Original Article

Prospective Study in Tertiary Care Hospital for Osteoarthritis Patients in Rural Area of Haryana

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ABSTRACT

Objectives: The objective of this study was to compare clinical outcomes of Nonsteroidal anti-inflammatory drugs as monotherapy and combinational therapy with glucosamine in osteoarthritis patients. **Methods:** A randomized prospective observational study was conducted between December 2018 and June 2019 at M. M. Institute of Medical Science and Research. Total 360 patients were recruited and were divided into four different groups. Patients received selective cyclooxegenase-2 inhibitor with and without glucosamine sulphate and non-selective cyclooxegenase-2 inhibitor with and without glucosamine sulphate. The primary outcomes were measured by liquesce index score and visual analogue scale at 2nd and 4th week. **Results:** Bodyweight and the age were found statistical significant among different groups. Both the combination treatment groups were statistical significant potent than individual treatment group after the four weeks of treatment. Statistical significant results were found in both liquesce index

(LI) and Visual Analogues Score (VAS). **Conclusion:** Marked improvement was observed in both the scores (Lequesne index and Visual Analogues) after four weeks of treatment and it would be better therapy in both the combination with Glucosamine than individual for osteoarthritis patient.

Key words: Cyclooxegenase-2 inhibitor, Follow up treatment, Glucosamine sulphate, Inflammation, Rheumatology, Visual Analogues Score.

INTRODUCTION

Osteoarthritis is the uncontrollable rheumatic disease which is generally characterized by local inflammation, pain and stiffness in joints, tenderness and limitation of movements. Osteoarthritis generally involves morphological as well as biochemical changes at synovial membrane leads to hypertrophy and white tissue loss near bones.[1-3] Most common site in the joints are hands, knees, spine, feet and also commonly in hip and shoulder joints. Aging is also one of the factors which give 80% the patients induce osteoarthritis. Life style is also one of the important aspect which can be induces risk for osteoarthritis like weight gain, absence of activity, work related damage, hereditary predisposition, injury and gender.[4] Stiffness is common problem in the morning when these patients do routine activities. This is due to damage of cartilage which leads to friction of joints and crunching or clicking sound observe during its movement.[5-7] Globally, population of America and Europe reflects highest prevalence of Osteoarthritis.[8] Gender wise, it is almost 9.6% male and 18% of females of above age 60 years are reported with symptomatic osteoarthrtitis.[9-10] The European League against Rheumatism reports 30% population over 65 years of age with radio-graphic proof of knee osteoarthritis.[11] Osteoarthritis is the second most common rheumatologic problem in India with prevalence of 22 % to 39%. In India, female is more prone risk to osteoarthritis than male. Nearly 45% of women over the age of 65 years have symptoms while radiological evidence is found in 70% of those over 65 years. According to study reported on Asian countries revealed that 13.7 % prevalence in rural areas than 6.9% in rural areas. In one of the Indian study reported that 56.6 % have osteoarthritis in rural region than 32.6 % in urban region.[12,13]

Treatment under lifestyle modification and drug regimen are also not fully supported to treat this disease.[14,15] Various drugs include Nonsteroidal anti-inflammatory drugs (NSAIDS), opioids analgesics, intra-articular agents and topical agents. Paracetamol is the first initial drug treatment to prescribe with other lifestyle modification. Nonsteroidal anti-inflammatory drugs and salicylates are prescribed for second choice when the patient does not relief from pain.[16,17] Side effects are also concern regarding anti osteoarthritis drug therapy. So, for better gastro intestinal tolerability, Cyclooxegenase-2 inhibitors (Cox-2) can be considered for the patient. Non-selective non steroidal anti inflammatory like etoricoxib (60 mg/day), valdecoxib (10 mg/day) and celecoxib (60 mg/day) are more efficacious as pain reliever. In combination of paracetamol and opioids (codeine) give better drug therapy than paracetamol alone.[18-20]

However, ongoing studies are evaluates for maintaining cardiovascular patients with cyclooxegenase-2.[21] Glucosamine sulfate (GS) is a subordinate of the naturally occurring amino monosaccharide glucosamine present in synovial liquid and joint cartilage. Glucosamine was proposed as a slow acting drug in treatment of osteoarthritis[21,22] It act as stimulator for proteoglycan synthesis by cultivated human chondrocytes on articular cartilage.[23-25] Two randomized controlled trial with twofold blinded study conducted in Belgium[26] and Czech Republic[27] which proposed that, this medication (1.5 g day by day) has a considerable indication and structure changing impact in patients with mild to moderate osteoarthritis of knee. The symptomatic efficacy of glucosamine in osteoarthritis has been analysed through high-quality quantitative systematic reviews.[28-30] However, no study has directly compared the clinical outcomes and efficacy between monotherapy (i.e

NSAIDS or glucosamine) and a combination of the two drugs. Thus, we conducted the study to find out more effectiveness with individual therapy (Glucosamine sulphate or NSAIDS) or in combination therapy of these two.

