

Comparison of the Effect of Intra Articular Hyaluronic Acid Injection Versus Glucosamine Sulfate for Pain & Range of Motion Relief of Patient with Grade II & III Knee Osteoarthritis. (A Comparative Study)

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ABSTRACT

Osteoarthritis(OA) is the most common joint disease of humans.the most common joint involved in is knee.among the elderly,knee OA is the leading cause of chronic disability in developed countries.intra-articular hyaluronic acid and glucosaminesulfateare are treatment method in recent years or curative of knee osteoarthritis.this study was conducted to compare the clinical efficacy of onedrug regimen of glucosamine with one drug regimen of intra-articular hyaluronic acid in treatment of knee Osteoarthritis.In recent study,goal was comparison the effect of intra articular hyaluronic acid injection versus glucosamine sulfate for pain & range of motion relief of patient with grade II & III knee osteoarthritis in emam-hossein hospital at 2013-2014.

Methods: This study is a prospective research.the study is including 40 patients with grade 2&3 knee osteoarthritis that were referred to Tehran imam hossein hospital in 2013-2014,patients divided in to two groups: group 1(20 patients) treated by a series of 3 weekly intra-articular injections of hyaluronic acid (HA) and group 2 (20patients) treated by oral glucosamine sulfate (GS) 500mg two times per day for 2months. Two groups were compared regarding pain and range of joint motion that by WOMAC were stimulated.

Results: Study included 40 patients from 38-72 years of age (mean:53.6 years). 13 patients were men and 27 patients were women.after 8weeks of treatment both groups showed improvements in knee function,the HA group showing a greater improvement compared to GS group in knee score.but results were not statistically significant between two groups.(p=0.052).the HA group also tended to have better result relative to the GS group in range of joint motion.results were statistically significant between two groups (p=0.023).

Discussion and conclusion: According to results,both HA and GS showed improvement in range of motion of knee but intra articular HA was superior to GS in improving range of joint motion with no difference in improving knee pain .

KEY WORDS: Osteoarthritis(OA)- glucosamine sulfate (GS)- hyaluronic acid(HA)-knee joint(KJ)-Intra Articular (IA)-PAIN-RANGE OF MOTION(ROM).

INTRODUCTION

Background

Degenerative joint disease (DJD) is one the most common chronic joint conflicts around the world and the most common one is osteoarthritis (1). Predisposing factors such as age, sex, genetic factors, obesity and trauma have been expressed for this disease. The major symptoms of that are pain and swelling, and limitation of motion in the involved joints (2).This disease commonly involves hip, knee, spine and the fingers. Osteoarthritis is the second cause of living disability and includes 3% of total disability. (1) The knee is the most common joint that is affected with osteoarthritis and plays an important role in weight bearing and mobility (3). According to the studies, the prevalence of knee osteoarthritis in the age of over 15 years is 7.9% (4).This illness suffers the 13-30% of people over the age of 65 and is the most common cause of disability in adults (7-5) in Iran knee osteoarthritis prevalence at

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ages over 15 years has been reported about 15.34% which is a high rate (4) this disease can have some damaging economic consequences because it can cause disturbances in the functioning (5). Rising life expectancy and increasing problems such as obesity cause that the number of patients with osteoarthritis of the knee and hence the need for knee replacement surgery has dramatically increased. The treatment of osteoarthritis of the knee includes reducing pain and modifying abnormalities in the knee. Definitive treatment of osteoarthritis of the knee is joint replacement surgery (Total Knee Arthroplasty) which is very expensive and risky and according to the limitations and problems of prostheses lives and great risks for REVISION surgery, these days they try to delay doing TKA as much as possible (15-8) from one point of view this surgery cures the pain of osteoarthritis and returns the patient to their previous activities, but not all patients are appropriate candidates for surgery, therefore medical treatments have become important (16). The medical treatments are mainly for reducing pain and inflammation and maintaining performance and normal movement of the joints (2) For this reason, several non-surgical treatments include the use of medications to reduce pain and glucosamine and Hyaluronic acid injection, physiotherapy, ortose treatment and prolotherapy with dextrose and educating patients and adjusting their activities have been presented and the results of treatment have been reported with these procedures in milder degrees of illness (8-15). In many of studies the effects of intra-articular injection of hyaluronic acid have been shown in improving pain control and patients' function (17-21). Hyaluronic acid is a natural component of cartilage composition of the glycosaminoglycan family and includes the long-chain polymers of repeating units - Acetyl glucosamine Na- glucuronate -N that can be seen in connective tissues, and by virtue of viscoelasticity feature causes softening and increasing pressure by the joint motion. Hyaluronic acid is lubricant of the joint. Mechanism of the effect of that is increasing the number of viable chondrocytes in the creation and restoration of cartilage thickness prevention of nitric oxide production in SYNOVIAL fluid and meniscus and chondrocyte apoptosis inhibition by binding to receptors CD44 and the ICAM1 in chondrocyte and decreasing disaccharides the 4 and 6 unsaturated sulfate chondroitin (Ddi-4s and Ddi-6s) and metalloproteinase-3 and interleukin-1 beta in synovial fluid and joint space (22-23 and 24-27). It has been shown that Hyaluronic acid reduces the number and caliber of vessels caused by inflammation of the synovial membrane and increases fibroblast cells and decreases the number of macrophages and lymphocytes, and mast cells and adipocytes, and increases the amount of collagen (28).

