uncontrolled diabetes mellitus, severe joint deformity, patient on anticoagulant therapy and allergies to avian products, patient with history of surgery in and around the knee. Additional exclusion criteria were a history of crystalline arthropathy, neuropathic arthropathy, an intra-articular knee injection with any corticosteroid or any hyaluronic acid preparation within the previous three months. Weight-bearing anterior-posterior, lateral, and patellar skyline radiographs were made for all patients prior to enrolment.

Online randomization is done by using graph pad software after patients' eligibility was confirmed (<http://www.graphpad.com/quickcalcs/index.cfm>). By using this software, randomization is simple and allotment to the three different groups was obtained.

Analgesics withdrawn in all three groups 24 hours before enrolment.

By inserting the needle into the lateral suprapatellar pouch, under aseptic conditions, administration of intra articular injection was given. To avoid any effusions, before each injection, arthrocentesis was performed. In this study one knee per patient was analysed to avoid bias. The patients treated with hyaluronic acid (A) received one course of three weekly injections. The patients treated with the steroid (B) received one injection at the time of enrollment in the study. In conservative group(C) NSAIDS (diclofenac 100mg) was given as per patient requirement but not over dosage. Physiotherapy including quadriceps and hamstrings strengthening exercise were also taught.

Instruments

Western Ontario McMaster University Osteoarthritis (WOMAC) [6].

The index is a 24-item questionnaire divided into three subscales which measure pain (5 items, score range 0–20), stiffness (2

items, score range 0–8), and physical function (17 items, score range 0–68). The three subscale values were summed to provide the WOMAC-total score.

Lequesne index [7]

Another tool use is the modified Lequesne index termed as the “algofunctional index”. Lequesne *et al* developed an index of severity for osteoarthritis for the knee. This can be used to assess the effectiveness of therapeutic interventions. It contain three parameters:

1. pain or discomfort
2. maximum distance walked
3. activities of daily living

The index of severity is the SUM (points for all parameters), with the minimum points for each section is 0 and the maximum points for each section is 8. The minimum index score is 0 and the maximum index score is 24. The interpretation is as follows 0(none), 1-4(mild), 5-7(moderate), 8-10(severe), 11-13(very severe) and >14 extremely severe.

Results

A total of 45 patients was included in this study, 15 for intra-articular steroid injection 15 for intra-articular hyaluronic acid and 15 for conservative therapy during the period of study from February 2013 to March 2014. All intra articular injections were given at operation theatre after taking consent in proper sterile techniques. We follow up at 2, 4 and 6 months. Comparison of WOMAC scores in all three groups [Table 2] was presented as mean \pm standard deviation. Similarly Lequesne knee score in the three groups were analysed statistically [Table3]. Outcome scores of all the three groups [Table 4] shows the mean WOMAC and Lequesne scores. All statistical analysis was done in IBM SPSS 19 (SPSS Inc, Chicago, IL). P value < 0.05 considered as significant level.

In group A on first visit WOMAC average score is 70.8 which improves to 68, 61.06 and then to 64 (p- 0.00001). In group B average score before injection is 71.2; the follow up average score 60.4, 66.93, 73.86(p-0.00001). In group C patients WOMAC score in first visit is 72; the follow up average score 68.53, 74.8, 79 (p <0.00001). No significance difference was found with the lequesne score. The best effect can be seen around 4 months with steep decrease in WOMAC score in group A. In group B it is seen that at 6 months the effect of corticosteroids has weaned away. In group C the improvement is slow and deteriorates with further follow up.

