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Research Article

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Low dose glucosamine and chondroitin sulfate use in knee osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a joint disease that most commonly accompanied with pain and joint deformity which eventually leads to disability. Burden of OA will be accounted second in women and fourth in men in Iran. Most therapies of knee osteoarthritis are symptomatic treatment. This study was designed to assess the efficacy of Glucosamine and Chondroitin sulfate in complete dose and one – third dose as a low cost protocol on treating of knee OA. Study was performed as a randomized double blind clinical trial. Symptomatic knee OA cases at Kellgren – Lawrence based stages I, II and III were enrolled in study following exclusion of systemic disease as well as joint disease. Cases were divided into 3 groups: complete dose treatment (Group I), One – third dose treatment (Group II) and placebo user (Group III). Then cases were followed for 12 weeks via Visual Analog Scale (VAS) and Western Ontario and McMaster universities (WOMAC) questionnaires associated with subsequent statistically analyzes. Statistically significant differences in the rate decline of pain, stiffness, functionality and eventually total scores as well as VAS scores were observed between both treatment groups (Group I and II) and placebo users (Group III) without any Statistically significant differences between themselves (Group I and Group II). Due to effects of Glucosamine and Chondroitin sulfate at one–third dose level recommends for OA as a low cost protocol in association with weight loss and muscles physiotherapy as well as healthy use of joints.

Key words: Knee osteoarthritis, Glucosamine, Chondroitin sulfate.

INTRODUCTION

OA is one of the pain and disability causes as well as the most common muscloskeletal disease around the world. OA causes progressive degeneration of cartilage and joint space loss. The most commonly affected joints are knees, hips, spine and small joints of the fingers. Due to uncertain correlation between clinical syndromes and radiologic findings, estimation of OA prevalence is not easy. However, OA prevalence is higher in females and increases with age. Knee osteoarthritis is the most common joint disease that causes pain and joint deformity and eventually leads to an inability. The disease classically refers to focal articular cartilage lesion with a hypertrophic response in the bone and subcondral region. Prevalence of symptomatic knee OA is 5.4% and 16% in men and women over 80 years respectively. Approximately 11% of symptomatic knee OA cases are at the ages over than 64 years. Most drugs for knee OA treatment are symptomatic therapy. In recent decades, many studies on the medications with modulating effects on articular structurality have been done. Dedicated treatments of knee osteoarthritis are usually provided for pain control and quality of life improvement as well as progressive arthetopathy prevention. OA therapy is divided into two groups. First non- pharmacotherapy which includes some educational efforts on healthy use of joints, muscle physiotherapy, aerobic exercise and weight loss in obese patients, heat therapy and

acupuncture. Second pharmacotherapy includes topical and oral NSAID, such as acetaminophen and intra-articular injections of corticosteroids and hyaluronic products and supplements such as Glucosamine and Chondroitin sulfate. Numerous studies about these supplements have been globally conducted from 1969. Some reviews in according to the evidence base medicine (EBM) showed Glucosamine and Chondroitin sulfate safety and effectiveness on OA. [1-3] Community Oriented Program for the Control of Rheumatic Diseases (COPCORD**)** study in Iran showed that OA prevalence in Iran was reached to 24.46% of men and 57.43% of women over 50 years as well as 5706% of men and 79.3% of women over 70 years. [4] Burden of OA will be accounted second in women and fourth in men in Iran. [5, 6] In according to mentioned prevalence and progressive pattern of OA which finally leading to patient's disability, it seems reasonable to reduce cost of OA control. Additionally this study was designed to rule out of pharmacotherapy outcome varieties in Iran in compare with others. Similar results have also been demonstrated in other studies: The study was conducted on 212 patients. At least 25-20% of patients showed improvement for three years. This improvement was also assessed by WOMAC questionnaire. Meanwhile, the drug safety and no side effects during the period of 3 years have been underlined. [7] Another study was conducted to use 1200/1500 mg dose of Glucosamine and Chondroitin sulfate in combination with daily exercise and placebo in patients with knee osteoarthritis. At the end of study, the WOMAC questionnaire scores between the two groups were not significant differences statistically. [8]