Glucosamine sulfate is one of other substances that its effects in reducing pain and improving function in patients with osteoarthritis have been studied in recent years (29-31). Glucosamine is an amino sugar (glucose synthesis and amine) that is necessary for glycoprotein and glycosaminoglycan's synthesis and proteoglycans that can be found in synovial fluid and articular ligaments and other structures. This supplement is available in two main forms: glucosamine hydrochloride and glucosamine sulfate. Its main mechanism is to stimulate the anabolic activity such as proteoglycans synthesis and hyaluronic and reduces catabolic activities such metalloprotease-3 (29). Glucosamine stimulates the chondrocytes secretion of glycosaminoglycan and proteoglycans (32-33). Glucosamine has an increasing result in the synthesis of proteoglycans and inverts the effect of IL-1B on UDP- glucuronosyl - transferase mRNA and inhibits IL-1B binding to its cellular receptor and interferes with the signal in the next receptor level. Glucosamine increases mRNA that type encoding receptors of IL- 2B. The results note the effect of glucosamine in osteoarthritis treatment through two pathways regulating protein IL-1B, 2B. (34)

Given the need to find a safe, simple and inexpensive non-surgical treatment to reduce pain and improve function in patients with osteoarthritis of the knee and delaying surgical and therapeutic effects of glucosamine sulfate and hyaluronic acid in knee function and pain relief and quality of life in patients with osteoarthritis, from one aspect, the lack of information in comparing the effects of intra-articular injection of hyaluronic acid with use of glucosamine sulfate in articles that require further studies, in the current situation, we do the research.

METHODS

This study was a randomized clinical trial on patients with osteoarthritis of the year 2013-2014 in Imam Hossein Hospital in Tehran.

Inclusion criteria for this study are the patients with primary osteoarthritis grade 2 and 3 is based on KELLGREN- LAWRENCE CLASSIFICATION that the pain and its symptoms are less than 3 months and range of knee motion is in the range of 0-100 degrees.

Exclusion criteria include:

1. The risk of osteoarthritis grades 1 and 4 on the kellgren-lawrence criteria
2. The history of knee injections such as cortisone
3. Secondary Osteoarthritis to SEPTIC & TRAUMATIC ARTRITS

4. Problems with the lower extremity such as the deformity, lack of sensation in lower limb such as DM and neuromuscular diseases
5. The presence of the knee joint inflammation, disease such as RA and gout
6. Intra-articular history of fractures in the knee joint
7. More than 10 degrees of alignment and valgus of valgus
- 8 BMI > 35
9. Surgery of the knee joint such as Arthroscopic in the past 12 months

This is a pre-test post-test study with evidence that the sample according to clinical and radiographic and inclusion and exclusion criteria and 40 women and men are randomly studied into 2 experimental groups of 20. Demographic data of the patients were collected (gender, age, body mass index BMI). 20 patients were treated with intra-articular hyaluronic acid by brand synvisc in the amount of 20mg/2ml 3 times in a row, within a week, other group were treated by oral glucosamine sulfate 500 mg twice daily for 8 weeks and rate of their pain was measured before and after treatment in both groups (pre-test) and then 4 weeks after the last injection of hyaluronic acid and 2 months after starting treatment with oral glucosamine sulfate (post-test) with standard western Ontario & McMaster universities (WOMAC). WOMAC checks pain and the mobility scale of the patient's knee in item 24 in patients with osteoarthritis of the knee. Statistical analysis of data for this study was done using the test MANCOVA (for knee pain and mobility) by SPSS14 statistical software.