Table 2: Comparison of WOMAC score in all three groups

	Group A (Hyaluronic acid injection) (n=15)	Group B (Steroid injection) (n=15)	Group C (Conservative treatment) (n=15)	Total (N=45)	p value
Baseline (at first visit)					
Mean \pm SD	70.8 \pm 4.82	71.2 \pm 5.22	72 \pm 5.65	71.33 \pm 5.15	0.817
Median Range	70,64-78	70,64-82	70,64-82	70,64-82	
1 st Follow up (2 months)					
Mean \pm SD	68 \pm 5.45	60.4 \pm 8.00	68.53 \pm 9.02	65.64 \pm 8.35	0.009
Median Range	70,58-74	60,52-74	66,56-84	64,32-84	
2 nd Follow up (4 months)					
Mean \pm SD	61.06 \pm 8.48	66.93 \pm 9.40	74.8 \pm 5.38	67.6 \pm 9.62	< 0.001
Median Range	60,50-78	70,80-80	74,68-86	70,50-86	
3 rd Follow up (6 months)					
Mean \pm SD	64 \pm 8.51	73.86 \pm 6.25	79.6 \pm 3.56	72.48 \pm 9.05	< 0.001
Median Range	64,50-80	74,60-84	78,74-86	76,50-86	
p value	0.00001	0.00001	<0.00001		

p<0.05 – test is significance

Table 3: Comparison of Lesquesne knee score in all three groups

	Group A (Hyaluronic acid injection) (n=15)	Group B (Steroid injection) (n=15)	Group C (Conservative treatment) (n=15)	Total (N=45)	p value
Baseline(at first visit)					
Mean \pm SD	8.06 \pm 1.03	7.93 \pm 1.38	8.33 \pm 1.29	8.11 \pm 1.22	0.672
Median Range	8,7-10	8,6-11	8,7-11	8,6-11	
1 st Follow up (2 months)					
Mean \pm SD	7.4 \pm 0.91	6.4 \pm 1.40	7.33 \pm 1.76	7.04 \pm 1.45	0.104
Median Range	8,6-9	6,5-9	7,5-11	7,5-11	
2 nd Follow up (4 months)					
Mean \pm SD	6.4 \pm 1.12	7.67 \pm 1.8	8.73 \pm 1.28	7.6 \pm 1.7	< 0.001
Median Range	6,5-9	8,5-10	9,7-12	8,5-12	
3 rd Follow up (6 months)					
Mean \pm SD	6.6 \pm 1.40	9.06 \pm 1.43	9.93 \pm 1.22	8.53 \pm 1.95	< 0.001
Median Range	6,5-10	9,6-11	10,8-12	9,5-12	
p value	0.00001	<0.00001	<0.00001		

$p < 0.05$ is significance

Table 4: Changes in mean outcome scores over time

Treatment	WOMAC (points)	Lesquesne knee score (points)
Hyaluronic Acid		
First visit	70.8	8.06
At 2 months	68	7.4
At 4 months	61.06	6.4
At 6 months	64	6.6
p value	0.00001	0.00001
STEROID		
First visit	71.2	7.93
At 2 months	60.4	6.4
At 4 months	66.93	7.67
At 6 months	73.86	9.06
p value	0.00001	<0.00001
Conservative		
First visit	72	8.33
At 2 months	68.53	7.33
At 4 months	74.8	8.73
At 6 months	79.6	9.93
p value	<0.0001	<0.00001

Test of significance done by Friedman test $p < 0.05$ – test is significance

Table 5: Injections and dose in different studies

Study	Hyaluronic acid and dose	Corticosteroids and dose
Leardini <i>et al.</i> , 1991 [10]	Hyalgan 2 ml (20 mg), 3 weekly injections	Methylprednisolone 1 ml (40 mg), 3 weekly injections
Jones <i>et al.</i> , 1995 [11]	Hyalgan 20 mg, 5 weekly injections	Triamcinolone hexacetonide 20 mg single injections followed by 4 placebo injections
Caborn <i>et al.</i> , 2004 [12]	Synvisc 2 ml (16 mg), 3 weekly injections	Triamcinolone hexacetonide 2 ml (40 mg), single injection
Leopold SS <i>et al.</i> 2003 [13]	Hylan G-F 20 2-mL syringe, which contained 16 mg three weekly injections	Betamethasone sodium phosphate-betamethasone acetate 2 mL single injection
Present study	Hyaluronic acid 2 ml (20 mg), 3 weekly injections	Methylprednisolone 2 ml (80 mg), single injection

