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Original Research Article

Effects of intra articular steroids, hyaluronic acid and combination of both among patients with knee osteoarthritis

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ABSTRACT

Background: Osteoarthritis (OA) is a common degenerative disorder of articular cartilage accompanied by hypertrophic changes of the bone. In the management of OA, though use of intra articular (IA) injection of steroids, hyaluronic acid (HA) separately plays an important role, their effects in terms of reducing pain, joint stiffness and movement restriction when it is used in combination remains a question. Hence this study was planned to assess the effects of HA and steroids alone with combination of both Ha and steroids.
Methods: Prospective randomized comparative study, among patients with osteoarthritis knee attending the outpatient department of Orthopedics in a tertiary care hospital during January 2017 to May 2018, were included. Patients were randomized in three groups (steroids, HA and combination of both) and a total of 96 patients were included and the outcome was assessed by WOMAC scale. Statistical analysis was done using SPSS Version 20.
Results: Pain and movement restriction, at the end of fourth week and pain, joint stiffness and movement restriction, were found to be statistically improved in combined steroids and HA group than the group with steroids alone. Similarly at the end of third month, pain and movement restriction were found to be statistically improved in combined steroids and HA group than HA group alone.
Conclusions: This study demonstrates that HA together with corticosteroid provides pain relief, reduction of joint stiffness and helps in improving joint movements within three months after treatment.

Keywords: Osteoarthritis, Hyaluronic acid, Triamcinolone acetonide

INTRODUCTION

Osteoarthritis (OA) is one of the most common form of arthritis, affects about more than 10% of population which is slowly progressive in nature and ends up with severe disability in the long term.[1] Men have more knee osteoarthritis before age 50, but its incidence in women rises after menopause, and by age 65 the prevalence is twice as high in women as in men.[2]

Standard supportive treatments include patient education, self-management programs, weight loss, physical and occupational therapy, exercises and devices that assist function. Pharmacologic therapies include use of acetaminophen, salicylates, NSAIDs, Glucosamine, chondrotin sulfate, intra articular (IA) glucocorticoids, hyaluronic acid, etc. Surgical therapy includes arthroscopy and joint replacement.[3]

Hyaluronic acid (HA) was first used in ophthalmology for cataract surgery in the 1970s.[4] Intra-articular use of HA has been approved in Japan and Italy since 1987, in Canada since 1992, in most of Europe since 1995, and in the United States since 1997.[4] A meta-analysis of eight randomized controlled trials (RCTs) reported that patients treated with HA were doing better than untreated patients

at the end of the treatment cycle and at the end of six months.[5]

Similarly, Intra-articular injection of steroid is a common treatment for osteoarthritis of the knee. Clinical evidence suggests that benefit is short lived, usually one to four weeks.[6] The short term effect of steroids shown by controlled trials and clinical experience vary, however, with some patients seen by rheumatologists achieving a significant and sustained response beyond a few weeks. This may be explained by only one injection usually being given in clinical trials and at a lower dose (20 mg) than the 40 mg triamcinolone recommended by the American College of Rheumatologists.[7] Pain scores may also be an insensitive outcome measure. Concern has been expressed that long term treatment could promote joint destruction and tissue atrophy.[6] Studies of cartilage damage, however, tend to suggest that changes are more likely due to the underlying disease than the steroid injection.[8]

For treatment with HA, most studies reported that clinical improvement begins with a delayed onset between 2 and 5 weeks, lasting 6 months or up to 1 year.[9] However, corticosteroids have been reported as fast-acting symptomatic drugs in management of OA.[10] The improvement in the signs of OA following corticosteroid injections seems to be due to anti-inflammatory effects on the joint. Hence, in this study, combined treatment with HA and corticosteroid was compared with HA treatment alone and corticosteroid treatment alone in terms of efficacy and safety in patients with knee OA.

Objectives

To compare the effects of intra articular injections combined steroids and HA with steroids and HA separately among the patients with knee osteoarthritis.

METHODS

This study was done as a prospective randomized comparative study, among patients with osteoarthritis knee attending the outpatient department of Orthopedics in Sri Muthukumaran Medical College and Research Institute. Patients who underwent pervious surgical procedures in knee, previous injections in knee, rheumatoid arthritis and secondary osteoarthritis were excluded from this study. The study was conducted from January 2017 to May 2018.

