

A COMPARATIVE STUDY OF INTRA-ARTICULAR SODIUM HYALURONATE ACID (Na-HA) AND CORTICOSTEROIDS IN THE PAIN MANAGEMENT OF KNEE-OSTEOARTHRITIS

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Abstract

A randomized control trial was conducted to determine the effect of intra-articular (IA) sodium hyaluronate (Na-HA) in controlling the pain related to knee osteoarthritis. The study conducted at the Shaikh Zayed Hospital, Lahore on 200 diagnosed patients of knee osteoarthritis. Patients of both genders of age between 45-70 years with uni/bilateral knee involvement with any grade of osteoarthritis (Kellgren & Lawrence grading) were included after radiological evidence. The mean pain score (MPS) was evaluated by visual analog scale (VAS). A t-test was applied to the comparison of the efficacy between two types of treatments. There were 66.5% male patients and 33.5% female patients. The total mean age of the all patients was 56.34. The mean duration of knee osteoarthritis was 2.21±1.12 years. The mean pain score (MPS) before treatment in both the group was 75.61. After one week treatment, the MPS in both groups was 54.32. After 2, 4, 8 and 12 weeks the MPS was 41.80, 37.62, 36.80 and 23.57, respectively. After 1, 4, 8 and 12 weeks, there was a significant difference ($p \leq 0.050$) in the lowering of pain score in both treatment groups. However, after two weeks only, both groups show the almost equal response after two week treatment. Because p-value showed that there was no significant difference in improvement of pain score in both groups after two weeks of treatment. There were a significant difference mostly in the mean pain score (MPS) improvements in the patients injected with articular sodium hyaluronate as compared to corticosteroids group.

Introduction

Among all ages related morbidities the Osteoarthritis (OA), is a very common ailment in elder patients of age up to 65 years. The patients come up with severe pain, disability related to morbidities followed by adverse quality of life (QOL). The cartilage loss is usually treated with joint replacement in the end-stage elder patients (Mushtaq *et al.*, 2011). The current study is a randomized control trial conducted to compare the mean improvement in pain after treatment of knee osteoarthritis with intra-articular (IA) sodium hyaluronate (Na-HA) and corticosteroids. Intra-articular injection of Na-HA will produce greater mean improvement in pain as compared to intra-articular corticosteroids injections in knee osteoarthritis. The study conducted at the Shaikh Zayed Hospital, Lahore for a period of six months on 200 diagnosed patients of knee osteoarthritis presenting at outpatient department. Patients of both genders of age between 45-70 years with uni/bilateral knee involvement with any grade of osteoarthritis (Kellgren & Lawrence grading) were included.

The osteoarthritis of the knee joint is a common disease of middle and old age group, with an estimated incidence rate of 240 per 100,000 people (National Center for Chronic Disease Prevention and Health Promotion, 2008). The Majority of the population experience knee joint pain above 55 years out of which half of these patients have radiographic findings of osteoarthritis (Zhang and Jordan, 2010; Zhang *et al.*, 2010; Zhang *et al.*, 2009). Knee Osteoarthritis (OA) has a high incidence world over (Cho *et al.*, 2011). There are different treatment modalities used for OA depending on the severity, starting from pharmacological drugs, such as NSAIDs (non-steroidal anti-inflammatory drugs), muscle relaxants, topical analgesia, corticosteroids and Na-HA. The advanced osteoarthritis requires a total knee arthroplasty (Cho *et al.*, 2011; Mushtaq *et al.*, 2011). Intra articular corticosteroids have an established role, however, only 60 % patients have good short term and 20% patients have a satisfactory long term response; but all these responses sometimes considered a temporary relief (Gatha *et al.*, 2011). Hyaluronic acid (HA), is an intra-articular intervention that is being widely used in the west. Hyaluronic acid (HA) is a huge 'viscoelastic glycosaminoglycan' which is naturally available in the joint fluid. It acts as a lubricant and a shock absorber (Mcgrath *et al.*, 2011). A study of Caborn *et al.*, (2004) determined that the mean improvement from baseline in pain by using VAS (visual analog scale) at 12 weeks follow-up was 31.3 ± 2.3 in hyaluronate group vs. 17.4 ± 2.41 in corticosteroids group.

