

# COMPARISON BETWEEN GLUCOSAMINE SULPHATE AND NIMESULIDE THERAPIES IN OSTEOARTHRITIS

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## ABSTRACT

- Objective* To examine the effects of glucosamine sulphate and nimesulide on parameters such as pain at rest, pain on movement and limitation of movements in patients suffering from osteoarthritis (OA) of at least one knee joint.
- Study design* Descriptive study.
- Place & Duration of study* The study was conducted at Jinnah Postgraduate Medical Centre, Karachi. Study period was 90 days.
- Methodology* Ninety patients of either sex, between 35 – 80 years suffering from OA of at least one knee joint were selected. Patients were divided into 3 groups, Group A, B, and C, of 30 patients each receiving capsule glucosamine sulphate (GS), tablet nimesulide and placebo treatment respectively.
- After the relevant radiological examination and laboratory tests the patients were asked to come for follow-up visits fortnightly. Statistical analysis of data was performed on day 0, 30, 60 and 90. Parameters of pain at rest, pain on movement and limitation of movements were evaluated by 4-point scale and goniometer.
- Results* Both glucosamine sulphate and nimesulide significantly reduced all the parameters at the end of the 90 days study period in comparison with placebo therapy.
- Conclusions* The use of glucosamine sulphate or nimesulide may be beneficial for the patients of osteoarthritis suffering from pain at rest and movement and also improve range of movements.
- Key words* Osteoarthritis, Glucosamine sulphate, Nimesulide.

## INTRODUCTION:

OA is generally seen as a disease of articular cartilage although it is clear that changes in subchondral bone are also important. Cartilage matrix turnover is a process of synthesis and degradation, which is balanced in healthy individuals. OA is a failure to maintain this homeostatic balance, because of reduced formation or increased catabolism.<sup>1,2</sup>

Osteoarthritis is the most common form of arthritis. It is a major cause of morbidity and disability as well as a burden on health-care resources, especially for the elderly. Osteoarthritic diseases result from both the mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes and extracellular matrix, and subchondral bone. Changes of both cells and matrix lead to a softening, fibrillation, ulceration, loss of articular cartilage and sclerosis of subchondral bone, osteophytes, and subchondral cysts.

When clinically evident, osteoarthritis is characterized

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by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation without systemic effects. Age is the strongest determinant of osteoarthritis with prevalence rates for all joints rising with increasing age, while obesity has been strongly linked to osteoarthritis of the knee and to a lesser extent, the hip. Women are at a higher risk of developing osteoarthritis than men, particularly after the menopause.

Glucosamine sulphate has recently emerged as an alternative treatment option for patients with OA. The beneficial effects of this chondroprotective agent have been reported to reverse or at least stop the progression of the disease without inducing serious adverse effects.<sup>3</sup> Glucosamine also reduces the generation of superoxide radicals by macrophages and inhibits lysosomal enzymes.<sup>1,4,5</sup>

NSAIDs are widely prescribed in patients suffering from arthritis and it is the inhibition of cyclooxygenase (COX), and hence the inhibition of prostaglandin (PG) production, that accounts at least in part for the anti-inflammatory properties of these drugs.<sup>6</sup> Two isoforms of COX have been identified. Increased expression of the isoenzyme COX-2 is responsible for elevated production of prostaglandins in inflamed joint tissues and is involved in the mediation of pain.<sup>7</sup>

Nimesulide is an NSAID with good anti-inflammatory, analgesic and antipyretic activities. Main pharmacological action includes a preferential inhibition of prostaglandin synthesis via COX-2, reduction in cytokine action/release, histamine release, the release of enzymes that degrade cartilage, and the release of superoxide anions and other toxic substances from neutrophils.<sup>8</sup>

#### **METHODOLOGY:**

This study was conducted in the department of Pharmacology, BMSI, JPMC, Karachi. Ninety patients of either sex, between 35 – 80 years suffering from OA of at least one knee joint were selected. Secondary cases were excluded with the help of various tests like ESR > 40, rheumatoid factor, serum uric acid, blood glucose etc.

The study period was for 90 days. Patients were divided into 3 groups of 30 patients each. Group A- received capsule glucosamine sulphate

500mg thrice daily.