Institutional Ethics Committee approval was obtained; written informed consent was taken from the patients before the conduct of study. Patients were randomized to three groups where patients in group A were administered with intra articular Triamcinolone acetonide 10 mg (1 ml), patients in group B were administered with intra articular sodium hyaluronic acid 60 mg (4 ml) and patients in group C were administered with combination of both triamcinolone acetonide and sodium hyaluronic acid. Randomization was based on computer generated random numbers. A total of 96 patients with osteoarthritis knee were included in the study with thirty two patients in each group.

At the baseline, all patients had a knee X-rays based on which the severity of osteoarthritis was determined by Kellgren-Lawrenc classification.[11] The severity of pain, joint stiffness and movement restrictions was measured using the WOMAC index at baseline and at end of first, fourth and twelfth week.[12]

Statistical analysis was done using SPSS Version 20, descriptive data was computed as frequency and percentage. Mean and standard deviation was calculated and comparison between two groups was done using independent sample t test. P value of less than 0.05 were considered as statistically significant.

RESULTS

In this study there were 6.3%,9.4% and 3.1% participants below the age of 40 years in Group A,B and C respectively. Most of the patients in our study was above 60 years of age in Group A (40.6%), Group B (43.8%) and Group C (37.5%). The mean age was found to be 59.11±11.4, 63.8±9.8 and 61.5±4.7 in Group A,B and C respectively. The p value was found to be not statistically significant (p value 0.847).

In Group A, B and C there were 46.9%, 34.4% and 37.5% male patients and 53.1%, 65.6% and 62.5% female patients respectively. The chi square value was 0.5676 for gender. The mean BMI was found to be 27.5±3.8 in Group A, 28.1±4.5 in Group B and 18.82±4.1 in Group C with no significant statistical value (p value 0.8268), shown in Table 1.

According to Kellgren Lawrence grading 6.3% in group A, 12.5% patients in group B and 12.5% in group C fell under Grade I, whereas 62.5%, 65.6% and 60% of Group A, B and C patients were under Grade II respectively. 31.3% of Group A patients, 21.9% of group B patients and 37.5% of group C patients were in Grade III. The p value was found to be not statistically significant.

Aspiration was done for maximum number of cases in this study. Group A (78.1%), Group B (68.8%) and Group C (62.5%) cases. P value was 0.3911 which was found to be insignificant statistically. Approaches used for administering intra articular injection of respective drugs to each group participants were given in figure 1.

On comparing group A and C, the effect of pain, joint stiffness and movement restriction at the baseline was found to be not statistically significant. At first week of therapy there was no difference between the steroid group and the steroid + hyaluronic acid group. The effect of therapy between Group A and Group C was found to be statistically significant for pain (p value 0.0327) and

movement restriction (p value 0.0049), at the end of fourth week. At the end of 12 week therapy, p value was found to be highly statistically significant for pain (p value 0.0025), joint stiffness (p value 0.0344) and movement restriction (p=0.0009), as shown in Table 3.

Likewise on comparing Group B and Group C at the baseline therapy there was no difference in pain, joint stiffness and movement restriction between the two groups. At first week of therapy the p value of joint stiffness (0.9730), pain (0.9115) and movement (0.5190) was not statistically significant.

Table 1: Characteristics of the study participants (n=32).

Variables	Group A	Group B	Group C	P value
	N (%)	N (%)	N (%)	
Age group (in years)				
≤40	2 (6.3)	3 (9.4)	1 (3.1)	0.847
41-50	9 (28.1)	6 (18.8)	7 (21.9)	
51-60	8 (25)	9 (28.1)	12 (37.5)	
>60	13 (40.6)	14 (43.8)	12 (37.5)	
Mean age	59.11±11.4	63.8±9.8	61.5±4.7	
Gender				
Male	15 (46.9)	11 (34.4)	12 (37.5)	0.5676
Female	17 (53.1)	21 (65.6)	20 (62.5)	
BMI				
Normal (18.5-24.9)	7 (21.9)	6 (18.8)	9 (28.1)	0.8268
Overweight (25-30)	16 (50)	15 (46.9)	12 (37.5)	
Obese (>30)	9 (28.1)	11 (34.4)	11 (34.4)	
Mean BMI	27.5±3.8	28.1±4.5	18.82±4.1	

Table 2: Clinical profile of the study participants (n=32).

