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Therapeutic Efficacy of Intra-Articular Hyaluronic Acid in Osteoarthritis Knee

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Abstract

Objective: To evaluate the effect of intra articular hyaluronic acid for patients with knee osteoarthritis by analysing data from trial of intra articular hyaluronic acid versus placebo.

Material and method: This prospective study was conducted in department of orthopaedics, S.N. Medical College, Agra. Approval for study was taken by the local ethical committee. Objective was to evaluate the effect of intra articular hyaluronic acid for patients with knee osteoarthritis by analysing data from trial of intra articular hyaluronic acid versus placebo.

Osteoarthritic knees of 112 patients (65 female and 47 male) with age of 40-80 years taken, patients were randomized to five weekly injections of intra articular hyaluronic acid or normal saline (control) and were observed for 36 weeks. The primary efficacy measures were resting pain, weight-bearing pain. VAS Score and WOMAC (Western Ontario and McMaster University Osteoarthritis Index) during study weeks 0–36.

Results: The intra-articular injections produced a significant reduction in weight-bearing pain, resting pain, VAS Score and WOMAC scores after 12 weeks. Knee pain reduced and the function improved in most patients of hyaluronic acid group and these beneficial effects maintain till the last follow up. Adverse reactions were noted in 4 patients of Group1 and 3 patients of Group 2, out of which local reaction (swelling, redness, warmth, effusion, itching and Bruising) was common.

Conclusion: Viscosupplementation with intra-articular hyaluronic acid is a reasonable treatment for patients with mild-to-moderate osteoarthritis of the knee who have ongoing pain or are unable to tolerate conservative treatment or joint replacement.

Key Words: Osteoarthritis, Knee, hyaluronic acid, VAS, WOMAC.

Introduction

Osteoarthritis (OA) is an increasingly important public health problem [1]. It is slowly progressive, can cause symptoms ranging from mild to disabiling. Osteoarthritis is a common cause of knee pain especially in the elderly. It is characterised by loss of articular cartilage, subchondral sclerosis, joint deterioration and osteophyte formation [1]. The current treatment for knee OA consists of conservative treatment such as exercise, physical therapy, pharmacological agents and, in some cases surgical treatment [2,3]. While many of the commonly used conservative treatments have been recognised to be effective [4], there is still insufficient evidence available. Among the pharmacological treatments for knee OA, oral non-steroidal anti-inflammatory drugs (NSAIDs) act rapidly and are recommended for the management of OA, although frequent and serious adverse effects of NSAIDs have been recognized [4].

The normal adult knee contains approximately 3.0 mL of synovial fluid (SF), with a hyaluronic acid (HA) concentration of 2.5 to 4.0 mg/mL-1[5]. In osteoarthritic knee, the concentration and molecular weight of HA are

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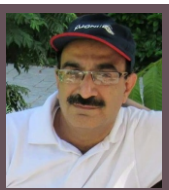
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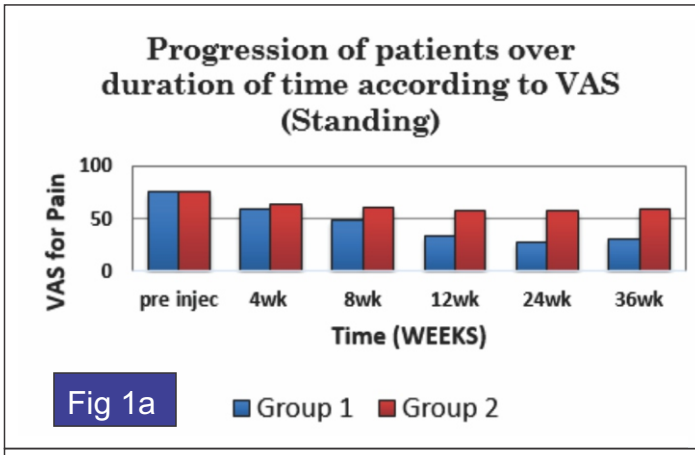