Group B- received tablet nimesulide 100mg twice daily.

Group C- received the placebo treatment once daily.

On entering the study, x – rays of the affected knee joint of each patient in antero-posterior and lateral weight bearing position were obtained. Laboratory tests like hemoglobin, ESR, blood urea and bleeding time were performed on day 0, 45 and finally on day 90. Patients were asked to come for follow-up visits fortnightly. Observations were made at follow up on 30, 60 and 90.

Parameters of pain at rest, pain on movement were evaluated by 4-point scale:

0 = None, no pain felt by the patient.

1 = Mild, Slight pain which can be tolerated

2 = Moderate, Pain causing discomfort to the patient

3 = Severe, Unbearable pain

The 4-point scale for pain was converted for measurement on Visual Analog Scale (VAS).<sup>9</sup>

0 = Up to 0.5 cms

1 = 0.6 – 3.5 cms

2 = 3.6 – 6.6 cms

3 = 6.7 – 10 cms

Range of movement was measured by goniometer.<sup>10</sup> Complete range of movement at knee joint in flexion and extension is 0 to 140°. Any limitation of movement in flexion or extension was expressed in degrees. Full extension was taken as 0 degree while full flexion (where no space is left between the hamstrings and calf muscles i.e. back of thigh and back of leg) ranges around 140 degrees. Active and passive movements were made to note any limitation of movement. Straight leg raising test was performed to exclude limitation of movement by causes other than OA. Analysis was performed and p value was taken out between day 0 and day 30, day 0 and day 60 and lastly between day 0 and day 90.

#### **RESULTS:**

In Group A highly significant p values i.e. < 0.001 were found on day 0 to day 30, day 0 to day 60 and day 0 to day 90 in parameters of pain at rest and pain on movement (table I). In the parameter of limitation of movement significant p values i.e. <0.005 was seen from day 0 to day 30 which improved to highly significant values i.e. <0.001 from day 0 to day 60 and day 0 to day 90.

Table- I: Therapeutic Efficacy In All Parameters At Day 0, 30, 60 and Day 90 With Capsule Glucosamine Sulfate (Group A)								
Parameters	Day 0	Day 30	Day 60	Day 90	Percentage Change Day 0-Day 90	p value		
						Day0-30	Day0-60	Day0-90
Pain at rest (cm.)	1.93± 0.18	1.46± 0.14	0.84± 0.09	0.34± 0.10	-82.83	<0.001 H.S.	<0.001 H.S.	<0.001 H.S.
Pain on movement (cm.)	7.25 ± 0.23	6.30± 0.27	3.29 ± 0.32	2.23± 0.36	-69.24	<0.001 H.S.	<0.001 H.S.	<0.001 H.S.
Limitation of Movement (Degrees)	10.0 ± 1.26	7.68± 1.01	5.18± 1.30	4.29± 0.76	-57.1	<0.005 S.	<0.001 H.S.	<0.001 H.S.

All the values are expressed in mean ± S.E.M. units.

H.S. – Highly significant, S. – Significant, N.S. – Non significant.

Negative (-) sign indicates reduction of symptoms compared between day 0 – day 90.

In Group B all the 30 patients improved remarkably well. Percentage change and p value were analysed between day 0 and day 90. Pain at rest improved the best although pain on movement showed p values <0.001 on day 30, 60 and 90. Limitation of movements showed significant improvement i.e. <0.002 after 30 days treatment which improved to highly significant values i.e. <0.001 after 60 days and again after 90 days treatment (table II).

In Group C none of the parameters showed significant improvement after 90 days treatment with p values >0.05. Pain at rest showed significant improvement after 60 days treatment, pain on movement after 30 and 60 days but all changed to non significant at the end of treatment. Limitation

of movements did not improve throughout the study period (table III).

When each parameter was compared individually between all the groups, in the parameter of pain at rest, measured on a 0 – 3 scale and then converted by the Visual analog scale into centimetres, it was seen that Group A showed better reduction in this symptom which was highly significant with p values <0.001. Group B showed slightly less improvement than Group A but nevertheless the change was highly significant with p value <0.001, while Group C showed non-significant change with p value >0.05 and slight increase in pain at the end of therapy (table IV).