Variables	Group A	Group B	Group C	P value
	N (%)	N (%)	N (%)	
Kellgren Lawrence grade				
Grade I	2 (6.3)	4 (12.5)	4 (12.5)	0.5837
Grade II	20 (62.5)	21 (65.6)	16 (60)	
Grade III	10 (31.3)	7 (21.9)	12 (37.5)	
Aspiration done				
Yes	25 (78.1)	22 (68.8)	20 (62.5)	0.3911
No	07 (21.9)	10 (31.3)	12 (37.5)	

Table 3: Mean WOMAC score at different times comparing group A and C participants (n=32).

	Group A	Group C	P value
Baseline			
Pain score	14.71±3.81	14.53±4.32	0.8603
Joint stiffness	4.75±1.39	4.82±1.26	0.8335
Movement restriction	44.54±11.67	41.67±12.45	0.3451
At 1st week			
Pain score	13.71±2.91	13.3±4.01	0.6413
Joint stiffness	4.15±1.21	4.02±1.23	0.6714
Movement restriction	40.46±10.4	38.2±10.53	0.391
At 4th week			
Pain score	13.0±2.34	11.4±3.42	0.0327*
Joint stiffness	4.11±1.5	3.61±1.23	0.1499
Movement restriction	40.09±9.12	33.3±9.5	0.0049*
At 12th week			
Pain score	12.56±3.1	10.4±2.33	0.0025*
Joint stiffness	3.8±1.7	3.0±1.22	0.0344*
Movement restriction	36.78±9.56	28.7±8.9	0.0009*

*Significant

Table 4: Mean WOMAC score at different times comparing group B and C participants (n=32).

	Group B	Group C	P value
Baseline			
Pain score	14.89±4.1	14.53±4.32	0.7336
Joint stiffness	4.71±1.34	4.82±1.26	0.7363
Movement restriction	43.5±10.23	41.67±12.45	0.5230
At 1st week			
Pain score	13.4±3.1	13.3±4.01	0.9115
Joint stiffness	4.01±1.12	4.02±1.23	0.9730
Movement restriction	39.82±9.42	38.2±10.53	0.5190
At 4th week			
Pain score	12.7±3.4	11.4±3.42	0.1324
Joint stiffness	3.92±1.1	3.61±1.23	0.2920
Movement restriction	35.8±8.42	33.3±9.5	0.2696
At 12th week			
Pain score	11.4±1.4	10.4±2.33	0.0047*
Joint stiffness	3.5±1.5	3.0±1.22	0.1486
Movement restriction	34.33±8.76	28.7±8.9	0.0132*

*Significant.

At the end of four weeks therapy the mean pain score was 12.7±3.4 and 11.4±3.42 in Group B and C respectively. The mean joint stiffness was found to be 3.92±1.1 and 3.61±1.23 and mean movement restriction was 35.8±8.42 and 33.3±9.5 in Group A and Group B accordingly. But the p values were not significant.

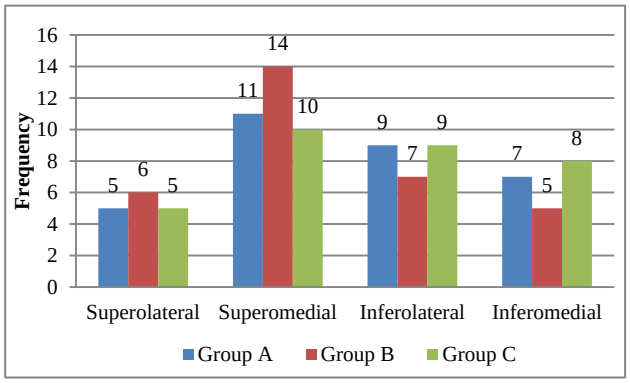

Figure 1: Approaches used for intra articular injection.

At the end of 12 weeks therapy in Group B and Group C pain score was found to be highly statistically significant with p value of 0.0047 and movement restriction was also found to be statistically significant (p=0.0132), which is shown in Table 4.

