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ORIGINAL ARTICLE

Role of Glucosamine Sulphate, Chrondoitin Sulphate and Vitamin C in the management of pain in Osteoarthritis

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ABSTRACT
Osteoarthritis (OA) is a degenerative joint disease involving the cartilage and many of its surrounding tissues. The objective of this study is to investigate the effects of vitamin C in combination therapy with chondroitin sulphate, glucosamine hydrochloride in the pain management of OA patients. The study was conducted among 3 different groups of patients in order to evaluate and compare the improved treatment outcomes. Superior effects were found in combination treatment with paracetamol, glucosamine hydrochloride, chrondoitin sulphate and vitamin C over the combination of acetaminophen, glucosamine hydrochloride and chrondoitin sulphate and over the single acetaminophen treated patients. Therefore, the study suggests that combination of vitamin C with glucosmine hydrochloride and chrondoitin sulphate may show an additive effect in alleviation of pain in knee OA patients.
Key words: *Chondroitin sulfate, Glucosamine hydrochloride, Vitamin C, Osteoarthritis, Combination therapy*

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INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease involving the cartilage and many of its surrounding tissues. In addition to damage and loss of articular cartilage, there is remodeling of subarticular bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles, and, in some cases, synovial inflammation. These changes may occur as a result of an imbalance in the equilibrium between the breakdown and repair of joint tissue. Primary symptoms of OA include joint pain, stiffness, and limitation of movement. Disease progression is usually slow but can ultimately lead to joint failure with pain and disability. [1] Conventional pharmacological approaches to symptom management in OA involve paracetamol, nonsteroidal anti-inflammatory drugs, selective cycloxygenase-2 inhibitors, and intra-articular injection of hyaluronan or corticosteroids. However, there are accumulating data showing that any of these pharmaceutical drugs frequently produce insufficient benefits, with an associated risk of untoward side effects. [2-4] It is therefore no wonder that patients with OA have embraced complementary and alternative approaches such as combination of glucosamine hydrochloride and chrondoitin sulphate for the management of OA symptoms, particularly pain. [5-6] Treatment guidelines in the United States, Great Britain, and Canada recommend NSAIDs as second line treatment (after paracetamol) for mild OA and as a first-line treatment for moderate to severe OA. [7-8] During OA progression, the chondrocytes are no longer able to fully compensate for the loss of collagen type II fibers and proteoglycans, even at increased synthesis rates. [9] It has been shown in many *in vitro* and *in vivo* trials and in numerous clinical studies that these chrondo-protectives can modify, stabilize, retard, or even reverse the pathology of OA. It has been shown that glucosamine enhances the production of cartilage matrix components in chondrocyte culture, such as aggrecan and collagen type II. [10-11] Glucosamine increases hyaluronic acid production in synovium explants. Further experiments have shown that glucosamine prevents collagen degeneration in chondrocytes by inhibiting lipoxidation reactions and protein oxidation. [12] Ascorbic acid stimulates collagen synthesis and modestly stimulates synthesis of aggrecan (a proteoglycan present in articular cartilage). Sulfated proteoglycan biosynthesis is significantly increased in the presence of ascorbic acid. [13] It was reported that the extra ascorbic acid

had a slight chondroprotective effect on the development of spontaneous lesions. [14-15] In the Framingham Osteoarthritis Cohort Study, a moderate intake of vitamin C (120-200 mg/day) resulted in a three-fold lower risk of OA progression. [16]

Therefore, the objective of the study was to investigate the improved treatment outcomes of using combination of glucosamine hydrochloride, chrondoitin sulfate & vitamin C and also to find out the impact of this treatment in reduction of analgesic use.