EXPERIMENTAL SECTION

Symptomatic knee OA cases at Kellgren – Lawrence based stages I, II and III were enrolled in study following exclusion of systemic disease as well as joint disease. These patients randomly divided into 3 groups and each intervention groups were treated with Glucosamine and Chondroitin sulfate in complete dose and one – third dose group as well as placebo group. OA of patients were characterized using American College of Rheumatology (ACR) standards and enrolled cases were in all stages of kellgren & Lawrence scaling system (I, II and III) except stage IV. Exclusion criteria were the presence of heart disease, lung disease, liver disease, diabetes and other rheumatic diseases, Glucosamine and Chondroitin sulfate use during past 3 months, grade IV osteoarthritis (complete destruction of the joints) and analgesic use and eventually 105 cases were enrolled. Patients randomly assigned to 3 mentioned groups based on computerized random number selection. Group I was treated with Glucosamine sulfate (1500 mg) and Chondroitin sulfate (1200 mg) per day. Group II was treated with one – third dose of Glucosamine sulfate (500 mg) and Chondroitin sulfate (400 mg) per day. Finally, group III was treated using placebo. Baseline blood tests including CBC, diff, Bun, Cr, ALT, AST, ESR and both knee PA and lateral view radiography were obtaind from all patients. Additionally, all cases were assessed by questionnaires for baseline WOMAC and VAS values obtaining. The OA patients were evaluated by WOMAC questionnaire via three indicators: pain, stiffness and functional limitation which contain five, two and seventeen questions respectively. Each patient was asked to give scores from 0 to 100 for each question. Every case was emphasized to avoid from any analgesic consumption during study enrolling. Initial experiments were repeated at the end of the third month of treatment to rule out possible side effects. After completion of the study, WOMAC and VAS scores at baseline and the end of the third month were obtained and a difference in the mean of the pain, stiffness and functionality score at the level of at least 20% decline was considered as drug efficacy cut off point between the groups. A method of evaluation that is widely used for evaluating patients with knee osteoarthritis is WOMAC questionnaire that are used to assess pain and disability. Reliability of questionnaire was standardized for cases. Meanwhile, the university ethics committee approval was obtained for this study.

RESULTS

Analysis was performed on 87 cases. Number of patients was 105 (35 cases for every group) at baseline. All of cases in group I (35 cases) and 27 cases (72%) of group II and 25 cases (71%) of placebo group (Group III) were completed trial. At group III, two people were referred to further treatment, three cases have left because of dyspepsia, three patients withdrew due to personal reasons, one case did not visit due to distance and one person was excluded due to NSAID use. At group II, two people have left because of dyspepsia, four patients withdrew due to personal reasons, one person did not visit due to distance and one people were referred to further treatment.

Table 1. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores at drug efficacy cut off point (at least 20% decline)

Variable	Number of cases in group I (full dose) (n=35)	Number of cases in group II (one – third dose) (n=27)	Number of cases in group III (Placebo) (n=25)	P_{value}
Pain	57.1% (n=20)	59.3% (n=16)	28% (n=15)	0.039
Stiffness	53.3% (n=16)	47.8% (n=11)	36.4% (n=8)	0.47
Functionality	60% (n=21)	63% (17)	28% (7)	0.019
Total WOMAC	60% (n=21)	66.7% (n=18)	32% (n=8)	0.028
VAS	60% (n=21)	55.6% (n=15)	36% (n=9)	0.16

While the number of cases with pain, functionality and Total WOMAC scores decrease (P_{value} = 0.039, P_{value} = 0.019 and P_{value} = 0.028 respectively) were statistically significant among groups I and II in compare with group III (Placebo) but it wasn't occurred about stiffness (P_{value} = 0.47) and VAS (P_{value} = 0.16) scores decrease at drug efficacy cut off point (Table 1). In according to following results, the pain, functionality and total WOMAC scores decline were statistically significant in the group I (Table 2). On the other hand, the chance of pain score reduction after full dose treatment in group I at the confidence interval (CI) level of 95% was 3.42 times more than placebo group (95% CI: 1.1 – 10.3, Odds Ratio = 3.42). These values were 95% CI: 1.27 – 11.63, Odds Ratio = 3.8 for the chance of functionality score reduction and 95% CI: 1.08 – 9.37, Odds Ratio = 3.1 for the chance of total WOMAC score reduction.