Fig 1a

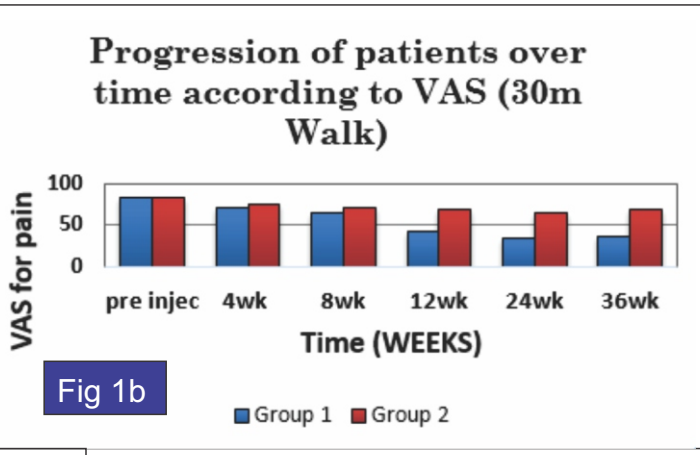

Fig 1b

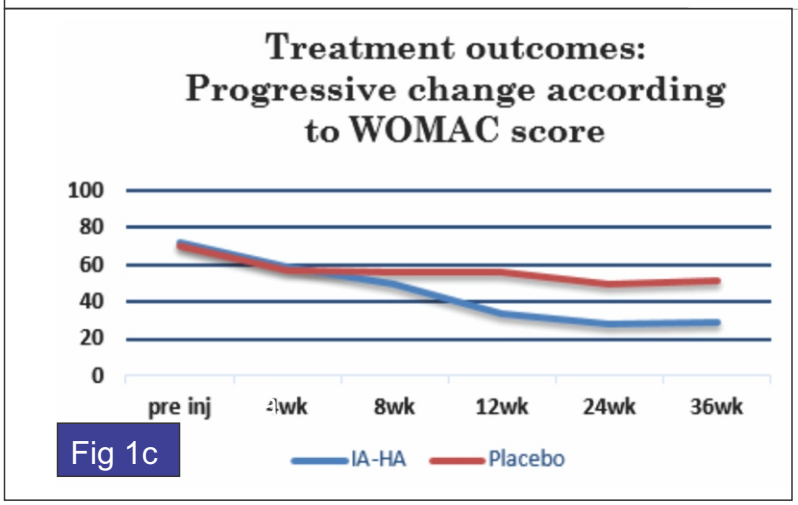

Fig 1c

decreased by 33% to 50% [6,7], resulting in less shock absorption, lubrication and protection of joints. The mechanism of action of hyaluronic acid injection is unclear but Basic science research suggests that intra-articular HA (IAHA) supplementation improves the viscoelasticity, flow characteristics of synovial fluid and also controls the arthritic disease process by promoting in vivo IAHA production and by providing an intra-articular anti-inflammatory effect[4,8,]. Preparations of HA can be divided into low and high-molecular-weight. Contra-indications to intra-articular HA include joint or skin infection, overlying skin disease, and allergy to chicken or eggs.

Numerous clinical trials and systemic reviews showed that patients treated with HA were doing better than untreated patients at the end of the treatment cycle and at the end of 6 months. Despite this, viscosupplementation for treatment of OA remains controversial and perhaps underused. Primary objective of this study was to determine whether HA injections improve pain and function in patients with OA in their knees.

Aims and Objectives

1. To evaluate the efficacy of intra-articular injection of hyaluronic acid in treatment of osteoarthritis of knee.
2. To compare against placebo the efficacy and safety of repeated injections of hyaluronic acid (HA) in osteoarthritis of knee.