DISCUSSION

Corticosteroids have both anti-inflammatory and immunosuppressive effect, but their mechanism of action is complex. Corticosteroids act directly on nuclear steroid receptors and interrupt the inflammatory and immune cascade at several levels. By this means, they reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes.[13] The clinical anti-inflammatory reflections of these actions are decreases in erythema, swelling, heat, and tenderness of the inflamed joints and an increase in relative viscosity with an increase in hyaluronic acid (HA) concentration.[13]

HA is a naturally occurring glycosaminoglycan and a component of SF and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize HA and secrete into the joint. HA enhances viscosity and elastic nature of SF. SF with normal HA concentration acts as a viscous lubricant during slow joint movements and as an elastic shock absorber during rapid joint movements.[14] The adaptive ability reduces stress and friction on cartilage.[15] It also forms the backbone for the proteoglycans of the extracellular matrix. HA functions through antiinflammatory, anabolic, analgesic, and chondroprotective mechanisms.[16] In the osteoarthritic joint, synovial inflammation leads to increased permeability of the synovial membrane for HA. Also, the elevated SF levels of free radicals, inflammatory cytokines, and proteolytic enzymes in osteoarthritic knees impair HA function and contribute to the progression of OA. Therefore in OA, both the molecular weight and the concentration of HA are decreased.[17]

The IA injection of HA is thought to restore normal viscoelastic properties of the pathologically altered SF, which explains the term of the approach: "viscosupplementation".[17] It is thought that HA temporarily restores the lubricating and shock-absorbing effects of SF. Moreover, several studies suggest that viscosupplements also have disease modifying effects,

such as reduction of synovial inflammation, protection against cartilage erosion, and promotion of IA HA production.[18-21] Although the precise in vivo mechanisms of action are poorly known in the joint, HA promotes tissue remodeling in other tissues, as well. It is used to optimize tissue restoration and minimize scarring in ophthalmic, thoracic and plastic surgery and is also used to prevent postoperative peritoneal and intrauterine adhesions.[22,23] Lastly, HA have indirect and direct analgesic activity within the joints. Indirect effect is via the anti-inflammatory properties of HA. Direct effect is by the direct inhibition of nociceptors and the decreased synthesis of bradykinin and substance P.[24,25]

In our study on comparing steroids group and combined steroids and HA group, pain relief and movement restriction by the WOMAC pain subscale was observed to be statistically significant at the end of first month among the patients who received combined drugs. Also at the end of third month pain score, stiffness and movement restriction were found to be statistically significant among patients administered with combination of steroid and HA.

Similarly, on comparing the HA group and combined steroids and HA group, pain score and movement restriction were found to be statistically significant among the combined group who were administered with steroid and HA than HA group alone. But this significance was found only at the end of third month and also there was no difference in the joint stiffness at the end of first month. Consequently, the possible synergetic effects of combined IA steroids and HA injections should be considered as a rapid and prolonged effect in improvement of knee OA. Grecomoro et al showed that better results in the management of knee OA pain were obtained with addition of corticosteroid to the first of five HA injections after 2 months.[26] Our findings support this data that HA injections combined with corticosteroid lead to better results in pain reduction. The fact that some studies reported the possibility of marked destructive cartilage changes resulting from use of IA corticosteroids has limited the usage of combined treatments.[27,28] Indeed, in today's clinical practice, although improvement in clinical parameters such as pain, reduction in stiffness and joint function is important, assessing the clinical benefits of treatment without evaluating cartilage damage and its progression following treatment is not enough for evaluating clinical outcome on symptomatic knee OA.

By contrast, in animal models of OA, some in vivo studies did not show the effects of IA corticosteroids on possible mediators, which play a role in the pathogenesis of joint damage.[29] In a recent double-blind, placebocontrolled, in vivo study, investigators demonstrated that IA corticosteroids do not influence the expression of some of the important mediators of cartilage destruction in OA.[30] Some clinical studies investigating the safety of IA corticosteroid injections also reported no deleterious effects on the anatomical structure of the knee over the long term.[31]

Intra-articular steroids and HA might be good combination therapy. Grecomoro et al found that adding dexamethasone to the first of five Hyalgan injections decreased pain further after 2 months.[26] The effect of steroids occurred earlier (at 4 to 6 weeks); the effect of HA was delayed but longer lived. Comparing HA injections with corticosteroids suggests that the former lasts longer but the latter works faster. Also, steroids might be more effective for joint effusion or other acute inflammation.

CONCLUSION

This study demonstrates that HA together with corticosteroid provides pain relief, reduction of joint stiffness and helps in improving joint movements within three months after treatment. Also it is well tolerated, and has no deleterious effects on joint structure in the management of knee OA. For the choice of IA treatment in patients with knee OA, our findings support that HA combined with corticosteroid should be prefer instead of HA alone or steroids alone.

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