Table- II: Therapeutic Efficacy In All Parameters At Day 0, 30, 60 and Day 90 With Tablet Nimesulide (Group B)								
Parameters	Day 0	Day 30	Day 60	Day 90	Percentage Change Day 0-Day 90	p value		
						Day0-30	Day0-60	Day0-90
Pain at rest (cm.)	1.93 ±0.17	1.67 ±0.17	1.02 ±0.13	0.40 ±0.13	-79.27	<0.001 HS	<0.001 HS	<0.001 HS
Pain on movement (cm.)	6.76 ±0.27	5.59 ±0.29	3.59 ±0.29	2.67 ±0.34	-60.50	<0.001 HS	<0.001 HS	<0.001 HS
Limitation of Movement (Degrees)	12.24 ±1.69	9.66 ±1.14	7.24 ±1.15	5.72 ±1.06	-53.26	<0.002 S	<0.001 HS	<0.001 HS

All the values are expressed in mean ± S.E.M. units.

HS – Highly significant, cm - centimeter

Negative (-) sign indicates reduction of symptoms compared between day 0 – day 90.

In pain on movement again the best percentage improvement was seen with Group A while Group B showed slightly less improvement than Group A, although both the groups showed highly significant improvement with p values <0.001. Group C showed slight improvement in this parameter but this was

**DISCUSSION:**

We have reported the results of administration of glucosamine sulphate and nimesulide over a period of 90 days in patients suffering from OA of at least one knee joint as knee is the commonest of the large joints to be affected by OA.<sup>11</sup> The results were

**Table- III: Therapeutic Efficacy In All Parameters At Day 0, 30, 60 and Day 90 With Placeb (Group C)**

Parameters	Day 0	Day 30	Day 60	Day 90	Percentage Change Day 0-Day 90	p value		
						Day0-30	Day0-60	Day0-90
Pain at rest (cm.)	1.89 ±0.20	2.02 ±0.25	1.89 ±0.20	1.93 ±0.21	2.11	>0.05 NS	<0.05 S	>0.05 NS
Pain on movement (cm.)	5.83 ±0.32	5.39 ±0.27	5.39 ±0.28	5.81 ±0.31	-0.34	<0.05 S	<0.05 S	>0.05 NS
Limitation of Movement (Degrees)	12.96 ±1.54	12.04 ±1.34	12.59 ±1.40	12.96 ±1.39	0	>0.05 NS	>0.05 NS	>0.05 NS

All the values are expressed in mean ± S.E.M. units.

S – Significant, NS – Non significant, cm. – centimeter.

Negative (-) sign indicates reduction of symptoms compared between day 0 – day 90.

**Table- IV: Comparison of Percentage Change and P Value Between Group A, Group B and Group C in all the Parameters Between Day 0 and Day 90**

GROUPS	DAY – 0	DAY - 90	%Change Day0 –Day 90	p value Day0 –Day 90
PAIN AT REST (cm)				
Group A n=28	1.93±0.18	0.34±0.10	-82.83	<0.001 H.S
Group B n=28	1.93±0.17	0.40±0.13	-79.27	<0.001 H.S
Group C n=27	1.89±0.20	1.93±0.21	2.11	>0.05 N.S
PAIN ON MOVEMENT (cm)				
Group A n=28	7.25±0.23	2.23±0.36	-82.83	<0.001 H.S
Group B n=28	6.76±0.27	2.67±0.34	-60.50	<0.001 H.S
Group C n=27	5.83±0.32	5.81±0.31	-0.34	>0.05 N.S
LIMITATION OF MOVEMENT (Degrees)				
Group A n=28	10.0±1.26	4.29±0.76	-57.10	<0.001 H.S
Group B n=28	12.24±1.69	5.72±1.06	-53.26	<0.001 H.S
Group C n=27	12.96±1.54	12.96±1.54	0	>0.05 N.S

HS: Highly significant.

NS. Non-significant.

non-significant with p value >0.05. The best improvement in the decrease of movement was seen in Group A while group B also showed highly significant improvement with p value <0.001. Group C showed no change with p value >0.05.

compared with each other and with placebo, when administered for the same period of time. In this study, GS and nimesulide both were associated with a statistically highly significant improvement in the signs and symptoms of pain in patients with OA of

of knee. Placebo produced non-significant improvement in all the parameters.

