ANTI-INFLAMMATORY DRUGS IN MANAGEMENT OF KNEE OSTEOARTHRITIS

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ABSTRACT

Objective: To compare the outcome of intra-articular hyaluronic acid injection with oral non-steroidal anti-inflammatory drugs in knee osteoarthritis in terms of mean pain score.

Study Design: Randomized controlled trial.

Place and Duration of Study: Outpatient orthopedics department of Combined Military Hospital, Rawalpindi from February 2015 to July 2016.

Patients and Methods: A total of 60 patients with knee osteoarthritis were enrolled as per inclusion and exclusion criteria by non-probability consecutive sampling. Thirty patients were assigned to group "A" and were given intra-articular injection of hyaluronic acid 20 mg (2 ml) into the knee joint aseptically for five consecutive weeks. Group "B", having thirty patients, was given oral non-steroidal anti-inflammatory drug Celecoxib 200mg/Naproxen 500mg twice daily after meals for twelve weeks. Outcome measure was mean pain score using visual analogue scale at twelve week follow-up.

Results: Statistically significant improvement in mean pain score on visual analogue scale at twelve week follow-up was found in patients of group "A", with improvement in score from 7.2 ± 0.92 at the start of the study to 5.6 ± 1.23 at twelve week follow-up (p<0.001). No statistically significant results were obtained in patients with group "B" having pain score on visual analogue scale of 7.4 ± 0.94 at the start of the study to 7.3 ± 0.95 at twelve week follow-up (p= 0.373).

Conclusion: The use of intra-articular injection of hyaluronic acid in knee osteoarthritis potentially offers a significantly greater clinical improvement in terms of pain relief, especially in radiological grades 1 to 3. Non-steroidal anti-inflammatory drugs, on the other hand, are of lower comparative efficacy in the treatment of knee osteoarthritis pain.

Keywords: Hyaluronic acid, Intra-articular injections, Non-steroidal anti-inflammatory drugs, Osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is a chronic disorder of synovial joints characterized by progressive softening and disintegration of articular cartilage accompanied by osteophytes, cyst formation, sclerosis in the subchondral bone, mild synovitis, and capsular fibrosis[1]. The symptomatic knee OA affects approximately 10% of men and 13% of women aged 60 years or more[2].

The commonest and most pertinent symptom is knee joint pain that eventually leads to impairment of function which is the most distressing of all symptoms manifesting as a limp, reduction of walking distance, difficulty in climbing stairs, progressive inability to perform activities of daily living (ADLs) and an overall poor quality of life (QOL). Typically these symptoms follow an intermittent course, with periods of remission sometimes lasting for months. At times there are acute flares with redness, swelling, and joint effusions. Commonly appreciated signs on physical examination are painful and restricted range of motion (ROM) along with bony crepitus and quadriceps wasting[3].

The American College of Rheumatology (ACR) has established various sets of criteria for diagnosing knee OA amongst these the ACR

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clinical classification criteria are famous according to which the presence of knee pain along with at least three of the following six items collectively can classify the knee OA which include age more than 50 years, morning stiffness less than 30 minutes duration, bony crepitus on knee motion, bony tenderness, bony enlargement, and absence of palpable warmth of knees[4].

The management of knee OA according to the ACR guidelines for medical management of OA of the knee is divided in to three steps which should be followed sequentially, moving to the next step if the patients' response proves inadequate to the previous step. These include non-pharmacologic management, pharmacologic management, and surgical management. Among different pharmacologic treatment options, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are considered one of the first line treatments for OA. Unfortunately, many patients suffer from various serious side-effects like gastrointestinal ulceration and bleeding[5]. This has led to the use of cyto-protective agents because of their improved safety profile. Joints affected by OA have lower synovial fluid elasticity and viscosity than that of normal joints. This decrease in rheological properties of the synovial fluid results from reduced molecular size and concentration of hyaluronic acid in synovial fluid[6]. This led to introduction of viscosupplementation (VS) therapy, which is the intra-articular (IA) injection of hyaluronic acid (HA) or its derivatives in an attempt to enhance the elasticity and thickness of the synovial fluid. The results of VS therapy depend on the rheological properties and molecular weight (MW) of the HA preparation[7].

To our knowledge, work regarding IA use of HA Injection in knee OA patients is limited in Pakistan. Early use of IA injection of HA in knee OA can help prevent the above mentioned complications which are the cause of repeated hospital visits, prolonged hospital stays, compromised functional status, and dependence in ADLs.

This study aims to emphasize the need and importance of IA injection of HA in the management of knee OA in elderly patients who are more prone to NSAIDs associated side effects, so as to evaluate the response to treatment with an intent to guide the primary care physicians to choose wisely among various available management options, thus avoiding various potential complications, minimizing associated morbidity and improving QOL.

