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Efficacy and Tolerability of Glucosamine - Chondroitin Sulphate - Methyl Sulfonyl Methane (MSM) in Osteoarthritis of Knee in Indian Patients

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ABSTRACT

Background & Objective. Osteoarthritis is progressive degenerative disease resulting in significant affection of joints. Nonsteroidal anti-inflammatory drugs (NSAIDS) are widely used in this condition but are associated with significant side effects; hence the aim of this study was to evaluate the efficacy and tolerability of nutritional supplements such as Glucosamine, Chondroitin sulphate and methyl sulfonyl methane in osteoarthritis as an alternative approach for this condition. **Patients & Methods.** Thirty-seven patients from medicine and orthopedic out patient departments were assessed for severity of osteoarthritis based on visual analog scale, Lequesne's index, goniometry, and radiography and enrolled into the open label study. All patients received cartivit (Glucosamine, Chondroitin sulphate and MSM) two tablets thrice a day for twelve weeks and were reassessed for changes in above parameters every four weeks. The tolerability was also assessed during the monthly visits. **Results.** Out of 32 patients who completed study, there was significant improvement in pain and Lequesne's index at four, eight and twelve weeks ($p < 0.05$). There was gradual improvement in joint mobility over twelve weeks. There was no improvement in radiological changes in twelve weeks study period. Patients tolerated the study medication well and there was no abnormality observed in the various biochemical markers during the study. **Conclusions.** Glucosamine, chondroitin sulphate and methyl sulfonyl methane combination was useful in decreasing pain, improving functional ability and improving joint mobility and was well tolerated in patients with osteoarthritis.

Keywords: *Osteoarthritis, Glucosamine, Lequesne's index, Goniometry, Visual analog scale*

Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of physical disability, increased health care usage, and impaired quality of life. Osteoarthritis of knee joint is the most prevalent cause of disability especially in the elderly population [1]. Osteoarthritis is due to degenerative process that results from metabolic, mechanical, genetic and other influences. Although non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat OA and have proved effective, their widespread use is associated with significant toxic effects on the gastrointestinal tract, especially in the elderly population [2, 3]. Even though cyclooxygenase-2 inhibitors have a decreased gastrointestinal tract complications than conventional NSAIDs, there remains an urgent need for finding pharmacological therapies for OA that are both effective and relatively safe.

Glucosamine is a hexosamine sugar and a basic building block for the biosynthesis of the glycosaminoglycans and proteoglycans that are important constituents of the articular cartilage. Chondroitin is a glycosaminoglycan that is found in the proteoglycans of articular cartilage. Both are animal products having antiarthritic and anti-inflammatory activities [4, 5]. Being safe, these compounds have great utility in the treatment of OA even if they show moderate efficacy [6, 7].

Glucosamine and chondroitin have been used for OA in Europe and USA for more than a decade and recently have acquired substantial popularity. A meta analysis by McAlindon and coworkers demonstrated improvement of pain in patients with OA [8]. Ganu and colleagues demonstrated that glucosamine reduce Metalloproteinases (MMPs) nitric oxide, and prostaglandin E2 [9]. All are thought to play an important role in the

Table 1. Lequesne's index [15] (Functional Index for OA of Knee).

Pain or Discomfort	Index†
During Nocturnal Bed rest:	
· None or insignificant	0
· Only on movement or in certain positions	1
· With no movement	2
Morning Stiffness Or Regressive Pain After Rising:	
· 1 minute or less	0
· More than 1 but less than 15 minutes	1
· 15 minutes or more	2
After Standing For 30 Minutes	0 to 1
While Ambulating:	
· None	0
· Only after ambulating some distance	1
· After initial ambulation and increasing with continued ambulation	2
· After initial ambulation, not increasing with continued ambulation	1
While Getting Up From Sitting Without The Help Of Arms	0 to 1
Maximum Distance Walked (may walk with pain):	
· Unlimited	0
· More than 1 km, but limited	1
· About a km in about 15 min	2
· From 500 to 900 m about 15 min	3
· From 300 to 500 m	4
· From 100 to 300 m	5
· Less than 100m	6
· With one walking stick or crutch	1
· With two walking sticks or crutches	2
Activities Of Daily Living:	
· Able to climb up a standard flight of stairs	0 to 2
· Able to climb down a standard flight of stairs	0 to 2
· Able to squat or bend on the knees	0 to 2
· Able to walk on uneven ground	0 to 2

† Without Difficulty: 0; With Small Difficulty: 0.5; Moderate: 1; Important Difficulty: 1.5; Unable: 2.

joint damage associated with OA. A systemic review by Richy F et al showed efficacy of glucosamine and chondroitin in knee osteoarthritis in all outcomes, including joint space narrowing [10]. Chondroitin was found to be effective based on Lequesne's index, visual analog scale, pain and joint mobility according to Cibere [11].