By 60 years of age, approximately 13 % women and 10% men have symptomatic knee OA. With the increase in age and rate of obesity in the general population, the proportion of affected people will increase (Zhang and Jordan, 2010). Females > 55 years have more chances of severe knee OA than any other joint. Middle-aged women reported to have a high incidence of medium to serious knee OA (Sowers *et al.*, 2011). In

previous literature, several contributing variables as risk factor were considered, in which the factors of squatting and kneeling have considered the primary main risk factors in relation to the disorder of knees (Reid, 2010). The correlation between osteoarthritis and body-mass index (BMI) is found linear and it was reported that 27% of hip arthroplasty cases and 69% knee arthroplasty cases were ascribed to obese conditions (Yoshimura *et al.*, 2012). It was also indicated that leptin system can lead to the metabolic abnormalities in obese people with an increased risk of osteoarthritis (Yoshimura *et al.*, 2012). Inflammation has associated with OA causing its developments and progress. In a study, the CRP median levels were elevated more than non-progressive disease (Martel-Pelletier and Pelletier, 2010). Vitamin D deficiency increases the risk of knee OA significantly as well. At the initial stage of disease, the levels of vitamin D are notably lower than persons without knee OA (Heidari *et al.*, 2011).

If pain is severe and unbearable, where the first and second line drugs fail to relieve pain, then physician can opt for opioid analgesics which should be carefully regulated and controlled. Nutritional supplements (Glucosamine Sulfate, Glucosamine Hydrochloride, and Chondroitin Sulfate) have a significant role in OA treatment, but there some controversy regarding their dosage and duration of therapy. Intra articular joint injections provide a quick and effective role in management of symptomatic knee joint. The most common IA (intra articular) liaisons are glucocorticoids for pain reduction, improving joint functions (Raynauld *et al.*, 2003). Recently, hyaluronic acid as an intra-articular agent has gained a worldwide acceptance which is a physiological component of cartilage matrix and synovial fluid (Dahl *et al.*, 1985). The hyaluronic acid stimulates a synovial cell membrane to secrete more hyaluronan and aggrecans acting as a disease modifying agent. HA stimulates chondrocyte growth and metabolism, synthesis of articular cartilage matrix components (e.g., collagen, proteoglycans, including endogenous hyaluronan, hyaladherins), Promotes healing and repair and maintains chondrocyte vitality (decreased apoptosis) (Goldberg *et al.*, 2005). Corticosteroid acts as anti-inflammatory and immunosuppression agent. It acts directly on the nuclear steroid receptors, interrupting inflammation and immune response at various levels which results in reduction of vascular permeability, restrict accumulation of inflammatory cells, phagocytosis and enhances production of metalloprotease, metalloprotease activator and neutrophil superoxide. Corticosteroid inhibits synthesis and secretion of leukotrienes and prostaglandin, thereby decreasing erythema, heat, tenderness and swelling of inflamed joints and increase relative viscosity of synovial fluid with an increase in HA concentration (Ahyan *et al.*, 2014).

Materials and Methods

Study Design: A randomized controlled trial has been conducted at the department of Orthopedics, Shaikh Zayed Hospital, Lahore, for six months. The aim of this study was to compare the mean improvement in pain after treatment of knee osteoarthritis with intra-articular sodium hyaluronate and corticosteroids. Intra-articular injection of sodium hyaluronate will produce greater mean improvement in pain as compared to intra-articular corticosteroids injections in knee osteoarthritis. Patients of both genders of age between 45-70 years with uni/bilateral knee involvement with any grade of osteoarthritis (Kellgren & Lawrence grading) were included. Radiological evidence was also collected for confirmation of presence of knee osteoarthritis.

Sample size and Sampling Techniques: Sample size of 200 cases (100 in each group) is calculated with 80% power of the test, 95% confidence level and taking expected mean \pm SD of mean improvement in both groups, *i.e.* 31.3 ± 2.3 in Hyalgan® drug group versus 17.4 ± 2.41 in corticosteroid drug groups in the treatment of osteoarthritis of the knee. Non probability purposive sampling was used.

Inclusion Criteria: Patient both male and female with age between 45-70 years were included. Patient with primary degenerative knee osteoarthritis was included in this study. Patients with unilateral or bilateral knee involvement were taken in this study. Grades 1, 2 and 3 osteoarthritis, according to Kellgren and Lawrence grading included in this study. Patients who report a chronic pain from three months and those patients who showed dissatisfaction with any previous trials of non-operative treatments (pharmacological and non-pharmacological).

Exclusion Criteria: Those Patients unwilling to participate in the study were not included. The patients with a history of local infection or inflammation, allergic to injection material or any blood coagulation disorder were excluded from the study. Patients with a history of mental illness were excluded. Those patients who got an intra-articular injection were excluded. The Grade 4 (according Kellgren-Lawrence Scale) osteoarthritis patients were also excluded.