Material And Method

This Randomised control study was carried out in the Department of Orthopaedics, S.N. Medical College, Agra. All consecutive patients were selected from the patients attending the outpatient department between 1st March 2014 to 30 October 2015. A detailed history, examination (General, systemic and local examination) along with investigation was carried out before doing procedure. Well informed consent was taken in all cases. Patients were selected on the basis of strict inclusion and exclusion criteria's.

Inclusion criteria:

1. Age group 40 to 80 years
2. Osteoarthritis knee not responding or intolerant to traditional pharmacological and non-pharmacological treatment.
3. Patients with Osteoarthritis of knee whom any surgical intervention not contemplated due to associated medical problem or due to financial or other constraints.

Exclusion criteria:

1. Patients with known hypersensitivity to hyaluronate preparation.
2. infection or skin diseases in the area of the injection site.
3. Pregnant and lactating women.
4. Patients with rheumatoid arthritis.
5. Patients with severe osteoarthritis with a K/L grade of 4.
6. Patients who had either hematological, cardiac, renal or hepatic disorders.

Table 1: Distribution of patients on the basis of classifications in relation to fracture stability

Outcome measure	Treatment group	No. of knees	Baseline	Mean changes during follow up				
				4wk	8wk	12wk	24wk	36wk
VAS(mm)								
Standing pain	HA placebo	75 75	76.3(4.82) 75.5(5.03)	58.7(2.22) 63.8(6.23)	49.1±3.12 61.1±5.02	34.1(0.96) 57.7(2.36)	28.5(2.34) 58.2(2.78)	31.1(2.42) 59.5(3.25)
Pain after walking	HA placebo	75 75	82.4(4.76) 8.2(0.66)	71.5(4.22) 75.6(3.84)	65.4±5.43 71.2±4.83	42.4(2.52) 69.4(6.57)	34.3(4.42) 65.3(6.68)	36.1(5.32) 68.8(6.21)
WOMAC								
Total score	HA Placebo	75 75	71.7(5.93) 70.5(6.79)	59.02(5.14) 57.3(5.32)	49.9±5.65 56.3±5.58	33.2(5.55) 55.8(5.82)	28.2(6) 49.9(6.14)	28.8(5.43) 51.8(6.38)
Pain	HA placebo	75 75	12.2(0.98) 12.1(0.99)	11.1(0.72) 10.7(1.1)	9.6±0.95 10.2±1.02	7.8(0.96) 10.2(1.04)	4.2(1.05) 9.2(0.80)	4.4(0.96) 9.7(0.70)
Stiffness	HA Placebo	75 75	5.4(0.31) 5.2(1.24)	3.8(0.90) 4.3(0.88)	3.5±0.86 4.2±0.91	3.1(0.90) 4.2(1.02)	2.2(0.60) 3.7(0.88)	2.05(0.65) 3.9(0.85)
Function	HA placebo	75 75	54.1(4.64) 53.2(4.56)	44.1(3.52) 42.2(3.34)	36.8±3.84 41.9±3.65	22.3(3.69) 41.4(3.76)	21.8(4.35) 37(4.46)	22.4(3.82) 38.2(4.78)

7. All patients who did not came for follow up atleast for 24weeks.

All good clinical practice (GCP) guidelines were followed and. Approval for study was taken by the local ethical committee. 150 osteoarthritic knees of 112 patients with 38 bilateral affected, were randomized into two groups of 75 knees each. Group1 patients received five intraarticular injections of high molecular weight 2,700 kDa (25 mg) hyaluronic acid at weekly intervals, whereas in the control group, five intraarticular injections of 2 mL saline were administered similarly during a week period. Routine strict aseptic technique was adhered to during the administration of the injections into the joint. After giving the injections patients were advised to avoid excessive weight bearing and strenuous or prolonged (>1hr) exercises for the next 48 hrs. They were also informed that they might develop transient pain or swelling after the injection.