MATERIAL AND METHOD

Study design

This is a prospective, randomized single blinded clinical trial to study and differentiate the efficacy of the combination therapy of glucosamine hydrochloride, chrondoitin sulfate and vitamin C in knee osteoarthritis compared to glucosamine hydrochloride, chrondoitin sulfate and paracetamol. The study was carried out from June 2013 to December 2013 and was conducted in the Physical Medicine Department of Dhaka Medical College Hospital. Dhaka Medical College Hospital is a tertiary care hospital in Bangladesh with complete physical medicine rehabilitation (PMR) unit with almost all modalities of physical therapy including Transcutaneous electrical nerve stimulation (TENS) and all necessary pathological and imaging facilities. Patients coming to Dhaka Medical College Hospital for treatment of knee osteoarthritis were made to undergo a full clinical examination performed by the physician on duty in order to evaluate the symptoms and possibility of including the patients to the study.

Patients were selected according to the below mentioned inclusion and exclusion criteria. Based on informed consent, patients were selected based on the following criteria: pain in anyone of knee joint, duration of pain is more than 3 months, Age between 40-70 years, Morning stiffness is less than 30 minutes, crepitus on active movement, bony tenderness, ESR < 40 mm in 1st hour, radiological evidence of OA knee like marginal osteophytes, subchondral sclerosis, cyst, joint space narrowing and osteochondral loose bodies. Exclusion criteria were selected based on factors that may hamper the evaluation in this study and included: history of trauma / fall/ sports injury of knee joint, genu varus / genu valgus deformity, history of knee surgery, inflammatory arthritis like rheumatoid arthritis (RA), spondyloarthropathy, infectious disease like tuberculosis, crystal associated artrhropathy like gout, pseudogout, skin infection over knee joint, uncontrolled diabetes mellitus, surgical treatment of knee joint(s) undergone or its necessity, routine use of health food or medicine containing hyaluronic acid, glucosamine and/or chondroitin sulfate and expected to be continued during the study period; treatment with bisphosphonates, hormones or other medicines that may affect the serum or urine concentrations of biomarkers of bone or cartilage metabolism; intra-articular hyaluronic acid within 2 weeks or corticosteroids within 3 months before inclusion; need to undergo such topical or systemic pharmacological treatments during the study period; occasional taking of hard exercise; a history of osseous or articular diseases other than OA within the past 3 months; treatment with warfarin, undergoing or needed to undergo during the study period; bronchial asthma or potential for developing allergy to the test supplement; pregnant women; nursing mothers or women of childbearing potential.

Treatment and subject assignment

The selected patients were then randomly allotted to one of the below 3 treatment groups. Group A patients were given Ace 500 mg tablets (paracetamol), Contilex Tablets (glucosamine hydrochloride 250 mg and Chondoitin sulphate 200 mg) 2 tablets, thrice daily and Ceevit Tablet (Ascorbic acid and Sodium ascorbate equivalent to 250 mg vitamin C) once daily. Group B patients were given Ace 500 mg tablets (paracetamol), Contilex Tablets (glucosamine hydrochloride 250 mg and chondoitin sulphate 200 mg) 2 tablets, thrice daily. Group C patients were given Ace 500 mg tablets (paracetamol).

Patients of all groups were instructed to refrain from taking Ace Tablets as much as possible and to take it only if necessary due to knee pain and not to exceed 3 tablets per day. All patients were instructed not to take any other analgesics during the trial period and were given an outline on the side effects/adverse effects of long term use of pain killers such as paracetamol as well as NSAIDS.

Activity of Daily living (ADL) instructions was given to all patients on the baseline date (week 0). Patients were instructed to refrain from putting excess stress on the knee joints. (i.e. not to kneel or sit in squatting position or lift heavy objects). Patients found to be overweight or obese were instructed to lose weight. The patients were also trained to do various types of muscle strengthening/isometric exercises with the goal of improving muscular balance which helps to reduce the load on the joint as a non-pharmacologic mode of treatment by on duty physiotherapists in the hospital gymnasium. The patients were advised to do the exercises at least 30 minutes every day. Patients were also advised to apply heat therapy to their knees.

All medicines were generously gifted by Square Pharmaceuticals Ltd., Bangladesh for research purpose and were provided from Dhaka Medical College Hospital to the patients on a 2 weekly basis in order to ensure that the patients visited the facility every 2 weeks.