Data Collection: Two hundred patients with knee osteoarthritis meeting the inclusion criteria were selected from the outpatient department (OPD) of the hospital included in the current study. The patients were examined

and X-rays were carried out for diagnosis and radiological grading of the disease. The diagnosis was established using history, clinical examination and the X-rays of the patients.

The visual analog scale (VAS) was recorded in the Proforma before the treatment. The informed consents were obtained from the patients before the procedure. The technique was explained to the patients accordingly. The patients were kept supine on the table with the knee extended. The lateral aspect of the Patella was palpated. The skin was washed with povidone-iodine solution. After aseptic measures, sterile gloves were worn. A 21-gauge, 1-inch needle was attached to a 10-mL syringe for the steroid injection, and for sodium hyaluronate – Na HA (Hyalgan®) injection in a pre-filled syringe with a 21-gauge needle. The needle inserted through a stretched skin. The needle directed at a 45 degree angle into the knee, tilted below the patella. Once the needle has been inserted 1-1/4 inch, the content then injected into the joint. The skin cleansed, an aseptic dressing was placed and a bandage applied over the puncture site.

All patients divided into two groups A and B at random, using random number tables. Group A received a Hyalgan® injection, 1 every week for three weeks, and group B was received a Methyl-Prednisolone injection 1 ml (40 mg/mL) with 2-3 mL 1% lignocaine once, at the start of study only. All intra-articular injections were given in the OPD (Out-Patient Door) under aseptic measures. Follow-up after treatment was carried out after 0, 1, 2, 4, 8 and 12 weeks, and the patients were reassessed and VAS was noted. Post treatment VAS was subtracted from base-line in order to measure improvement.

Data analysis: The mean pain score (MPS) was evaluated by visual analog scale (VAS). All data was entered and processed in SPSS version 20. Quantitative variables like age and pre and post treatment pain score were described by mean \pm standard deviations. Qualitative variables like gender were presented by frequency and percentages. Variables of interest such as ‘mean improvement in pain score’ after improvement in both groups were compared using t-test (independent samples). A p-value of ≤ 0.050 was taken as significant. Post-treatment readings were subtracted from base-line to measure the improvement.

Results

We compared the mean improvement in pain after treatment of knee osteoarthritis with intra-articular sodium hyaluronate and corticosteroids through a randomized control trial. Out of total 200 patients there were 133 (66.5%) males and 67 (33.5%) were females. The total mean age of the all patients was 56.34 (SD \pm 10.24). The mean duration of knee osteoarthritis was 2.21 ± 1.12 years. The mean pain score (MPS) before treatment in both the group was 75.61 with a standard error of 7.33 (Table 1). After one week treatment, the MPS in both groups was 54.32 with a standard error of ± 10.89 (Table 1). After two weeks the MPS was 41.80 with a standard error of ± 7.68 (Table 1). Pain score after four weeks in both groups was 37.62 with a standard error of ± 6.55 (Table 1). After eight weeks there was no considerable reduction in pain score as mean was 36.80 ± 10.78 (Table 1). After twelve weeks, the mean score was 23.57 with a standard error of 14.48 (Table 1).

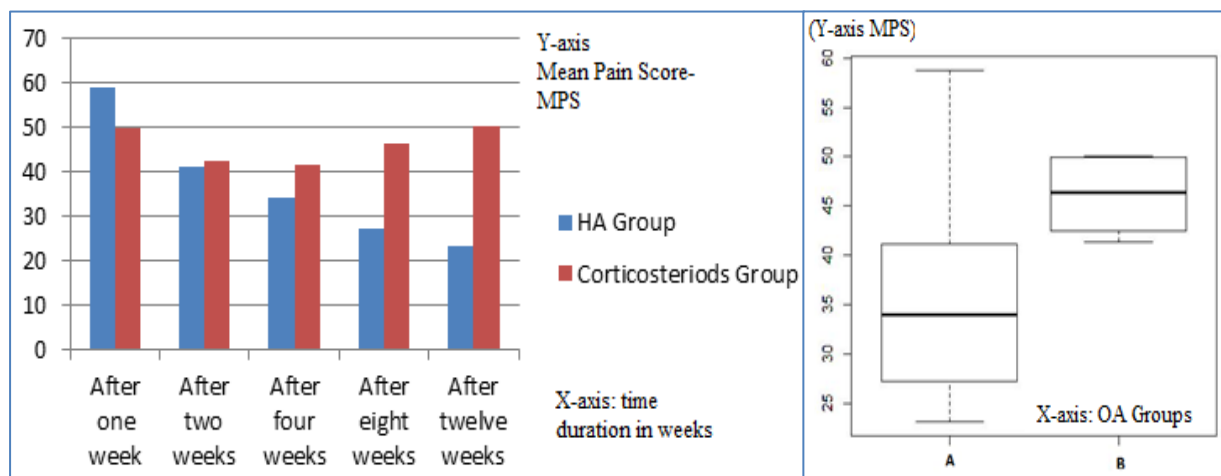


Fig. 1. Graphical comparisons through bar chart and a box-whisker plot between Group A (sodium hyaluronate) and Group B (corticosteroid treatment).