MATERIALS AND METHODS

Study design

The study was approved from Institutional Ethics Committee (IEC1313, dated: 19.12.2018) and then planned for randomized, prospective observational study. The study was conducted between the period of December 2018 to June 2019 in Department of Orthopedics, Maharishi Markandeshwar Institute of Medical Science and Research.

Study population

Sample size was calculated on total population (approximately 30,000) around 30 km, out of which 1600 people have osteoarthritis. A sample of 70 patients will be sufficient to represent the osteoarthritis population residing in the rural area under investigation. A questionnaire was prepared for recruitment which included the details of patients: Sociodemographic profile (age, sex, chief complaints, past history, any other disease), duration, x-ray report (standing Anterior-Posterior / Lateral/weight bearing/axial view) and symptoms were recorded. All patients were assessed for disease and pain severity by using validated and reliable Lequesne index[28] and visual analogue scale and divided into four groups according to therapy.

Osteoarthritis patients were selected between the age of 30 years to 70 years shows the symptoms of knee pain and confirmed on the basis of radiographic evidence and clinical criteria were included in the study. Patients between the age of less than 30 years and more than 70 years had infectious disease, psychotic disorders; gastrointestinal disorder, knee surgery and other musculoskeletal disease were excluded out.

Drug therapy for the patients

A total 90 patients were recruited in each group by prospective method and received specific drug only in a given order. 1. Selective Cox-2 inhibitors (Celecoxib, trade name: Celebrex) 2. Selective Cox-2 inhibitors (Celecoxib) + Glucosamine sulphate 750 mg, b.d. (cartigen) 3. Nonselective Cox-2 inhibitors (Diclofenac sodium, trade name: (Dilona forte) 4. Nonselective Cox-2 inhibitors (Diclofenac sodium, trade name: (Dilona forte) + Glucosamine sulphate 750 mg, b.d. (cartigen). Data was noted at 15th day interval after the treatment.

Outcome measures

The primary outcomes were assured in the terms of lequesne index[31] score and visual analogue scale. Scoring of both scales is measured at baseline and after the treatment at 2nd and 4th week. Lequesne is an algo-functional index used to asses scoring of patient. It is divided into 3 sections i.e. pain or discomfort having 5 questions (duration of stiffness, pain scoring during bed rest, walking, getting up), second section with 2 questions assessing score according to distance walked i.e. maximum distance walked >1 km to <100 m, (0-6), third section of daily living activities (climb up, climb down, bend/squat, walking at unable ground) interpretation of LI is based on scoring in each section. Min. score- 0 and max score-24.

Statistical Analysis

Data analysis was done with the help of an SPSS version 14.5. Continuous variables are expressed as means ± SD. Intergroup comparisons are made using students t test using Turkey's range. *P* value ≤ 0.05 was considered statistically significant.

RESULTS

Patient characteristics

In our study, the prevalence rate of osteoarthritis in tertiary hospital was found to be 26.9 %. Our prospective study suggested that, total 1564 patients visited in outpatient department of orthopaedics in a period of 6 months, out of which 422 patients confirmed osteoarthritis patients. A total 90 patients in each group were enrolled in the study and randomly distributed to treatment groups. Baseline characteristics of patients and their distribution according to treatment groups are presented in Table 1. Female population was found to be more predominant in every group at the range of 70% to 90%. *i.e.* n=285/360 when compared with male population which was only 75 cases out of 360. Most of the patients visited at the age of 51-60 years. All four groups with respect to age were higher (*p<0.0001*) statistical significant. Body weights were also higher statistical significant difference between all treated groups. Among cases, some of the patients developed prone to other risk diseases includes 24 patients had type 2 diabetes mellitus, 22 patients were hypertensive, one hypothyroidism and 46 were co associated with type 2 diabetes mellitus with hypertension during treatment. Maximum number of patients from all four groups had bilateral knee involvement (*i.e.* 84.4%), followed by patients with right knee involved [*i.e.*11.6%] and patients with left knee involved [*n*=3.8%]. Patients showed duration of symptoms was not less than 3 months.

Lequesne Index Score

Baseline data at 0 week revealed the lequesne index as shown in Table 1. Highest (12.68 ± 2.23) was found in second group (Glucosamine sulphate with celecoxib) and the lowest (9.13 ± 2.47) was with diclofenac sodium treated group as compared within all groups. After the assigned treatments (Table 2), data was calculated at different time intervals and showed the highest percentage at 4th week with combination of glucosamine sulphate and diclofenac sodium treated group (47.70 %) as compared with other treated groups respectively (18.60 %; 14.27 % and 31.65 %) and similar data was also found to be at 2nd week. Interesting results was obtained, diclofenac sodium treated group showed highest percentage (31.65 %), when we compared with celecoxib treated group and in combination of glucosamine sulphate with celecoxib treated group. Data was found to be statistical significant in all the groups.