Running this study had no problem in terms of medical ethics, however, informed consent was obtained from patients before treatment and none of the patients were excluded from the study.

The method in this case is that the patient is placed supine with the knee flexed to 10-15 degrees in the medial knee landmark of the injection area is specified then the injection site gets disinfected with Povidone Iodine fluid and by injecting 1cc of LIDOCAINE 2%, the regional gets anesthetic and by using a 27-gauge needle after aspiration and ensuring of the correct placement in the joint 20mg/2ml Hyaluronic acid will be injected. All vials of hyaluronic acid in the study are from the company CROMA in Austria. In the glucosamine sulfate group, glucosamine sulfate was administered by the manufacturer ENEREX in Canada.

FINDINGS

This study is a prospective study of 40 patients, ranging in age from 38 to 72 years, with an average of 53.6 years. 13 patients were male (32.5%) and 27 of them were female (67.5 %) and 12 patients were less than 45 years and 23 patients were 45-65 years and 5 of them were more than 65 years. The average age of the study was 53.6±9.93, and patients in the 2 groups of 20 were treated with oral glucosamine sulfate and hyaluronic acid in the joints and all patients participated until the end of the study and no specific medical complications happened for patients during this period.

Table 1. Characteristics Patients to the Osteoarthritis on the Age and Sex and to the Resolution Group Health

SD	The mean age	Gender		Number	Groups
		The number of males	The number of females		
8/53	47/4	5	15	20	Glucosamine group
6/97	59/8	8	12	20	Hyaluronic acid
		13	27	40	Total

Table 2. Descriptive data (average ± SD) of the WOMAC questionnaire in the pre-test (before treatment) and post-test (after treatment) in the treatment of glucosamine and hyaluronic acid

SD	Mean	Number	Time	Group
1/09	7/45	20	pretest	Glucosamine
1/86	5/7	20	Post-test	
0/95	7/8	20	Pretest	Hyaluronic acid
1/48	5	20	Post-test	

Table 3. Comparison between pain and motility of knee by index (WOMAC) in the pre-test (before treatment) and post-test (after treatment) in patients treated with glucosamine and hyaluronic acid

Statistical estimation	F	Mean Square	SD	Average	Number	Time	Group	variable
=0/052p	4/045	9/706	1/09	7/45	20	Pretest	Glucosamine	Amount of pain
			1/86	5/7	20	Post-test		
			0/95	7/8	20	Pretest	Hyaluronic acid	
			1/48	5	20	Post-test		
=0/023p	5/643	602/835	7/59	100/5	20	Pretest	Glucosamine	The difference in mobility
			11/47	105	20	Post-test		
			12/16	96/05	20	Pretest	Hyaluronic acid	
			8/94	112	20	Post-test		

By using the test Mancova and Multivariate GLM (multivariate analysis of covariance), it was determined that by counting the amount of pain and angular motion of the knee with dependent variables and values, including pain and knee angular momentum before treatment as a covariate variables and considering the variable group (glucosamine acid Hyaluronic) as independent variables, there was no significant difference in the level of $\alpha=0.05$ and 95% of sureness in the pain scale between the two groups before and after treatment ($p = 0.052$). But there is a statistically significant differences in the level of $\alpha=0.05$ and 95% of sureness in the mobility of the knee before and after treatment between the two groups of used drugs ($p=0.023$). It should be noted that the average amount of pain in the group treated with hyaluronic acid before treatment was 7.8 and after treatment was 5 but in the glucosamine group, before treatment this average was 7.45 and after treatment was 5.7. It means that the hyaluronic acid is superior to glucosamine on reducing pain but it is not statistically significant.

DISCUSSION

The study showed that in both glucosamine sulfate (GS) and hyaluronic acid (HA) group, function of knee was associated with an improvement but intra-articular hyaluronic acid is superior to oral glucosamine sulfate on improving range of motion of knee.

In 1980 Pujalt, Liavore and Ylescupidéz, in a study, chose 20 people with knee osteoarthritis and randomly gave them placebo or 250 mg glucosamine sulfate daily for 3 months. A considerable improvement was observed in pain, joint tenderness and swelling in the group receiving treatment, while there was no such thing in the control group (35-37).

In a study done by Dos et al. in America in 1999, a significant improvement was observed in the clinical symptoms of osteoarthritis of the knee after taking glucosamine and chondroitin sulfate with a dose of 400 mg during 4-6 months in 72 patients comparing to the control group, however, gastrointestinal symptoms such as abdominal pain and vomiting were seen in patients taking glucosamine (38).