Efficacy assessment

The selected patients were then assessed for the following on the baseline date and every subsequent 2 weeks for a period of 8 weeks based on the JOA criteria 97: pain at rest (with the help of visual analogue scale), pain while walking (with the help of Visual analogue scale), pain while climbing up or down stairs (with the help of Visual analogue scale), time required for walking a distance of 50 feet, ADL instructions followed or not (only in the last week), quantity of Paracetamol taken every 2 weeks, and tenderness index scale (0 = No pain, 1 = Describes pain, 2 = Patient winches, 3 = Patient winches and withdraw the affected part, 4 = The patient will not allow the joint to be touched).

RESULTS AND DISCUSSIONS

20 participants in the 3 separate groups were included in this study. Majority of the patients described their pain to be in their right legs. In all 3 groups, higher number of the patients had a gradual onset of pain. Majority of the patients were diagnosed with tibiofemoral osteoarthritis on one or both legs. Very few were diagnosed with patellofemoral osteoarthritis on one leg.

Reduction of pain from baseline at rest

The average pain at rest of the patients reduced least amongst patients of group C on every subsequent week from baseline. Whereas, both Group A and Group B showed significant reduction on pain with Group a showing highest reduction from baseline.

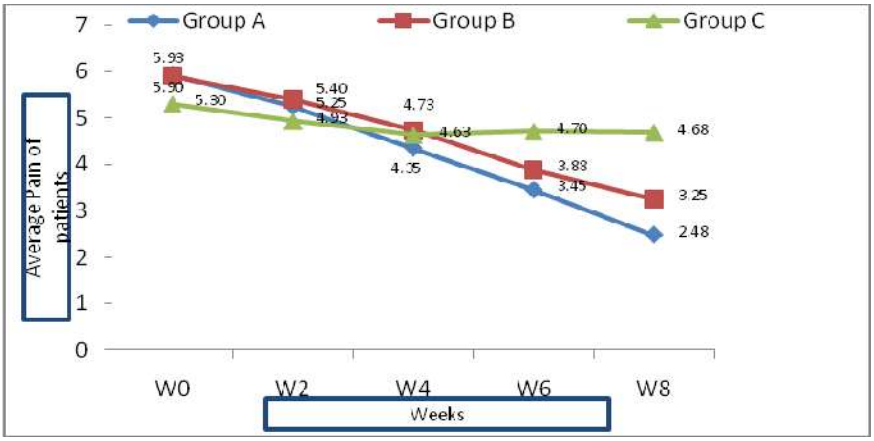

Figure 1: Reduction of average pain amongst the 3 groups from baseline

Group A resulted in the highest reduction of average pain (58.18%) after the period of 8 weeks with group C had a maximum reduction of 12.64% at Week 4 after that the average pain reduction of the patients remained fairly similar for the subsequent weeks.

Reduction of pain from baseline during walking

The average pain during walking amongst the patients reduced least amongst patients of group C on every subsequent week from baseline. Whereas, both Group A and Group B showed significant reduction on pain with Group A showing highest reduction from baseline.