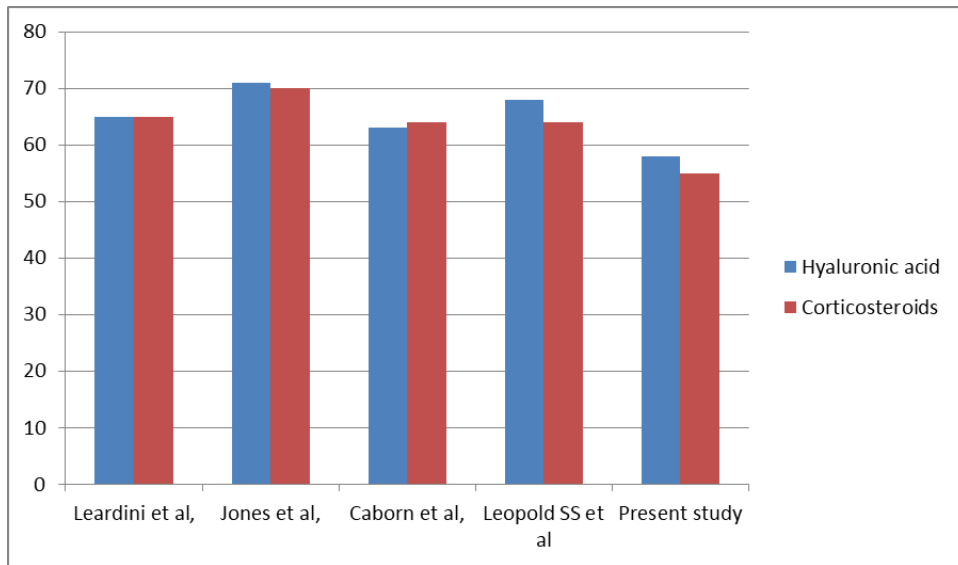


Fig 1: Mean Age in years

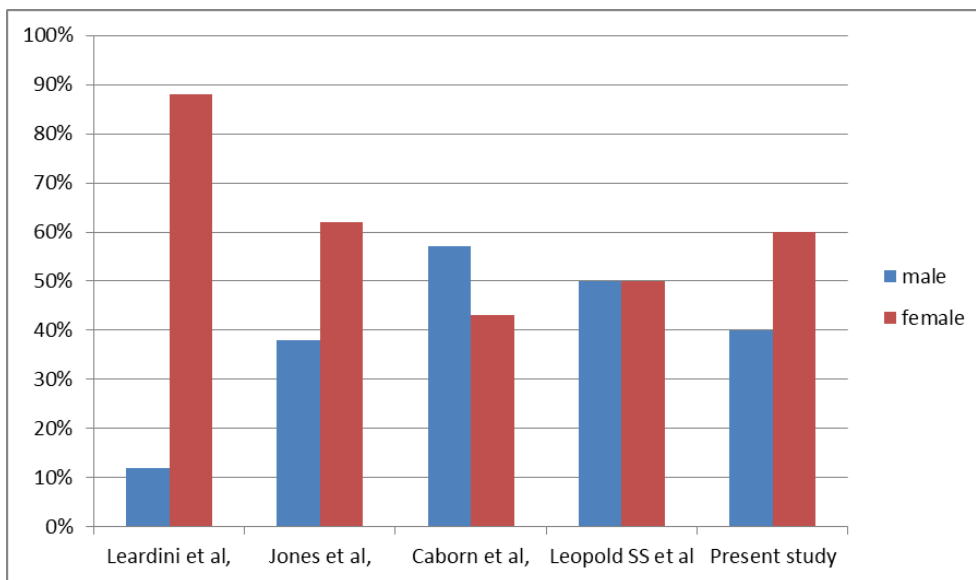


Fig 2: Shows Sex distribution in different studies.