Visual Analogues Score

At baseline data, (Table 3) Value revealed 5.22 ± 1.44 with the treated group (Combination of glucosamine with diclofenac sodium) than other combination (Glucosamine sulphate with celecoxib treated group), the value was 7.22 ± 1.99. After follow up treatments, the VAS score was in order of glucosamine sulphate with diclofenac sodium > diclofenac sodium > celecoxib > glucosamine with celecoxib (37.16% > 31.05% > 24.87% > 18.14%). The value was statistical higher significant difference between the treated groups.

DISCUSSION

Osteoarthritis is the most common among form of arthritis diseases. This is due to immovable joints at the onset of above 35 years but sometimes, it occurs at lower age of the patient also.[32,33] Two guidelines[34,35] are available on the management of knee OA include European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) indicated specific treatment suggested initially with physiotherapy, paracetamol and lifestyle advice and then adding further treatment in a step wise manner. The use of complementary medicine and therapies are growing in popularity in patients with knee

osteoarthritis. Glucosamine sulphate and chondroitin sulphate are added drug therapy for the management of osteoarthritis. Drug prescription pattern study in Chinese population was conducted and suggested that combinational drug therapy showed adverse effect and the patterns of drug therapy were noticed that 16% were on glucosamine, 12% was on chondroitin and 14% was on non-steroidal anti inflammatory drug.[36] Our findings indicated that, after one month treatment, Glucosamine sulphate with diclofenac sodium treated group and diclofenac sodium treated group showed much better results in terms of efficacy than other group which was celecoxib individual and in combination with glucosamine. Study demonstrated that both therapies show clinical improvement. Patients who received NSAID monotherapy shows more symptomatic relief during first two weeks whereas, glucosamine exerts its peak effect after 2 weeks of drug therapy.

According to ILAR classification, action of glucosamine was come under the category of symptomatic slow acting drugs in osteoarthritis[35] NSAIDS may act as Inhibition of cyclooxygenase enzyme and prostaglandins synthesis.[37] Efficacy and safety of NSAID's in osteoarthritis treatment has been reviewed in various studies.[38-40] Many studies demonstrate that

particular non selective COX inhibitors are as efficacious as selective COX-2 inhibitors (etoricoxib 60mg/day, valdecoxib 10mg/day) in pain relive.[41-43] Chronic use of NSAID's can lead to increased risk of GI[43,44] and renal complications.[44] Selective COX-2 inhibitors like celecoxib are considered for use due to better GI tolerability. Whereas, one of the study demonstrated that canal treatment long term use of celecoxib showed increase the risk of Gastro intestinal bleeding up to 9% in root canal treatment[45] and cardiovascular safety of COX-2 inhibitors is still challenging.[46] Glucosamine sulphate, a derivative of the natural amino monosaccharide normally present in cartilage and synovial fluid of joints. Two randomized, controlled twofold blinded trials in Belgium[26] and Czech Republic[27] proposed that this medication (1.5 g day by day) has a considerable indication and structure changing impact in patients with mild to moderate osteoarthritis of knee. In a comparative study between glucosamine sulphate (1,500 mg/day) and placebo, GS shows significant improvement in function parameters and pain.[47] In a study, done in 200 hospitalized knee OA patients, GS was compared to traditional NSAID's. This study demonstrates same success rate between ibuprofen (1,200 mg) and GS (1,500 mg orally). After 4 weeks of therapy, success rate were 52

Table 1: Baseline Characteristics of patients between treatment groups.

Variables	Celecoxib	Glucosamine sulphate + Celecoxib	Diclofenac sodium	Glucosamine + Diclofenac sodium	*P value*
No. of patients	90	90	90	90	
Men/Women	26/64	12/78	14/76	23/67	
	28.8%/71.2%	13.3%/86.6%	15.6%/84.4%	25.6%/74.4%	
Age (years)	53.65±9.47	58.77±9.04	60.14±9.38	51.44±8.76	*P<0.0001*
Age **categories**					d_f=359
31-40	0 (M: 0, F: 0)	3 (M=0, F=3)	3 (M=1, F=2)	3 (M=0, F=3)	f=18.25
41-50	7 (M=1, F=6)	9 (M=1, F=8)	7 (M=1, F=6)	15 (M=11, F=4)	
51-60	61 (M=13, F=48)	58 (M=9, F=49)	54 (M=6, F=48)	55 (M=6, F=49)	
61-70	22 (M=12, F=10)	20 (M=2, F=18)	26 (M=1, F=25)	17 (M=3, F=14)	
Body weight	70.56±6.8	73±5.34	72.31±7.77	75.40±6.10	*P<0.0001* d_f=359 f=8.39
Underlying disease,					
Type-2 DM	5	9	3	7	
Hypertension	4	7	6	5	
Hypothyroidism	0	1	0	0	
T2DM with HTN.	22	10	7	7	
Localization					
Left	0	4	6	4	
Right	12	10	9	11	
Bilateral	78	76	75	75	
Duration of symptoms (months)	3.11±1.04	5.01±1.89	4.1±1.03	3.23±1.11	*P<0.0001* d_f=359 f=40.41
VAS	8±2.25	7.2±1.99	6.15±1.90	5.22±1.44	*P<0.0001* d_f=359 f=36.06
Lequesne index	10.21±2.01	12.68±2.23	9.13±2.97	9.79±2.47	*P<0.0001* d_f=359 f=36.14