The patients were followed up at intervals of 4 weeks for three months and then at intervals of three months up to 36 weeks. In each follow up, patients were evaluated for their (1) Baseline characteristic, (2) Radiographic analysis of the knee, (3) Compliance with the treatment, (4) Clinical manifestations, and (5) Safety. The results were graded into excellent/ good / fair / poor according to the improvement in following scores.

1. Visual Analogue Score (VAS),
2. Western Ontario and Mc- Master University Osteoarthritis Index (WOMAC) score.

Results

112 patients were recruited for the study. Randomised into two Groups, majority of patients in both group were from 51-60 year age group accounting for 50.8% of all cases. Mean age of viscosupplementation group (group 1) and placebo group (group 2) was 57.4+9.05 and 58.6+10.1 respectively. There were 47 males and 65 females. Most

patients did not have normal body weight. 47% were overweight, 25% were obese and 2.6% were morbidly obese according to their calculated BMI. On radiological evaluation, majority of patients (51.7%) were from KELLGREN LAWRENCE GRADE II.

Pain was assessed by use of the visual analogue score (VAS), revealed an average pain score for hyaluronic acid group was 76.3 pre-injection for standing and 82.4 for 30m walking. From this base line, the value dropped to 58.7 and 71.5 respectively at 4 weeks after fifth injection. There was continuous improvement, with the value 49.1 and 61.1 at 8 week, 34.1 and 42.4 at 12 week and 28.57 and 34.3 at 24 week. At last follow up at 36week, VAS Score with standing was 31.1 and 36.1 after 30m walk. For visual analogue pain score, hyaluronic acid was significantly effective than saline at 12 week, at 24 week, and 36week ($p<0.05$) (figure 1a &1b).

Knee pain and function was also assessed by the WOMAC (Western Ontario and McMaster Universities) instrument in both groups, with significant differences between the active treatments and placebo. WOMAC score for affected knee was 71.9 before treatment. From this base line, the value dropped to 59.02 at 4 weeks. There was continuous improvement, with the value 49.9, 33.2 and 28.2 at 8week, 12 week and at 24 weeks respectively and 28.8 at last follow up at 36week. For Western Ontario and McMaster Universities Osteoarthritis Index pain, hyaluronic acid was significantly more effective than saline at 12weeks, at 24 weeks and at 36 week ($p<0.05$). A significant benefit of hyaluronic acid versus saline also was observed for knee stiffness ($p<0.05$) and physical function ($p <0.05$) at 12week, 24week and at 36 week. Treatment with intraarticular hyaluronic acid improved knee pain and function with no significant differences between the active and placebo during first 8 weeks. Significant improvement ($p<0.05$) were reported with IA-HA as compared to placebo at 12 weeks, further improvement at 24 weeks and continued upto 36 week. According to WOMAC score, 30% patients reported with excellent improvement at last follow up after active treatment. 38% and 22% patients were found to be good and fair result, respectively. Only 10% patients were reported with poor result.(Table -1)

Treatment with intra-articular hyaluronic acid was shown to be safe form of treatment. During the follow up period of 36 weeks, adverse reactions were noted in 4 patients of Group 1 and 3 patients of Group 2, out of which most common was local reaction(swelling, redness, warmth, effusion, itching and Bruising). Patients recovered uneventfully with only analgesics and anti-inflammatory medications. No significant differences ($p > 0.05$) between the two groups were found.

Discussion

Pain was the single most important reason for the patients to seek medical attention for their knee problems. Activity related discomfort led to variable timing of presentation of these patients for medical treatment. There is variation in each individual pain threshold, some are able to withstand pain for longer duration than others. Intraarticular hyaluronic acid is not a new treatment for osteoarthritis. Many studies have shown that it is helpful in reducing the sign and symptoms of osteoarthritis. The patients age, sex, BMI, sign and symptoms of osteoarthritis, grading of osteoarthritis and adverse effects associated with intra-articular hyaluronic acid were taken into consideration in both groups of study.The safety and efficacy of several hyaluronic acid formulations have been investigated in patients with osteoarthritis of the knee [9].In present study patients were followed with regular interval up to 36 weeks. VAS and WOMAC score showed gradual but significant improvement in terms of pain at rest or after 30m walk at 12 weeks and sustained pain relief till the end of thirty six weeks. Only 11 (10%) patients were reported with poor results.