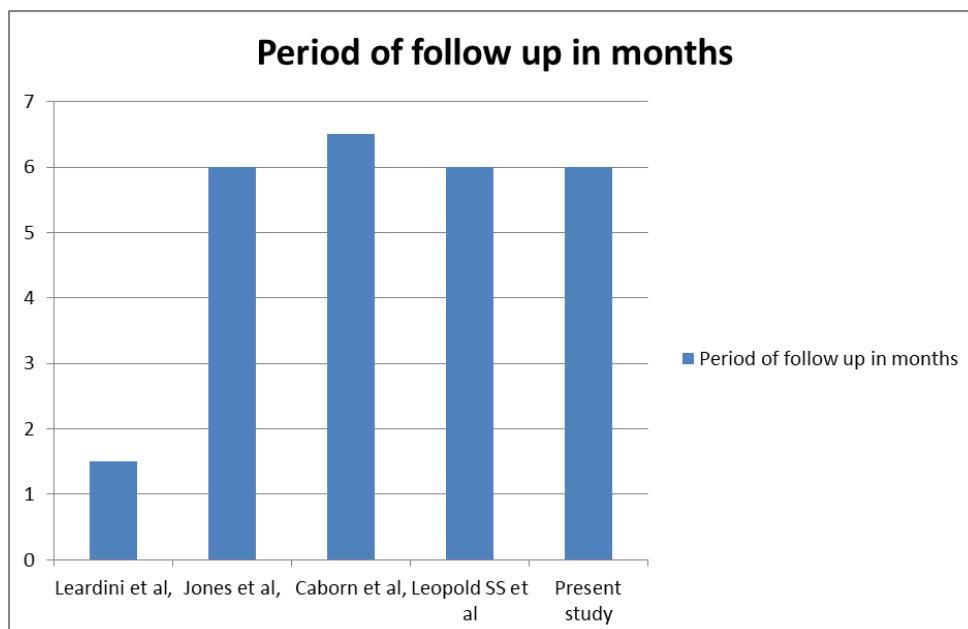


Fig 3: Period of follow up in different studies

Discussion

Osteoarthritis is the most common type of arthritis or degenerative joint disease. It is a common chronic, progressive musculoskeletal disorder characterized by gradual loss of articular cartilage. It is the leading cause of chronic disability. The disease most commonly affects the middle-aged and elderly, although younger people may be affected as a result of injury or overuse. Age is the strongest predictor of the disease and therefore extended life expectancy will result in a greater occurrence of the disease [8].

The management of Osteoarthritis is broadly divided into non-pharmacological, pharmacological, and surgical treatments. Surgical management is generally reserved for failed medical management where functional disability affects a patient's quality of life. Pharmacological management includes control of pain and improvement in function and quality of life while limiting drug toxicity.

Patients with Osteoarthritis suffer from pain and loss of function. Objectives of Osteoarthritis management are to reduce the level of pain, reduce inflammation, slow cartilage degradation, improve function and reduce disability [9].

Leardini *et al* study showed that for up to one week after the end of treatment hyaluronic acid's analgesic activity was comparable to that of the steroid, while at the end of the follow-up (45 days after the end of treatment) all the pain monitoring parameters presented significant differences in favour of the hyaluronic acid treated group. Both treatments were well tolerated, since no local or systemic adverse reactions were observed [10].

Jones *et al*, 1995 study use visual analog scores (VAS) for pain; duration of stiffness; range of movement; joint effusion; local heat; synovial thickening; joint-line and periarticular tenderness. However, there was a high drop-out rate and intention to treat analysis failed to demonstrate statistically significant differences between the groups. In patients remaining in the study, significantly less pain was experienced by the hyaluronic acid group during the 6 month follow-up period compare to steroids [11].

Another study done by Caborn *et al*, in 2004 to assess prospectively the efficacy and tolerability of hylan G-F 20 (HG-F 20; Synvisc) and intra-articular triamcinolone hexacetonide for treatment of osteoarthritis knee pain in a 26 week, randomized, multicenter, evaluator-blind study. The study concludes that Maximum pain relief occurred at 1-2 weeks for triamcinolone hexacetonide and at Week 12 for HG-F 20. At Weeks 12 and 26, HG-F 20 was significantly better than triamcinolone hexacetonide. They concluded that Viscosupplementation with HG-F 20 resulted in a longer duration of effect than triamcinolone hexacetonide with a comparable tolerability profile [12].