Table 2: Lequesne index at weekly intervals in different treated groups.

Week	Celecoxib	Glucosamine sulphate + Celecoxib	Diclofenac sodium	Glucosamine + Diclofenac sodium
0	10.21±2.01	12.68±2.23	9.13 ±2.97	9.79±2.47
2	9.16±1.22 (10.28%)	11.10±2.09 (12.46%)	7.43±2.24 (18.61%)	7.26±3.11 (25.84%)
4	8.31±2.99 (18.60%)	10.87±2.88 (14.27%)	6.24±2.31 (31.65%)	5.12±2.99 (47.70%)
P value	$P<0.0001$ $f= 20.18$, $d_f= 269$	$P<0.001$ $f= 14.86$ $d_f= 269$	$P<0.001$ $f= 29.70$ $d_f= 269$	$P<0.001$ $f= 59.70$ $d_f= 269$

Table 3: Visual analogue scales at weekly intervals in different treated groups.

Week	Celecoxib	Glucosamine sulphate + Celecoxib	Diclofenac sodium	Glucosamine + Diclofenac sodium
0	8±2.25	7.22±1.99	6.15±1.90	5.22±1.44
2	7.05±1.54 (11.87%)	6.01±1.43 (16.75%)	5.35±1.73 (13.0%)	4.18±1.65 (19.92%)
4	6.01 ±1.50 (24.87%)	5.91±1.95 (18.14%)	4.24±1.75 (31.05%)	3.28±1.64 (37.16%)
P value	$P<0.0001$ $f= 27.62$ $d_f = 269$	$P<0.001$ $f= 14.63$ $d_f= 269$	$P<0.001$ $f= 28.42$ $d_f= 269$	$P<0.001$ $f= 33.99$ $d_f= 269$

% for ibuprofen and 48% for GS. Ibuprofen onset of effect occurs sooner than that of GS, with the success rate of 48 % for ibuprofen and 28 % for GS.[48] In our study, pattern of drug response was similar to this study. Our study demonstrates lesser significant difference in improvement between selective COX-2 inhibitors monotherapy and glucosamine plus selective COX-2 inhibitors after 2 weeks of therapy. After 4 weeks, patients who were on glucosamine plus selective COX-2 inhibitors show more improvement and decrease in lequesne scores as compared to selective COX-2 inhibitor monotherapy. This pattern of drug response was also favoured by another study done in 68 Chinese patients with knee OA and no significant difference was observed between GS and ibuprofen in terms of symptoms relieve. This study also demonstrates better GI tolerability of GS as compared to ibuprofen.[49,50] Another study conducted and demonstrates that those patients who received GS therapy showed a significant decrease in pain measured by visual analogue scale in different time intervals and suggested to prescribe in large population.[51] Similar results were found in Thai population which shows that monotherapy of glucosamine improves pain by WOMAC score as compared with combination therapy diacerin and glucosamine.[52] Over all, drug therapy prescribed by the physician that depend upon the patient condition whether they need combinational or monotherapy. The main limitation is to control the adverse effects of NSAIDS drugs.

CONCLUSION

From the study, it can be concluded that both monotherapy of NSAID's and co-administration of glucosamine with NSAID's can significantly reduce lequesne score and VAS score in patients with Knee osteoarthritis. Moreover, when glucosamine sulphate was combined with NSAID's, impact on lequesne index was found to be more profound, especially when glucosamine was co-administered with non-selective COX inhibitors whereas similar results were also observed in VAS scores.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ACR: American College of Rheumatology; **Cox-2I:** Cyclooxegenase-2 inhibitors; **EULAR:** European League Against Rheumatism; **ILAR:** International League against Rheumatism; **LI:** Lequesne index; **NSAIDS:** Non Steroidal Anti inflammatory Drugs; **SD:** standard deviation; **VAS:** Visual Analogues Score; **WOMAC:** Western Ontario and McMaster Universities Osteoarthritis Index.

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