MATERIAL AND METHODS

After taking formal approval from hospital ethical committee for commencement of this randomized controlled trial, a total of 60 patients with knee OA were sampled through non-probability consecutive sampling from the outpatient orthopedics department of Combined Military Hospital, Rawalpindi from February 2015 to July 2016. Patients included both males and females of 60 to 75 years of age having knee OA with persistent pain of more than 3 months duration. The sample size was calculated using WHO sample size calculator with anticipated population mean being 19 and level of significance being 5%[5]. The participants had a clinical history of spontaneous knee pain along with morning stiffness not longer than 30 minutes duration, knee examination showing crepitus on movements and tenderness of bony margins, and plain x-rays showing Kellgren-Lawrence radiological grade of 1-4. Patients with depression, neuroses, acute synovitis, morbid obesity (>30% above normal body weight), knee deformity on radiographs (varus or valgus of >15°), those who were on chronic daily steroid therapy for 3 months, and who underwent knee surgery or had any IA injection within previous three months were excluded from the study.

Each patient's informed consent for participation in the study was taken after explaining the objectives and benefits of the study. Thirty patients were assigned each to group "A" and "B" randomly by lottery method. Group "A" patients were given once weekly IA injection of HA sodium salt (Hyalgan®) 20mg (2ml) by the

principal investigator for five consecutive weeks in to the affected knee observing proper aseptic technique. Group "B" patients were given oral COX-2 inhibitor NSAID "Celecoxib" 200mg twice daily after meals for 12 weeks. Patients with a history of gastric irritation or epigastric pain were given oral Omeprazole 20mg once daily as well for gastro-protection. Patients with history of ischemic heart disease (IHD) or cardiovascular accident (CVA) were given oral non-selective COX inhibitor NSAID "Naproxen" 500mg twice daily with oral Omeprazole 20mg once daily. Standard aseptic technique was used for IA injections by the principal investigator to minimize the chances of infection. Following treatment, participants were educated about all possible side effects and the ways to respond in case of emergency. Patients were advised to avoid all running activities and high impact activities. Patients' pain scores on visual analogue scale (VAS) were recorded at initiation of management and then at 12 weeks follow-up to observe any improvement in mean pain score. All the information was recorded on an especially designed proforma.

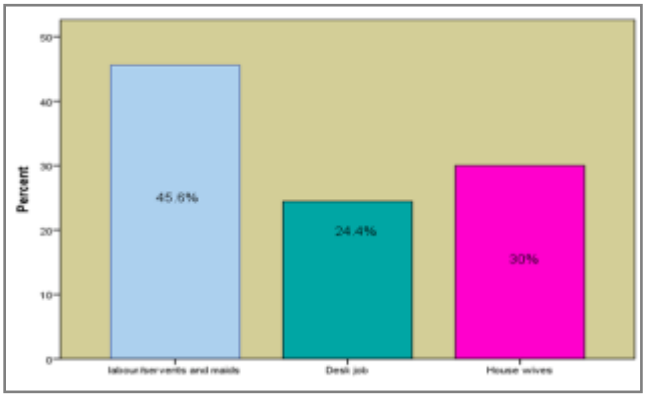

Figure-1: Occupation of patients (n=60).

Data were analyzed with the help of statistical analysis program SPSS version 10. Descriptive statistics were applied to calculate mean and standard deviation of age and pain score in both groups after treatment at 12 weeks. The mean of pain score at 12 weeks was taken. Frequency and percentage were calculated for side of pain and gender of the patients. Independent sample T test was used for comparison of mean pain score at 12 weeks follow-up after treatment in both groups. Paired t-test was used for the pre & post comparison. A *p*-value ≤0.05 was considered statistically significant.

RESULTS

All 60 patients completed the study with no drop out. Basic demographics of the patients are given in table-I. Among group "A" patients, the mean age was 67.01 ± 5.6 years, out of which 15 (50%) were males and 15 (50%) were females. The mean age of the patients in group "B" was 66.02 ± 5.8 years with 17 (56.66%) being females and 13 (43.34%) males. Among group "A" patients the right knee was involved in 7 (23.33%) patients, left knee in 13 (43.33%) patients and both knees were involved in 10 (33.33%) patients. While in group "B" the right knee was involved in 6 (20%) patients, left knee in 17 (56.66%) patients and both knees were involved in 7 (23.33%) patients (table-I). Of all, 28 (46.6%) patients were laborers (including servants and maids) by profession (fig-1).

The overall initial pain score of total 60 patients was 7.3 ± 0.92. When patients were assigned into groups, no statistically significant difference in the initial mean pain score was found among the two groups (p=0.408). Statistically significant improvement in mean pain score on VAS at twelve week follow-up was found in patients of group "A", with improvement in score from 7.2 ± 0.92 at the start of the study to 5.6 ± 1.23 at twelve week follow-up (p<0.001). However no statistically significant results were obtained in patients with group "B" having pain score on VAS of 7.4 ± 0.94 at the start of the study to 7.3 ± 0.95 at twelve week follow-up (p=0.373) (table-II).

DISCUSSION

According to the statistics from United States of America, knee OA is one of the top 5 causes of disability among non-institutionalized Americans. More than half of those with OA are under 65 years of age. Nearly 60% of Americans with arthritis are women[2]. In our study, we found

that mean age was 67.01 ± 5.6 years and 53.33% patients were females.