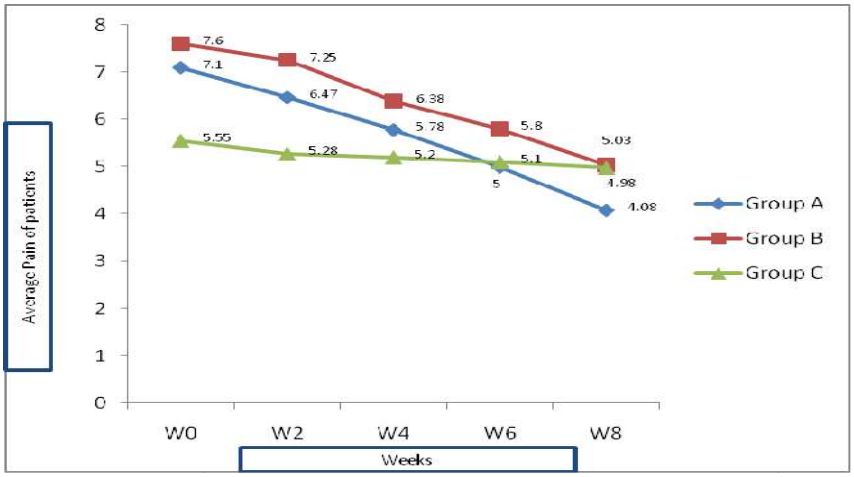

Figure 2: Reduction of average pain from baseline amongst the 3 groups from baseline during walking

Reduction of pain from baseline in ascending/descending stairs

The average pain during ascending/descending stairs amongst the patients reduced least amongst patients of group C on every subsequent week from baseline. Whereas, both Group A and Group B showed significant reduction on pain with Group a showing highest reduction from baseline.

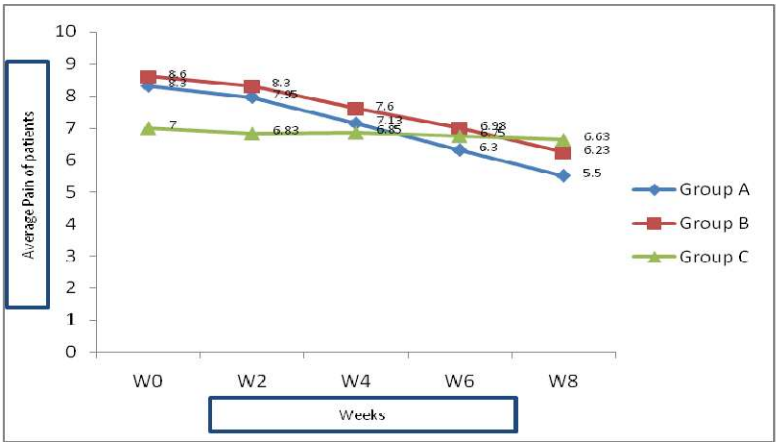

Figure 3: Reduction of average pain amongst the 3 groups from baseline in ascending/descending stairs

Reduction in walking time from baseline

Group C showed least reduction in walking time after a period of 8 weeks, whereas Group A and B showed similar reductions in walking time after 8 weeks.

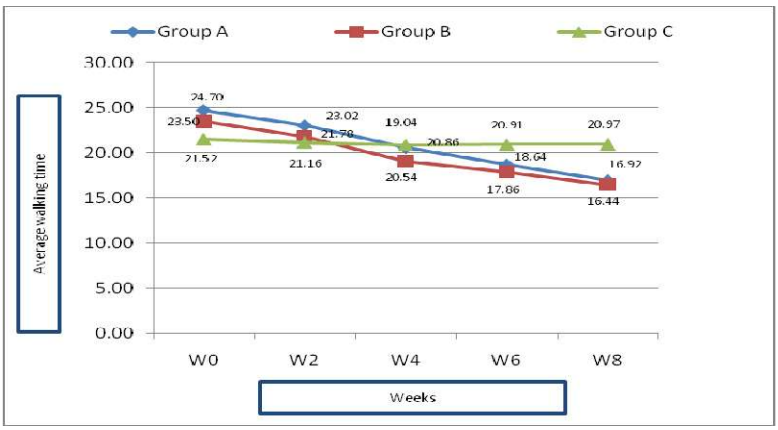

Figure 4: Reduction of walking time from baseline amongst the 3 groups from baseline

Quantity of analgesics taken

Group A and B showed the highest reduction in analgesics taken by the patients after the 8 week study period (48% and 49% respectively). Group C had the lowest reduction in analgesics taken.