Methyl Sulphonyl Methane (MSM) is a naturally occurring nutrient found in normal diet [12]. There is a need for supplementation of MSM since it is lost in the process of cooking. MSM can restore the flexibility and permeability of the cell walls. This helps to equalize the pressure and reduce or eliminate the cause of pain. The arthritis study conducted in mice by Oregon Health Sciences University did not reveal degeneration of the articular cartilage by MSM. It can rebuild ligaments and tendons with healthy, flexible new cells [12]. However, there have been questions raised about the efficacy of combination as mentioned earlier. Hence this study was undertaken to evaluate efficacy and tolerability of glucosamine, chondroitin and methyl sulfonyl methane combination in the treatment of OA in Indian elderly patient population.

PATIENTS AND METHODS

Study Design

The present open label study was conducted in medicine unit of Dr. TMA Pai Hospital Udupi and Orthopedic department attached to Kasturba Medical College Hospital Manipal, India.

Selection of Patients

Inclusion Criteria

- Patients of either sex aged more than 50 years.
- Patients fulfilling the American College of Rheumatology (ACR) Criteria of clinical, laboratory and radiographic findings [13].
- Patients diagnosed with primary osteoarthritis with Lequesne's score in the range of 10-18.
- Patients who can understand the study procedure so that they can come for the regular follow up.

Exclusion Criteria

- Patients with arthritis due to other causes like Rheumatoid arthritis and Gout.
- Patients with hepatic and renal dysfunction or those who had any other serious medical illness.
- Patients who had received the study medication in the past month and had participated in any of the clinical trials in past month.
- Patients who cannot tolerate the two-week wash out.

At the screening visit, patient's medical history was taken and clinical assessment was done in detail. Patient who were diagnosed in the past according to the American College of Rheumatology were also considered for the trial if they meet the inclusion criteria. The knee joint was examined on the grounds of local examination and specific parameters for assessing the severity of arthritis subjectively as well as objectively. All patients were asked to grade the severity of pain based on visual analogue scale (VAS) ranging from no pain at the bot-

Table 2. Radiological scoring for Knee osteoarthritis [18].

Radiological scoring	X-ray finding
0	Normal
1	Doubtful narrowing of joint space/possible osteophytes lipping
2	Definite osteophytes/absent or questionable narrowing of joint space
3	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, possible joint deformity of bone ends
4	Large osteophytes, marked narrowing of joint space, severe sclerosis, definitive joint deformity of bone ends and subchondral cysts may be present.

tom of the scale to unbearable pain at the top of the 100 mm colored scale. The other variable in the scale were mild, moderate and severe pain separated by 20 mm each [14]. Lequesne's index (Table 1) which is a functional scoring system was measured accordingly [15]. The objective assessment of the knee joint was done by noting the presence or absence of swelling, deformities, tenderness, warmth, crepitus, joint effusion and muscle atrophy [16]. The joint mobility was assessed by doing goniometry of the knee joint [17]. Global assessment of disease was also recorded as very poor, poor, good and very good (1-4) by physician based on the VAS, Lequesne's index, joint mobility and by patient himself/herself based on his/her assessment of the disease initially and during the monthly visits [14].

Laboratory investigations such as Complete Blood Picture (CBP), Random Blood Sugar (RBS) and Electrocardiogram (ECG) were done before and at the end of the study. Renal and liver function tests, knee joint X-rays (Anteroposterior and Lateral) were done on each follow up and Magnetic Resonance Imaging (MRI) was done in ten patients. They were graded by a scoring system of 1-4 by the radiologist. (Table 2) [18, 19]. Serum uric acid, and Rheumatoid factor measurement were made to exclude patients of other joint disorders in the beginning of study.

Thirty-seven patients were enrolled in the study based on the inclusion and exclusion criteria. The study was undertaken after the institutional ethical committee clearance was obtained. A written informed consent was obtained from all patients in accordance with good clinical practice guidelines.

All patients were given two tablets of Cartivit (A combination of 500 mg glucosamine, 400 mg chondroitin sulphate sodium and 250 mg methyl sulfonyl methane) thrice a day by the study coordinator who also took the tablet count to quantify compliance. All patients were instructed not to take any analgesics except paracetamol (only if needed) during the study period and asked to report the number of paracetamol tablet they had taken during each visit interval.

Patients were followed up at the end of four, eight and twelve weeks. The knee joint was examined on each clinical visit based on the above-mentioned parameters.

Table 3. General Characteristics of the study group.