Table 1. Mean Pain Scores (MPS) of All Osteoarthritis Patients (n=200).

N	200
1-Pain score before treatment	
Mean	75.6150
Std. Deviation	7.33
2-Pain score after one week	
Mean	54.3200
Std. Deviation	10.89731
3-Pain score after two weeks	
Mean	41.8000
Std. Deviation	7.68474
4-Pain score after four weeks	
Mean	37.6250
Std. Deviation	6.55356
5-Pain score after eight weeks	
Mean	36.8000
Std. Deviation	10.78618
6-Pain score after twelve weeks	
Mean	23.57
Std. Deviation	14.48945

Table 2. The t-test analysis of significant difference ‘mean values of pain scores’ between group A (n=100) and group B (n=100) patients.

Duration	t-test for Equality of Means						
	t	*df	p-value	Mean (Group A)	Mean (Group B)	Std. Deviation (Group A)	Std. Deviation (Group B)
After one week	6.26	198	0.0001	58.74	49.9	12.15441	7.17670
After two weeks	1.29	198	0.198	41.10	42.50	9.93	4.35
After four weeks	9.56	198	0.0001	33.95	41.30	0.736134	0.22042
After eight weeks	27.11	198	0.0001	27.25	46.35	5.70198	4.13503
After twelve weeks	35.28	198	0.0001	23.15	50.00	7.60964	0.76096

*df: degree of freedom

Table 2 shows the t-test analysis of significant difference ‘mean values of pain scores’ between Hyalgan Acid group ‘A’ (n=100) and Methyl-Prednisolone group ‘B’ (n=100) patients. The mean pain score in (MPS) group A and B after one week of treatment was 58.74 ± 12.15 and 49.90 ± 7.17 respectively. It shows that group B shows more lowering in the pain score as group A. While the p-value (0.0001) showed that there was a significant difference in the lowering of pain score in both treatment groups.

The MPS of group A was 41.10 ± 9.93 , while the group B has an MPS of 42.50 ± 4.35 . The p-value showed that there was no significant difference in improvement of pain score in both groups after two weeks of treatment. Both groups show the almost equal response after two week treatment.

The MPS in group A and B after four weeks of treatment was 33.95 ± 7.36 and 41.30 ± 2.20 respectively. It shows that group A shows more lowering in the pain score as group B, ignoring the margin of error. While the p-value (0.0001) showed that there was a significant difference in the lowering of pain score in both treatment groups.

The MPS in group A and B after eight weeks of treatment was 27.25 ± 5.70 and 46.35 ± 4.13 , respectively. It shows that group A shows more lowering in the pain score as group B. While the p-value (0.0001) showed that there was a significant difference in the lowering of pain score in both treatment groups.

The MPS in group A and B after twelve weeks of treatment was 23.15 ± 7.60 and 50.0 ± 0.00 respectively. It shows that group A shows more lowering in the pain score as group B, ignoring the margin of error. While the p-value (0.0001) showed that there was a significant difference in the lowering of pain score in both treatment groups.

Discussion

Intra-articular (IA) injection of sodium hyaluronate (Na-HA) will produce a greater mean improvement in knee osteoarthritis (OA) pain as compared to IA corticosteroids injections in knee osteoarthritis. Osteoarthritis of the knee impacts up to 10% of the adults. The condition is usually treated by intra-articular (IA) injection of Na-HA (Arrich *et al.*, 2005). We conducted a randomized controlled trial at the department of Orthopedics, Shaikh Zayed Hospital, Lahore, for six months. All knee osteoarthritis patients were divided into two groups A and B, the group A patients received a Hyalgan® injection, one every week for three weeks, and group B patients received a Methyl-prednisolone injection 1-ml (40 mg/mL) with 2-3 ml 1% lignocaine once. We compared the mean improvement in pain (MPS) after treatments of knee osteoarthritis with IA sodium hyaluronate and IA corticosteroids injection treatments. Intra-articular injection of sodium hyaluronate produced a greater mean improvement in knee osteoarthritis (OA) pain as compared to intra-articular corticosteroids injections in knee osteoarthritis patient group A. In the current study, overall results have shown that corticosteroids can be helpful for a smaller duration, but for long term treatment, sodium hyaluronate acid (Na-HA) is the best treatment, as there was a significant difference (p-value 0.0001) between pain score improved between corticosteroids and HA.