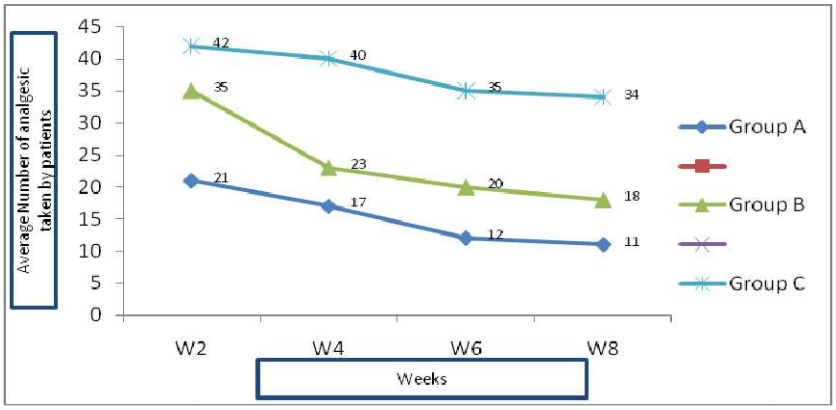

Figure 5: Average quantity of analgesics taken by the patients of the different groups during the study

Adherence to ADL (Activities of daily living) instructions

During the study period, the patients were asked whether they were following the different ADL. The results were as given in the figure below. Most patients followed ADL instructions as recommended. However, many patients only partially followed it. i.e. Even though they exercised as recommended, they kneeled during prayers, sat in a squatting position in the toilet, etc. which placed extra pressure on the knees. Some patients did not even exercise as prescribed.

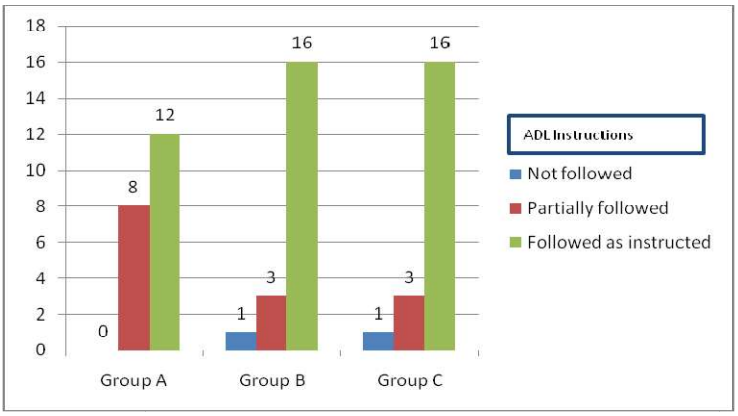

Figure 6: Comparison between adherence to ADL instructions amongst the 3 groups of patients

Efficacy of different treatment groups in mild, moderate and severe pain

In order to understand the efficacy of the treatment groups, the VAS pain scale was further categorized into the following. Pain sub scale 1-3 considered as low pain, pain subscale of 4-7 considered as moderate pain, while pain sub scale of 8-10 considered as severe pain. Further analysis was not done on the low pain subscale since very few patients were within that group.

When comparing the % reduction in average pain amongst patients having moderate or severe pain at rest, it was found that all 3 groups showed better efficacy amongst patients having moderate pain, rather than severe pain. In both cases group A had the highest reduction of pain from the baseline 66.30% in moderate pain and 36.36% in severe pain. Group C showed a negative trend in severe pain reduction after 6th week indicating that it was ineffective in reducing pain of the group of patients.

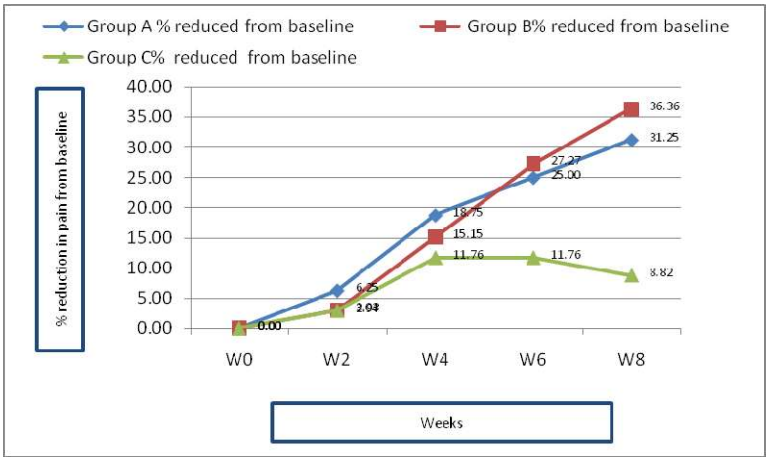

Figure 7: Percentage reduction in average pain amongst patients having severe pain at rest