According to a Nigerian study[8], occupation wise, the highest prevalence was recorded among the homemakers 38.3% while our study results show that most 46.66% patients were labor, servants or maids.

The results of our study indicated that the use of once weekly IA injection of 20mg (2ml) HA sodium salt (Hyalgan®) by the principal investigator for five consecutive weeks in to the affected knee, observing proper aseptic technique, was superior to use of oral NSAID Celecoxib 200mg/ Naproxen 500mg twice daily after meals at 12 weeks which supported our hypothesis.

In our study the mean pain score on VAS among group "B" patient was 7.4 ± 0.94 at the start of study which improved to 7.3 ± 0.95 that was not statistically significant with a *p*-value of >0.05. The mean pain score on VAS among group "A" patient was 7.2 ± 0.92 at the beginning of treatment which improved to 5.6 ± 1.2 that was statistically significant with a *p*-value of <0.05. Stratification of group "A" was done on basis of knee OA radiological grades 1 to 4. The mean pain score on VAS among group "A", OA grade 1 to 3 was 6.50 ± 1.0, 7.54 ± 1.3, 7.11 ± 1.1 respectively at the beginning of treatment which improved to 3.75 ± 0.5, 5.85 ± 1.1 and 5.44 ± 0.54 respectively that was statistically significant with a *p*-value of <0.05. The mean pain score on VAS among OA grade 4 was 7.50 ± 0.57 at the beginning of treatment which improved to 7.25 ± 0.5 that was statistically not significant with a *p*-value of >0.05.

Extensive literature review reveals that more than 100 controlled clinical trials have been published on knee OA comparing IA injection of various HA derivatives with placebo, NSAIDs, IA corticosteroid injections or some reference HA derivate. Although a systematic review of overlapping meta-analyses revealed no clinically relevant significant differences in the efficacy of IA injection of HA as compared to NSAIDs regarding pain and function[9], our results are in accordance with the findings published by Bellamy *et al*[10] and Pagnano *et al*[11] demonstrating that the IA use of HA was comparable to NSAIDs with respect to efficacy in OA Kellgren-Lawrence grade 1 to 3 and that HA was safe and effective in treatment of knee OA pain. This disagreement with the meta-analysis and agreement with the other two studies actually emphasizes that the effects of IA injection of HA are more pronounced in less advanced disease i.e. Kellgren-Lawrence grade 1 to 3, and that in advanced disease the effects are not that much pronounced. The other possible explanation for this disagreement is the varied methodology used in the different clinical trials. Bannuru's meta-analysis[12]

Table-I: Basic demographics of the patients.

Characteristics	Group "A" (n=30)	Group "B" (n=30)	*p*–value
Age (Mean ± SD)	67.01 ± 5.6	66.02 ± 5.8	0.50
Gender n (%)			
Male	15 (50%)	13 (43.34%)	0.60
Female	15 (50%)	17 (56.66%)	
Knee Side involvement n (%)			
Right	07 (23.33%)	06 (20%)	0.57
Left	13 (43.33%)	17 (56.66%)	
Both	10 (33.33%)	07 (23.33%)	

Table-II: Comparison of mean pain score at 0 and 12 weeks.

Group	Pain score at 0 week Mean ± SD	Pain score at 12 week Mean ± SD	*p*-value*
"A" (n=30)	7.2 ± 0.92	5.6 ± 1.23	<0.0001
"B" (n=30)	7.4 ± 0.94	7.3 ± 0.95	0.373

*$p \leq 0.05$ is statistically significant, *Paired Sample t-test

also concluded that IA therapy of knee OA with HA was at least as effective as NSAIDs, with better tolerance.

Although our study was devised based on the best evidence available, our results cannot be generalized to NSAIDs and IA injections of HA other than what we had used in our study. Short term follow-up, use of blind technique for injections, radiographic grading of OA which at times could be misleading, lack of group with combination therapy or placebo, and use of only a subjective pain assessment tool as VAS without measurement of functional outcome on knees were the major limitations of our study.

CONCLUSION

The use of intra-articular injection of hyaluronic acid in knee osteoarthritis potentially offers a significantly greater clinical improvement in terms of pain relief, especially in radiological grades 1 to 3. Non-steroidal anti-inflammatory drugs, on the other hand, are of lower comparative efficacy in the treatment of knee osteoarthritis pain.

RECOMMENDATIONS

Knee OA, especially in early stages, should be treated with serial IA injections of HA ahead of NSAIDs. This will help alleviate pain and will let the patient, at the same time, to avoid potential toxic effects of NSAIDs.

Further studies are recommended to compare the long term follow-up of IA injections of HA versus NSAIDs not only with a subjective pain outcome measure as VAS but also to see effect on ROM and functional improvement of the knee joint in patients with knee OA.

Disclosure

This is an FCPS dissertation based article.

CONFLICT OF INTEREST

There are no identified conflicts of interest to declare by any author.

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