In our hospital setup, we have frequently used corticosteroids, but have recently started the use of hyaluronic acid (HYALGAN®). Bannuru *et al.* (2009) had also suggested that corticosteroid knee OA (osteoarthritis) treatment is more profound as compared to HA treatment when short duration efficacy is required (i.e., 1-4 weeks). The recurrent cycles of IA hyaluronate acid injections can improve symptoms of knee OA along with a marked 'carry-over' effect for a minimum of one year from the previous cycle (Navarro-Sarabia *et al.*, 2011). A study had also favored the use of hyaluronic acid in female patients with knee OA on the basis of Lequesne indices as compared to the group who had treated with 6-MPA (6-methylprednisolone acetate) (Tascioglu and Oner, 2003). Various other studies have discussed these two treatment modalities through their researches. Zhang *et al.* (2009) summarized that in the treatment of osteoarthritis, the diagnosis at the early stage is a significant factor. A study by Bellamy *et al.* (2006), reported a symptomatic pain relief in knee osteoarthritis patients against the treatment of hyaluronate injection within a 40 month follow-up duration. This study reported the hyaluronate treatment showed a significant improvement (22%) with regard to the pain-score as compared to the corticosteroids treatment. A comparative study was conducted by Caborn *et al.* (2004) to assess the efficacy of the following drugs: Hylan (G-F 20) and IA 'triamcinolone hexacetonide' to treat knee pain from OA. It was concluded that 'Viscosupplementation; with Hylan (G-F 20) resulted in a longer duration of effect than 'triamcinolone hexacetonide-TH'. Therefore, they favored the use of Hylan (G-F 20 over TH for treatment of chronic OA knee pain. A similar result was also reported by Tang *et al.* (2012) and stated that the hyaluronate treatment was though prolonged, but more effective with regard to the symptomatic improvement. Lundsgaard *et al.* (2008) had evaluated two trials concerning corticosteroids and hyaluronic acid (HA) treatments through VAS (visual analog scale) and evaluated statistically significant MPS-mean pain scores. However, they (Lundsgaard *et al.*, 2008) reported that the intra-articular hyaluronate with physiological saline did not significantly reduce pain as compared to the physiological saline in patients with osteoarthritis of the knee.

The study of Jones *et al.* (1995) had favored the treatment of corticosteroids up to 8 weeks, but at around 26 weeks, the HA treatment was favored. Petrella *et al.*, (2006) conducted a study for knee osteoarthritis treatments and concluded that the HA treatment strategy showed effective improvement ($p < 0.05$) in knee pain and a better function as compared to overall WOMAC score and VAS pain following walking and stepping activity at the end of three weeks. Zhang *et al.* (2009) presented a clinical trial in which they identified trials with placebo groups and few untreated control groups. The surgical, pharmacological and non-pharmacological therapies were employed. Placebo was effective at relieving pain, improving function and stiffness. However, Arrich *et al.* (2005) in the study found that intra-articular hyaluronic acid has not been proven clinically effective and may be associated with a greater risk of adverse events. Arrich *et al.* (2005) has suggested that large trials with clinically relevant and uniform end points are necessary to clarify the benefit-risk ratio. The platelet-rich plasma (PRP) treatment is a recent advancement to replace or maintain a damaged cartilage due to (GF) growth factors (such as TGF- β and PDGF-platelet derived growth factors and IGF) accumulated in a-granules of platelets (Ulrich-Vinther *et al.*, 2003). Following growth factors are being considered: IGF-insulin like growth factors,

PDGF-platelet derived growth factors and TGF β -transforming growth factor beta (Ulrich-Vinther *et al.*, 2003; Pujol *et al.*, 2008).

Conclusion

There was a significant difference in the mean pain score (MPS) improvements in the patients injected with articular sodium hyaluronate as compared to corticosteroids group. Moreover, the patients can be treated with HA (hyaluronate acid) for long lasting effects with lesser complication. The hyaluronate acid treatment is beneficial in long term treatment, but with great effectiveness, whereas, the corticosteroids treatment is effective for only short term course. Such pattern of diverse response from these synergistic borne treatments may lead the physicians for the co-administration of comprehensive knee OA treatment plans. Further, larger studies are required to confirm this effect. The patient selection was random in this study and few patients opted for intra articular corticosteroid injection due to financial issue as sodium hyaluronic acid is 10 times more expensive than corticosteroid.

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