ROLE OF GLUCOSAMINE SULPHATE ON PAIN AND TENDERNESS IN OSTEOARTHRITIS

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ABSTRACT
The purpose of this study was to establish the role of Glucosamine Sulphate in reducing the common symptoms of Osteoarthritis like pain at rest, pain on movement and tenderness. 2 groups of 30 patients each were made, one of the groups received Glucosamine Sulphate therapy while the other was given placebo treatment. In the group that received Glucosamine Sulphate, there was a highly significant improvement in all the parameters at the end of therapy while there was non-significant improvement with placebo treatment. The use of Glucosamine Sulphate seems to be beneficial for the patients of Osteoarthritis.

INTRODUCTION
Osteoarthritis (OA) is the most common joint disorder resulting from biologic and biomechanical hyaline cartilage failure (Cole and Harner, 1999; Shikhtman et al., 2001). It is designated as Primary (idiopathic) when no cause is obvious most common form of the disease, and is localized when single sites like hands, and feet, hips and knees are affected while generalized when 3 or more of these sites are involved. It is designated as Secondary when it follows a demonstrable abnormality to an underlying cause (Brandt, 2001; Solomon, 2001).

Major risk factors for OA are age, genetic factors, joint trauma, repetitive stress obesity, congenital/developmental defects, climate, prior inflammatory joint diseases and metabolic/endocrine disorders.

OA continues to be a major public health problem related to pain and most patients seek medical attention because of it. Elderly women suffer the highest occurrence of OA while OA of the knee is a major cause of pain in older people (March et al., 1994).

Glucosamine Sulphate (GS) represents a new generation of drugs, which possesses potentially chondroprotective or disease modifying properties and was originally suggested to promote the repair of damaged cartilage. Since it has been shown that it can be used as a single pharmacologic agent to treat OA, it is being consumed by many OA patients (Shikhman et al., 2001).

The main objective of this study was to evaluate patient responses to OS in terms of overall efficacy, pain relief, immediate side effects and general well being.

MATERIALS AND METHOD
Sulphate (C3cvolox) 500 mg, were obtained from Hilton Pharma (Pvt.) Ltd, Pakistan.

Placebo capsule packed by K. Ahmed and Sons, Karachi, Pakistan.

Study Protocol
This study was conducted in the department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center, Karachi. A total of 60 patients of either sex, between 35-80 years suffering from OA of at least one knee joint
were selected. The study period was for 90 days. Patients were divided into 2 groups, Group A and Group B, of 30 patients each. Group A received Capsule Glucosamine Sulphate 500mg thrice daily while Group B received the Placebo treatment once a day for 90 days. Each patient gave written consent to join the study and was given a 72-hour wash out period for any medication that the patient might have been taking previously. Only patients suffering from Primary OA of at least one knee joint were selected while Secondary cases were excluded with the help of various tests like ESR> 40, Rheumatoid Factor, Serum Uric Acid, Blood Glucose etc.

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 Hb%, 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 every fortnightly while statistical analysis of data was performed between day 0, 30, 60 and day 90.

Parameters of Pain at rest, Pain on Movement and Tenderness were evaluated by 4-point scale that is:

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) (Huskisson, 1974).

0 = Up to 0.5 cms
1 = 0.6-3.5 cms
2 = 3.6-6.6 cms
3 = 6.7-10 cms

Of the various methods for measuring pain VAS seems to be the most sensitive (Hewer et al., 1949; Huskisson, 1974, Vaz, 1982; Wigler et al., 1999; Bellamy et al., 1999; Pincus et al., 2001).

For tenderness, local examination of knee was performed and pain felt at specific sites such as patella in full extension of foot and knee and on medial condyl of femur. 4-point scale for tenderness indicates:

0 = Very slight
1 = Definite
2 = Wincing
3 = Withdrawal

This was converted on VAS as in measurement of Pain.

RESULTS

The results obtained in the present study are summarized in Table 1-3. Within the group statistical analysis was done with “Paired t test” while inter group analysis was done with “Student t-test”.

The Mean ± SEM values are shown on day 0, 30, 60 and day 90 with percentage change between day 0 and day 90 while p values were taken out between day 0 and day 30, day 0 and day 60 and day 0 and day 90.

GS produced highly significant (p<0.001) improvement in all the parameters after only 30 days of treatment. There was an 83%, 69% and 84% reduction in Pain at rest, Pain on movement and Tenderness respectively vide Table 1.

2 patients were lost to follow up. 5 patients (17.85%) complained of side effects, 2 of dyspepsia, 1 of diarrhea and 2 of slight abdominal pain.

Treatment with placebo did not produce any significant (p>0.05) improvement in any of the parameters at the end of the 90 days period. There was only a 0.34% improvement in Pain on movement at the end of therapy which was non-significant while Pain at rest
and tenderness depict a worsening of these symptoms vide Table 2.

3 patients were lost to follow up. 5 patients (18.51%) complained of side effects, 2 of itching over the whole body, 1 of headache and 1 of nausea and 1 of body ache in general.