Leopold SS *et al* 2003 a prospective, randomized trial shows that both the group treated with the corticosteroid and the group treated with Hylan G-F 20 demonstrated improvements from baseline WOMAC scores (a median decrease from 55 to 40 points and from 54 to 44 points, respectively; $p < 0.01$ for both). The scores according to the Knee Society system did not significantly improve for the patients who received the corticosteroid (median, 58 to 70 points; $p = 0.06$) or for those who received Hylan G-F 20 (median, 58 to 68 points; $p = 0.15$). The scores on the visual analog scale improved for patients receiving Hylan G-F 20 (median, 70 to 52 mm; $p < 0.01$) but not for the patients who received the corticosteroid (median, 64 to 52 mm; $p = 0.28$). No significant differences between the two treatment groups were found with respect to the WOMAC, Knee Society system, or visual analog scale results. Women

demonstrated a significant improvement in only one of the six possible outcome-treatment combinations (the WOMAC scale), whereas men demonstrated significant improvements in five of the six outcomes. They conclude that there is no differences detected between patients treated with intra-articular injections of Hylan G-F 20 and those treated with the corticosteroid with respect to pain relief or function at six months of follow-up. However women demonstrated significantly less response to treatment than men did for both treatments on all three outcome scales [13].

In our study we use WOMAC score and Lequesne knee score for evaluating the functional outcomes. However compare to the other studies our objective is to find out the results of conservative therapy, intra articular steroid injection therapy and intra articular hyaluronic acid injection therapy in primary osteoarthritis of knee.

Patients receiving hyaluronic acid mean baseline WOMAC score is 70 ± 4.82 . Then at 2 months, 4 months and 6 months follow up the mean WOMAC score is 68 ± 5.45 , 61.06 ± 8.48 , 64 ± 8.51 ($p = 0.00001$). The above results shows that the maximum effect of hyaluronic acid is between 2nd month and 4th month. However there is a good amount of response till the 6 months of follow up. Similarly using the Lequesne knee score the same results is seen at first visit the mean score is 8.06 ± 1.03 then at 2nd, 4th, and 6th months the Lequesne knee score is 7.4 ± 0.91 , 6.4 ± 1.12 , 6.6 ± 1.40 ($p = 0.00001$).

In case of patients receiving methylprednisolone injection the mean baseline WOMAC score is 71.2 ± 5.22 then at 2 months, 4 months and 6 months follow up the mean WOMAC score is 60.4 ± 8.00 , 66.93 ± 9.40 , 73.86 ± 6.25 ($p = 0.00001$). In this group of patients the best effect can be seen at first follow up i.e. At 2 months. At 4 months and 6 months the effect started to wean off. The Lequesne knee score at first visit is 7.93 ± 1.38 , then at 2 months, 4 months and 6 months the mean score 6.4 ± 1.40 , 7.67 ± 1.8 , 9.06 ± 1.43 ($p < 0.00001$).

In the last group of patients who were treated conservatively, here the mean baseline 72 ± 5.65 , then at 2 months, 4 months and 6 months follow up the mean WOMAC score is 68.53 ± 9.02 , 74.8 ± 5.38 , 79.6 ± 3.56 ($p < 0.00001$). In this group there is not so much of improvement at the first follow up, however in the second and third follow up there is increase in WOMAC score suggesting of deterioration of this therapy. In this group the Lequesne score at first visit is 8.33 ± 1.29 then at 2 months, 4 months, and 6 months the mean score is 7.33 ± 1.76 , 8.73 ± 1.28 , 9.93 ± 1.22 ($p < 0.00001$).

Conclusion

In summary, the results from our study suggests that corticosteroids are more effective than hyaluronic acid in the short term (2 months), whereas hyaluronic acid is more effective in the long term (2nd month upto 4th month). In case of patients undergoing conservative therapy there is no much significance improvement. Awareness of this pattern of response is useful to the clinician in formulating a therapeutic plan for patients with knee OA.

However this study includes only a small number of patients, further clinical trials need to be asses for better understanding.

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