HA is a large glycosaminoglycan composed of repeating disaccharides of glucuronic acid and N-acetyl glucosamine that is naturally present in synovial fluid. Several protective properties of HA have been reported including shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface and lubrication [10,11]. Numerous clinical trials, meta-analyses and systematic reviews have indicated its clinical efficacy for knee osteoarthritis [12,13]. However, controversy remains regarding the efficacy of HA in treating knee osteoarthritis [14]. A recent meta-analysis concluded that the pain reduction by IA-HA is observed later than that of intra-articular corticosteroids [12]. In addition, the effects of IA-HA for knee osteoarthritis pain continued over six months post-intervention [13]. However, few studies have been conducted to clarify the early effects and safety of IA-HA in comparison to those of

placebo. The results of this study clearly indicated that the early efficacy of IA-HA was not inferior in comparison to that of the placebo. A number of HA products with a variety of the molecular weights, ranging from approximately 600 to 6,000 kDa, have been developed as IA-HA for the treatment of osteoarthritis[14]. The considerable heterogeneity of outcomes between trials may be due in part to difference in hyaluronic acid products [15]. High-molecular-weight HA (>6,000 kDa) is suggested to have greater effects in comparison to lower-molecular-weight hyaluronic acid [14]. On the other hand, the intra-articular injection of high-molecular-weight hyaluronic acid (>6,000 kDa) showed a greater frequency of adverse events, such as pain flares, and hot and swollen knees, which typically occurred 24 to 72 hours after injection [16]. In our study we were reported only 4 cases with pain full, hot or swollen knees after injections. The molecular mechanisms underlying the efficacy of IA-HA for osteoarthritis remain unclear. It has recently been reported that HA inhibits the activities of matrix metalloproteinases and aggrecanases which are, at least in part, involved by pro-inflammatory cytokines, such as interleukin(IL)-1[13]. Therefore, hyaluronic acid is speculated to modify the structural damage of joints and the rate of osteoarthritis progression in addition to the symptom modifying effect [8], although further studies are required.

In our study, significant differences in Western Ontario and McMaster Universities Osteoarthritis Index scores were observed between group1 and group 2 patients throughout the study after 12 weeks. Hyaluronic acid ameliorated knee pain and stiffness and improved function and mobility (30m walk). After the series of five injections, the symptom relief advantages of hyaluronic acid at Week 12 was consistent with the durability of pain relief reported with other hyaluronic acid formulations[17].

It should be noted that hyaluronic acid injections can play a role in early management of osteoarthritis especially for those with allergies to glucosamine and also those with severe gastrointestinal tract disorders secondary to NSAIDS. At the other extreme, are the surgical candidates for knee replacement who are not fit for surgery, so would require intraarticular injections for symptomatic relief. Patients who benefited most from these injections were those with early, mild to moderate osteoarthritis. We believe that a treatment regime of five injections resulted in satisfactory outcome in current study but there is still room for improvement in the formula of hyaluronic preparation, duration of regime and perhaps also in technique for administering the injection.

Conclusion

Viscosupplementation with intra-articular hyaluronic acid is a reasonable treatment for patients with mild-to-moderate osteoarthritis of the knee who have ongoing pain or are unable to tolerate conservative treatment or joint replacement. The effect lasts longer with high-molecular-weight preparations, and patients can experience improvement in clinical outcomes for up to 36 weeks. Intra-articular HA appears to have a slower onset of action than placebo but the effects seem to last longer. Patients should be warned of cost and of potential side effects, including local swelling.

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