Number of Patients recruited	37
Number of Patients completed the study	32
Age	56.08 ± 11.64 (yr., Mean ± SD)
Duration of Osteoarthritis	3.42 ± 3.72 (yr., Mean ± SD)
Sex (M:F)	8:24

Statistical analysis. The Mean±S.D of VAS, Lequesne's index, Goniometry assessment radiological index, physician's and patient's assessment were taken at different clinical visits and percentage improvement at 4th, 8th and 12th week were compared with the baseline values by paired *t*-test using SPSS. The *p*-value less than 0.05 were considered as significant. The patient compliance was considered good if the patient had taken more than 80% of the tablets dispensed to him/her during a particular clinical visit.

RESULTS

Out of the thirty-seven patients included into the study, five patients were dropped because of non-medical reasons (change of residence and personal reasons). The patient characteristics are given in the Table 3.

Pain score (VAS) based on patients perception of pain, improved significantly ($p < 0.05$) from baseline score of 66.44 ± 22.28 to 39.84 ± 20.34 at the end of twelve weeks (Table 4). The improvement was 19.09%, 25.22% and 39.85% respectively at the end of four, eight and twelve week.

Improvement in functional status based on Lesquesne's index was also highly significant ($p < 0.05$). This was13.96 ± 4.74 at baseline which decreased to 8.06 ± 5.25 at end of twelve weeks (Table 4). The percentage improvement at 4th, 8th and 12th weeks was 17.19, 25.22 and 39.85 respectively. Joint mobility assessed by goniometry showed changes by 8th week and significant improvement by 12th weeks (Table 4). The percentage improvement was 9.19, 16.60 and 27.59 respectively at 4th, 8th and 12th week.

There was no significant change in the radiological parameters such as X-rays and MRI of knee joint (Table 5). There was significant improvement in the physician's assessment of the disease as well as patient's assessment ($p < 0.05$) (Table 5). The number of tablets of paracetamol used as and when required basis (sos) by patients came down from an average of four per week at the beginning of the study to two per week by four weeks. At the end of twelve weeks, only six patients needed paracetamol once a week on a sos basis. This shows that a decreased usage of analgesics, thereby less adverse effects and improved patient compliance.

The drug did not alter the biochemical markers (Table 6). Patient compliance was very good as adher-

Table 4. Depicting the functional score, Joint mobility and pain score and the percentage of improvement at different visits.

Parameters	Baselines	4thweek (Mean±S.D)	8th week (Mean±S.D)	12th week (Mean±S.D)
Lequesne's index	13.96 ± 4.74	11.56±4.94 [a] (17.19%)	9.18±5.47 [a] (34.24%)	8.06±5.25 [a] (42.26%)
Goniometry	91.03±48.56	99.40± 41.54 (9.19%)	106.56±51.11 (16.60%)	116.15±51.09 [b] (27.59%)
Visual Analog scale	66.44± 22.28	53.75±22.14 [c] (19.09%)	49.68±23.13 [c] (25.22%)	39.84 ± 20.34 [c] (39.85%)

[a] $p < 0.05$, Baseline Lesquesne's index values V/S 4th, 8th and 12th week.
[b] $p < 0.05$, Baseline goniometry values V/S 12th week.
[c] $p < 0.05$,Baseline visual analogue scale values V/S 4th, 8th 12th week.
The values in the bracket show the percentage of improvement in the respective parameters at different weeks of visit.

Table 5. Showing the study parameters at the end of different clinical visits.

Parameter	Baseline	4th week	8th week	12th week
Radiological Scoring	2.00± 0 . 1 4	1.93± 0 . 0 9	1.87± 0 . 0 7	1.93± 0 . 0 9
Physician's assessment [14]	2.12± 0 . 1 6	2.22± 0 . 1 9	2.37± 0 . 2 4	2.81± 0 . 3 [a]
Patient's assessment [14]	1.75± 0 . 0 9	2.12± 0 . 1 6	2.41± 0 . 2 8	2.72± 0 . 4 [b]

[a] $p < 0.05$ Baseline value of Physician's assessment Versus 12th week.
[b] $p < 0.05$ Baseline value of patient's assessment Versus 12th week.

ence to the treatment was more than 80%. Only two of them had missed the treatment schedule by two days on one occasion. Two patients complained of diarrhea initially during the treatment, whose causality could not be established.

Discussion

Osteoarthritis (OA) is characterized by progressive loss of articular cartilage and bony overgrowth seen mostly in elderly individuals. The initial bland progression of OA may become clinically relevant as an inflammation brought about by the increasing deposition of cartilaginous debris [20]. For the patient, the most important aspect of the condition is pain and associated impairment of movement [21]. Because cartilage is not innervated, the pain arises from secondary effects, such as synovial inflammation and fluid accumulation leading to joint capsule distension and stretching of the periosteal nerve endings.