Comparison between % Reduction of average pain from baseline amongst patients having moderate and severe pain while walking

When comparing the % reduction in average pain amongst patients having moderate or severe pain while walking, it was found that all 3 groups showed better efficacy amongst patients having moderate pain, rather than severe pain. Group A had the highest reduction of pain from the baseline 50.98% in moderate pain and 33.54% in severe pain. Group C showed a negative trend in severe pain reduction after 2nd week indicating that it was ineffective in reducing pain of the group of patients.

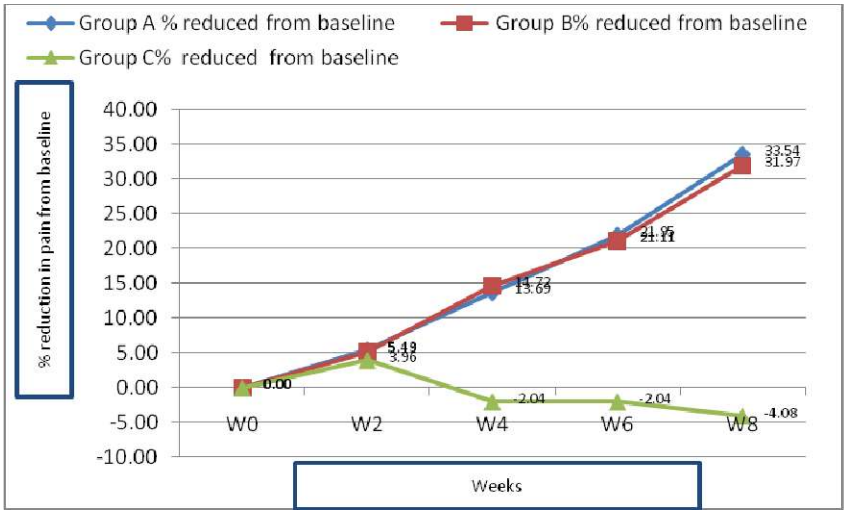

Figure 8: Percentage reduction in average pain amongst patients having severe pain while walking

Comparison between % Reduction of average pain from baseline amongst patients having moderate and severe pain while ascending/descending stairs

When comparing the % reduction in average pain amongst patients having moderate or severe pain while ascending/descending stairs, it was found that groups A and B showed better efficacy amongst patients having moderate pain, rather than severe pain. Group C had no patients with moderate pain in this category. Group A & B had the highest reduction of pain from the baseline 33.29% in moderate pain while Group A showed highest reduction in average pain in severe pain 31.49%. Group C showed a negative trend in severe pain reduction after 2nd week indicating that it was ineffective in reducing pain of the group of patients.