Leffler and Philippi in 1997, in a study on 34 patients with knee OA who were members of the Navy Army, concluded that after 16 weeks of treatment with glucosamine with a dose of 400 mg, the knee pain of patients decreased (39-41)

Rovati in 1997 in a study on 319 patients that were randomized in two groups of glucosamine sulfate daily 1500mg and placebo, showed that glucosamine sulfate significantly improved symptoms of knee osteoarthritis patients in a long duration (42).

Petrella et al. conducted a prospective study in 2006 entitled ((Evaluation of intra-articular hyaluronic acid in knee osteoarthritis)) in Canada. They studied 106 patients with osteoarthritis in the period of 3-6-12 weeks and the patients were divided in two groups. 2 ml of hyaluronic acid was injected to one group and the exact amount of intra-articular placebo to other group in 3 consecutive weeks, every week one injection, and their pain intensity was assessed by WOMAC. They concluded that hyaluronic is superior to placebo in the treatment of knee pain (43).

Dudek A et al. conducted a prospective study in 2007 entitled ((Effect of glucosamine sulfate in osteoarthritis patients)) in Poland. They studied 50 patients with OA in a 12-week period. The patients were treated with glucosamine in level of 500mg 3 times a day. They concluded that using glucosamine improves the function and pain in patients with osteoarthritis (44).

Reginster JY et al. conducted a study in 2007 entitled ((Common role of glucosamine in osteoarthritis)) in Belgium. They read all articles published in the midline of the effect of glucosamine. They concluded that using glucosamine has a positive effect on symptoms of knee structure prognosis (45).

Muller FH et al. conducted a prospective study in 1994 entitled ((comparing glucosamine to ibuprofen in osteoarthritis)) in Germany. They treated a group with 400 mg ibuprofen 3 times a day and another group with 500

mg glucosamine 3 times a day and compared them with each other over a period of 3 months. They concluded that using glucosamine for osteoarthritis symptoms is more effective than ibuprofen. (46)

In this study, intra-articular hyaluronic acid was better than oral glucosamine sulfate in improving the range of motion of the knee joint, but there was no difference between the two groups in curing the knee pain. According to studies carried out in the domestic and foreign literature, no study was found in this area and this issue makes trouble in comparing this data with other research papers. The limitations of this study include the small sample size and short follow-up periods. Studies with a larger sample size and longer follow-up course and comparing different doses of the two drug can be helpful in treating the disease.

Conclusion

In this study hyaluronic acid clearly reduces knee joint pain and a significant difference can be seen in WOMAC before and after treatment with hyaluronic acid ($p=0.0001$) which is similar with the result of a study conducted by Petrella in 2006 in Canada named "evaluating the impact of intra-articular hyaluronic acid for knee osteoarthritis". They concluded that hyaluronic acid is superior to placebo in the treatment of knee pain.

In this research, knee pain is decreased with glucosamine sulfate and a statistically significant difference can be seen in WOMAC before and after treatment with glucosamine sulfate ($p=0.0001$) which is similar with the result of a study conducted by Dudek et al. in 2007 in Poland named "studying glucosamine sulfate in patients with osteoarthritis of the knee". They concluded that using glucosamine improves performance and pain in patients with osteoarthritis.

In this study, glucosamine sulfate and hyaluronic acid both increase motility (ROM) and a statistically significant difference can be seen between the joint mobility in the two groups before and after treatment which means that in both groups increasing in the level of joint mobility can be seen after treatment ($p=0.007$ for hyaluronic acid and $p=0.016$ for glucosamine sulfate) which is similar with the result of the research conducted by Altman et al. in 1998 in the United States and the research conducted by Pretrellain 2006 on hyaluronic acid and also Dudek's researches on glucosamine sulfate in 2007 in Poland.

In this study, hyaluronic acid is superior to glucosamine sulfate in increasing the motility of a joint (ROM) ($p=0.023$), which means that by 95% sureness it can be said hyaluronic acid is superior to glucosamine sulfate in increasing joint mobility.

In pain reduction, although hyaluronic acid reduces pain in higher amounts, no statistically significant difference can be seen between the two groups ($p=0.052$). Considering the results obtained it can be concluded that the hyaluronic acid improves the symptoms of knee osteoarthritis in a greater extent compared to glucosamine sulfate.

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