The therapeutic effects of GS were quickly realized over the 90 days treatment period and were greatest at the last evaluation. Indeed, GS rapidly reduced pain at rest (83%), pain on movement, but with a relatively lesser effect on limitation of movement. The improvement in efficacy variables demonstrated with GS in this study are in close agreement with other clinical investigations in OA. Drovanti et al<sup>12</sup> and Pujalte et al<sup>13</sup> conducted placebo controlled studies on 80 and 20 patients respectively. 72% patients in the 1<sup>st</sup> study while 80% patients in the 2<sup>nd</sup> study improved highly significantly (p 0.001) after 4 weeks of GS therapy in the signs and symptoms of pain.

Vaz<sup>9</sup> gave 1.5 g GS t.i.d to 40 patients suffering from OA of knee. There was a significant (p 0.01) improvement in signs and symptoms of pain at the end of 8 week study period. The studies conducted by Noack et al<sup>14</sup> and Reichelt et al<sup>15</sup> on 252 and 155 patients respectively with knee OA. Highly significant (p0.001) results showed at the end of 60 days study period. Non-significant (p 0.05) improvement with placebo was seen.

The significant and highly significant improvement in symptoms as early as 30 days after commencement of therapy may be due to cartilage unrelated effects, as GS possesses a unique range of anti-inflammatory activities such as inhibition of inducible nitric oxide synthesis, inhibition of super-oxide synthesis, inhibition of super-oxide generation and interleukin (IL)-6 production. The sustained highly significant results uptill the end of therapy could be due to the effects of GS on cartilage metabolism, including stimulation of anabolic activities, such as synthesis of proteoglycans, and depression of catabolic effects of metalloproteinases.<sup>3,16,17</sup>

Our study is not in accordance with Rindone et al<sup>18</sup> where 49 patients in each group either received 500mg glucosamine t.i.d or placebo for 60 days. No statistical difference between the 2 groups in any of the parameters at day 30 and day 60 was found which was non-significant, may be because here only glucosamine was used and not the salt glucosamine. Glucosamine alone does not appear to have active intestinal transport as it is excreted in feces as a lectin-glucosamine complex.<sup>5</sup> The therapeutic effects of nimesulide were quickly realized after 30 days of treatment which were sustained until the end of the study period. Indeed, nimesulide rapidly reduced pain at rest (79%), but

a relatively lesser effect on pain on movement (60%) was observed. Placebo produced non-significant improvement in all the parameters.

The improvement in efficacy variables demonstrated with nimesulide in this study are in close agreement with other clinical investigations in OA. For example, Bardi et al.<sup>19</sup> compared nimesulide with placebo in 40 OA patients in a treatment cycle of 90 days. Reduction in all the parameters was highly significant (p 0.001) at the end of the study period. Our study is also in accordance with the studies of Bennett and Villa<sup>8</sup> and Kriegel et al<sup>20</sup> where nimesulide was associated with a statistically significant (p 0.05) improvement in the signs and symptoms of pain and limitation of movement. The benefits achieved were essentially similar to those in our study. Non-significant improvement with placebo was seen.

The significant and highly significant improvement in symptoms as early as 30 days after commencement of therapy of nimesulide may be due to inhibition of the release of oxidants from activated neutrophils and has a scavenging effect on hypochlorous acid without affecting neutrophils function. Nimesulide also decreases histamine release from tissue mast cells and inhibits the production of platelet-activating factor by human basophils. It inhibits the release of stromelysin and blocks metalloproteinase activity.<sup>19</sup> In addition to their anti-inflammatory and analgesic benefits, it may have a protective effect in OA through the inhibition of apoptosis in chondrocytes.<sup>21</sup>

Our study is not similar to the study of Dreiser and Riebenfeld<sup>22</sup> where nimesulide gave non-significant results in all the parameters as their study was for only 2 weeks. In the current investigation, glucosamine sulphate and nimesulide were well tolerated. Additional comparative studies are required to confirm nimesulide and glucosamine sulphate long term efficacy and safety profile.

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