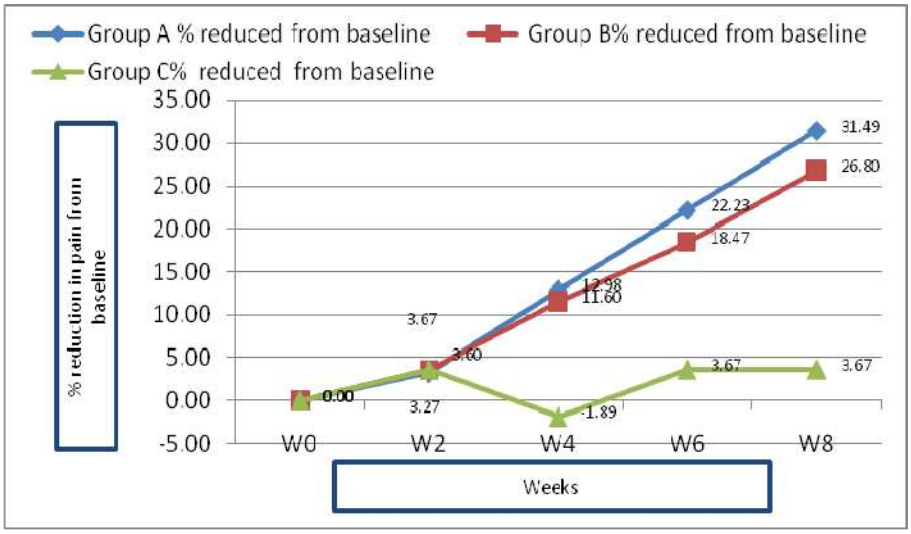

Figure 9: Percentage reduction in average pain amongst patients having severe pain while ascending/descending stairs

Tenderness Index scale

The tenderness index scale yielded insignificant results. The average was more or less the same upto 8 weeks. As a result the data has not been used to draw any further inferences.

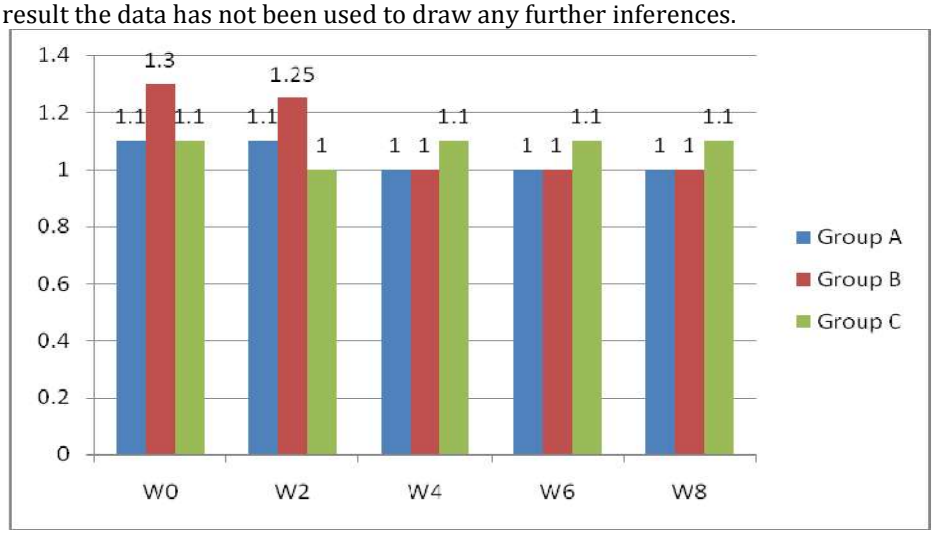

Figure 10: Tenderness index scales of the 3 groups of patients

CONCLUSIONS

The prospective, randomized single blinded clinical trial was carried out to evaluate and differentiate between the effects of the 3 treatment groups Group A (Glucosamine sulphate + Chrondoitin sulphate + Vitamin C + Paracetamol), Group (Glucosamine sulphate + Chrondoitin sulphate + Paracetamol) and Group C (Paracetamol only).

Even though extensive studies have been conducted on efficacy of glucosamine and chrondoitin sulphate, in most of the studies, the combination was always given alone without any analgesics. However, as per a number of previous studies it has been shown that glucosamine sulphate and chrondoitin sulphate is not appropriate for short-term analgesia, but is suitable for medium- to long-term management of knee OA, producing global clinical improvements. [17-18] Ascorbic acid stimulates collagen synthesis and modestly stimulates synthesis of aggrecan (a proteoglycan present in articular cartilage). Sulfated proteoglycan biosynthesis is significantly increased in the presence of ascorbic acid. [13]

Therefore, in this study the outcome of combining the analgesic with combination of glucosamine sulphate, chrondoitin sulphate and vitamin C was checked.