Table 2. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores at drug efficacy cut off point between group I and III

Variable	Number of cases in group I (full dose) (n=35)	Number of cases in group III (Placebo) (n=25)	P_{value}
Pain	57.1% (n=20)	28% (n=15)	0.025
Stiffness	53.3% (n=16)	36.4% (n=8)	0.22
Functionality	60% (n=21)	28% (7)	0.014
Total WOMAC	60% (n=21)	32% (n=8)	0.03
VAS	60% (n=21)	36% (n=9)	0.06

Table 3. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores at drug efficacy cut off point between group II and III

Variable	Number of cases in group II (one – third dose) (n=27)	Number of cases in group III (Placebo) (n=25)	P_{value}
Pain	59.3% (n=16)	28% (n=15)	0.023
Stiffness	47.8% (n=11)	36.4% (n=8)	0.43
Functionality	63% (17)	28% (7)	0.012
Total WOMAC	66.7% (n=18)	32% (n=8)	0.012
VAS	55.6% (n=15)	36% (n=9)	0.15

In according to results, similar to group I comparison with placebo group, the pain, functionality and total WOMAC scores decline were statistically significant in the group II too (Table 3). On the other hand, the chance of pain score reduction after one – third dose treatment in group II at the confidence interval (CI) level of 95% was 3.74 times more than placebo group (95% CI: 1.1 – 11.9, Odds Ratio = 3.74). These values were 95% CI: 1.35 – 14.10, Odds Ratio = 4.37 for the chance of functionality score reduction and 95% CI: 1.33 – 13.56, Odds Ratio = 4.25 for the chance of total WOMAC score reduction.

Table 4. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores at drug efficacy cut off point between group I and II

Variable	Number of cases in group I (full dose) (n=35)	Number of cases in group II (one – third dose) (n=27)	P_{value}
Pain	57.1% (n=20)	59.3% (n=16)	0.86
Stiffness	53.3% (n=16)	47.8% (n=11)	0.69
Functionality	60% (n=21)	63% (17)	0.81
Total WOMAC	60% (n=21)	66.7% (n=18)	0.59
VAS	60% (n=21)	55.6% (n=15)	0.72

As seen in the table 4, there were not statistically significant between group I (full dose treatment group) in compare with group II (one – third dose treatment group) on the based on pain, stiffness and functionality scores as well as VAS and total WOMAC scores ($P_{value} \geq 0.05$).

DISCUSSION

The study was completed by 87 cases (82%) of total 105 enrolled patients finally. There were not statistically significant differences among groups in terms of gender, age and BMI distribution at baseline. Our results showed that treatment using full dose and one – third dose of Glucosamine and Chondroitin sulfate in terms of reduction in the pain, functionality and total WOMAC scores had similar effect on patients. The following results were obtained in a similar study in 2009. Glucosamine and Chondroitin sulfate effect were revealed after 12 to 16 weeks of treatment ($P_{value} < 0.05$). [9] This story was repeated in tow clinical trials that performed on 380 knee Osteoarthritis cases ($P_{value} = 0.004$). [10] Long-term studies on the Glucosamine Sulfate derivatives are pending too. [11] In according to evidence base research during 2002 to 2006, Osteoarthritis Research Society International (OARSI) has concluded in 2010 that pain by taking Glucosamine sulfate has declined, but the results were different, and in some cases evidence of bias was observed. [12] According to some studies, it was recommended that the Glucosamine Sulfate blood level must be considered in order to demonstrate therapeutic effects which probably handled via NO or PGE2 derivatives. [13, 14] We recommend more patients enrollment in such studies or combination of similar studies for better conclusion. For example, it is better to be considered the effect of BMI or stage of osteoarthritis (Kellgren-Lawrence I, II, III) based on the primary WOMAC Osteoarthritis stage (grades 125>, 300-125 and 400-300 of 400 <) in therapeutic outcomes.

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