NSAIDs have been widely used in the relief of pain in-patients with osteoarthritis. Jones reported a post marketing surveillance study of sustained release form of diclofenac on 7438 osteoarthritis patients, in which the drug had to be withdrawn in 18% of the patients due to side effects [22]. In another study involving 336 patients with osteoarthritis over six months, Hosie et al reported that about 10% patients withdrew from the study due to adverse effects following diclofenac therapy [23].

Due to this fact, there has been a search for oral medication that will work to reduce patient's symptoms, that will regenerate cartilage and act as anti-inflammatory without causing many side effects. Glucosamine and chondroitin combination has been used in many studies in osteoarthritis all over the world as nutritional supplements aiding cartilage repair. They are found to be uniformly safe in all studies compared to NSAIDs and almost as effective [3, 5, 8]. Muller-Fassbender et al [24] have demonstrated the efficacy of glucosamine-chondroitin versus ibuprofen in a double blind ,parallel group study, where they found this combination was as effective as ibuprofen with much less side effects. However there have been not many Indian studies showing efficacy of chondroitin and glucosamine in OA. A study by G H Tilve et al using oral enzyme preparation (phlegozyme) showed good improvement in joint pain, joint mobility when compared to diclofenac in active osteoarthritis [25]. There is no documented study on the efficacy and tolerability of combination of the Glucosamine-Chondroitin-MSM in osteoarthritis in Indian scenario.

Table 6. Showing haematological and biochemical parameters during study period.

Parameters	Mean ± SD (0 wk)	Mean ± SD (12 wk)
Hemoglobin (Gm%)	12.00 ± 1.39	12.72 ± 1.40 †
Total WBC count	8766 ± 1698	9352 ± 2020
ESR	31.46 ± 18.40	27.42 ± 21.09
Blood Glucose (mg/dl)	109.69 ± 14.86	108.42 ± 15.08
Blood Urea (mg/dl)	22.46 ± 7.19	19.78 ± 5.39
S. Creatinine (mg/dl)	0.90 ± 0.13	0.85 ± 0.15
AST (IU)	30.51 ± 10.61	31.44 ± 14.46
ALT (IU)	25.62 ± 15.01	28.85 ± 13.87

† $p < 0.05$, Baseline V/S 12th week.

In our study MSM in combination with glucosamine and chondroitin sulfate has worked very well in all patients. The pain score was assessed using the standard visual analogue scale in which the patient identified the degree of pain with the color code. This parameter started showing improvement even at four weeks and improved steadily over eight and twelve weeks to a significant level ($p < 0.05$). Most patients had a good compliance with the drug. Lequesne's index, a scoring system based on functional mobility of the joint assessing patient's daily activities and hence is a direct evidence of the extent of the disability. This score also showed significant improvement ($p < 0.05$) demonstrating that patient's symptoms improved very well with this drug. Such a result was documented in earlier studies by Muller et al [24]. Noack et al [26] used this index to quantify improvement with glucosamine-chondroitin combination in a study on osteoarthritis of the knee and found this index to be a sensitive indicator of improvement.

Objective evidence of improvement in joint mobility was noted with goniometry. This is a simple technique, which assesses the angle of flexion and extension in the knee joint as an index of joint mobility. This parameter started to improve early, but significant change was seen by twelfth week ($p < 0.05$). This seems logical; as anatomical improvements in the joint condition will take a longer time to improve after functional improvement sets in.

The radiological changes in osteoarthritis as evidenced by X-ray and MRI are probably late and may not correlate with the patient's symptomatology. There was no significant difference in scoring of the X-rays or MRI in the patients. Many patients may have severe functional disability in spite of near normal radiological investigations. Thus these investigations may not be useful to judge efficacy of short-term treatment with drugs in osteoarthritis. Further the anatomical changes in the joints may take a long time to regress [27]. Pavelka et al [28] used glucosamine in a randomized placebo controlled study for a three year period, and compared anatomical parameters such as joint space width, and noted that this drug retarded progression of osteoarthritis. As our study was of short duration, such a result would probably not be demonstrated.

Conclusion

- Glucosamine, chondroitin sulfate and methyl sulfonyl methane combination is definitely useful in decreasing pain, improving functional ability and joint mobility in patients with osteoarthritis.
- This combination does not seem to alter the hematological and biochemical parameters.

- The tolerability of the drug is good as evidenced by the patient compliance and the fact that there were no significant untoward adverse effects noted during the study.
- Since this study was done as an unblinded trial and without control group, a placebo effect showing improvement in symptoms cannot be ruled out. A double blind, randomized control trial would have better significance in assessing usefulness of this drug.

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