The results of the of the study show that the combination treatment of Group A (Chrondoitin sulphate + Glucosamine + paracetamol) was superior in reduction of pain from baseline when compared to the other 2 groups (Group B & C) at rest, while walking or even ascending/descending stairs amongst the patients.

This shows that the effectiveness of all 3 treatment modalities decreases as a whole when at rest compared with while walking or climbing stairs. As expected pain reduction was lowest in Group C who were given Paracetamol which is only effective in mild OA. [7-8] On the other hand the superior reduction in pain Group A compared to Group B may be attributed to combined effects of vitamin C, chrondoitin sulphate and glucosamine. *In vitro* studies have shown that glucosamine enhances the production of cartilage matrix components in chondrocyte culture, such as aggrecan and collagen type II. [10-11] Glucosamine increases hyaluronic acid production in synovium explants. Further experiments have shown that glucosamine prevents collagen degeneration in chondrocytes by inhibiting lipoxidation reactions and protein oxidation. [12] The negative charge of Chrondoitin Sulphate, makes it responsible for the water retention of the cartilage, which is important for pressure resistance. [17] Both of these nutrients were also found to modulate the inflammatory process and act as antioxidants reducing oxidative stress. Both of these functions are beneficial in OA. [19-21] Vitamin C is a very good antioxidant. In studies involving animals protective effect on experimentally induced cartilage degeneration of the knee. [14-15] These effects have been also demonstrated in humans in the Framingham study. [16]

The results of the reduction from baseline has been further reinforced by the reduction in the quantity of analgesics taken by patients after 8 weeks compared to baseline (2^{nd} week) in group A (48%) and Group B (49%) compared to group C (19%).

While comparing the effectiveness of the pain relief in moderate and severe pain, it was found that groups A and B treatments were better in reduction of average pain from baseline inpatients having moderate pain while at rest or walking. Group A treatment was superior to other 2 groups in all cases, except for average reduction in moderate pain of patients while ascending/descending stairs. These findings are inline with previous study where glucosamine sulphate and chrondoitin sulphate were found to be effective in moderate osteoarthritis. [22]

While comparing the average time taken for walking 50 feet distance, it was found that treatment groups A and B yielded almost similar results after 8 weeks (approx. 30-31% reduction from baseline), while group C had the least reduction (2.56%)

Even though none of a larger number of randomized clinical trials gave positive results, suggesting an ambiguity of the benefit of the two nutraceuticals glucosamine sulphate and chrondoitin sulfate in OA. [23] Most of the trials compared the effects of glucosamine sulphate and chrondoitin sulphate with NSAIDS which is inappropriate.

The outcome of the treatment with glucosamine and chrondoitin sulphate will always be inferior compared to NSAIDS for short term pain relief. Glucosamine and chrondoitin sulphate are more effective for long term relief of pain with lasting effects even after completion of treatment as per a number of studies. [18, 22]

NSAIDS are highly relied upon by physicians for short term pain relief in patients with knee OA. [24-25] This fact has been shown in a number of studies and is further reinforced in our study by the fact that 57 out of 60 patients had taken NSAIDS before for their pain relief. Unfortunately, the pain relief achieved from NSAIDS is only for a short term and therefore, patients need to continue taking the NSAIDS to ensure prolonged pain relief. Many NSAIDS are available over the counter which also accounts for its widespread use after prescription. [26-27] After being prescribed due to disability of movement cause by knee osteoarthritis, majority of the patients do not return to the doctor for a follow up but continue taking the NSAIDS as over the counter medicines, since they offer a prompt relief from pain.

This is particularly problematic since long term use of NSAIDS is associated with many adverse events including the destruction of articular cartilage thereby accelerating OA, the disease for which they are so commonly prescribed. [28]

This study has a number of limitations including its sample size was small and short duration of treatment. Therefore, a larger study comprising a bigger sample size for a longer duration need to be undertaken in order to further confirm the findings of this study.

CONFLICT OF INTEREST: None

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