When Group A and Group B were compared with each other between day 0 and day 90, in all the three parameters highly

Table 1
Therapeutic efficacy in all parameters at day 0, 30, 60 and day 90 with capsule Glucosamine sulfate 500 mg t.i.d. (Group A)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 0</th>
<th>Day 30</th>
<th>Day 60</th>
<th>Day 90</th>
<th>% Change Day 0 – Day 90</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0-3</td>
<td>Day 0-60</td>
<td>Day 0-90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at rest (cm.)</td>
<td>1.93 ± 0.18</td>
<td>1.46 ± 0.14</td>
<td>0.84 ± 0.09</td>
<td>0.34 ± 0.10</td>
<td>-82.83 H.S.</td>
<td>&lt;0.001 H.S.</td>
</tr>
<tr>
<td>Pain on movement (cm.)</td>
<td>7.25 ± 0.23</td>
<td>6.30 ± 0.27</td>
<td>3.29 ± 0.32</td>
<td>2.23 ± 0.36</td>
<td>-69.24 H.S.</td>
<td>&lt;0.001 H.S.</td>
</tr>
<tr>
<td>Tenderness (cm.)</td>
<td>4.39 ± 0.39</td>
<td>2.91 ± 0.29</td>
<td>1.57 ± 0.22</td>
<td>0.71 ± 0.21</td>
<td>-83.82 H.S.</td>
<td>&lt;0.001 H.S.</td>
</tr>
</tbody>
</table>

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.

Table 2
Therapeutic efficacy in all parameters at day 0, 30, 60 and day 90 with placebo (Group B)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 0</th>
<th>Day 30</th>
<th>Day 60</th>
<th>Day 90</th>
<th>% Change Day 0 – Day 90</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0-3</td>
<td>Day 0-60</td>
<td>Day 0-90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at rest (cm.)</td>
<td>1.89 ± 0.20</td>
<td>2.02 ± 0.25</td>
<td>1.89 ± 0.20</td>
<td>1.93 ± 0.21</td>
<td>2.11 H.S.</td>
<td>&lt;0.05 H.S.</td>
</tr>
<tr>
<td>Pain on movement (cm.)</td>
<td>5.83 ± 0.32</td>
<td>5.39 ± 0.27</td>
<td>5.39 ± 0.28</td>
<td>5.81 ± 0.31</td>
<td>-69.24 S.</td>
<td>&lt;0.05 S.</td>
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<tr>
<td>Tenderness (cm.)</td>
<td>4.56 ± 0.37</td>
<td>3.98 ± 0.37</td>
<td>4.20 ± 0.33</td>
<td>4.57 ± 0.35</td>
<td>-83.82 S.</td>
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All the values are expressed in mean ± S.E.M. units. S. – Significant, N.S. – Non significant. Negative (-) sign indicates reduction of symptoms compared between day 0 – day 90.
significant (p<0.001) improvement with Group A is seen vide Table 3.

**DISCUSSION**

In this study, GS was associated with a statistically highly significant improvement in the signs and symptoms of pain in patients with OA of knee. Placebo produced non-significant improvement in all the parameters.

In this investigation, the therapeutic effects of (35 were quickly realized over the 90 days treatment period and were greatest at the last evaluation. Indeed, OS rapidly reduced pain at rest (83%) and tenderness (84%) but with a relatively lesser effect on pain on movement (69%).

The improvement in efficacy variables demonstrated with GS in this study are in close agreement with other clinical investigations in OA. For example, Drovanti *et al.* and Pujalte *et al.* (both in 1980) conducted placebo controlled studies on 80 and 20 patients respectively. 72% patients in the 1st study while 80% patients in the 2nd, improved highly significantly (p<0.001) after 4 weeks of GS therapy in the signs and symptoms of pain.

Vaz in 1982 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 and coworkers (1994) and Reichelt *et al.* (1998) on 252 and 155 patients respectively with knee OA, highly significant (p<0.001) results were obtained 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.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day – 0</th>
<th>Day – 90</th>
<th>% Change Day 0 – Day 90</th>
<th>P-Value Day 0 – Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at Rest (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A n=28</td>
<td>1.93 ± 0.18</td>
<td>0.34 ± 0.10</td>
<td>-82.83</td>
<td>&lt;0.001 H.S.</td>
</tr>
<tr>
<td>Group B n=27</td>
<td>1.89 ± 0.20</td>
<td>1.93 ± 0.21</td>
<td>2.11</td>
<td>&gt;0.05 N.S.</td>
</tr>
<tr>
<td>Pain on Movement (cm)</td>
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Group A – Capsule Glucosamine Sulphate, Group B – Placebo, n – Number of patients
H.S. – Highly Significant, N.S. – Non-significant
synthesis, inhibition of super-oxide generation and interleukin (IL)-6 production. The sustained highly significant results up till 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 activities like effects of metalloproteases (Deal and Moskowitz 1999; Reginster et al., 2001 and Shikhman et al., 2001).

Our study is not in accordance with Rindone et al. (2000) where 49 patients in each group either received 500 mg GS 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 seen which was non-significant, may be because here only Glucosamine was used and not the salt Glucosamine Sulphate. Glucosamine alone does not appear to have active intestinal transport as it is excreted in feces as a lectin-glucossamine complex (Deal and Moskowitz, 1999).

In the current investigation, (IS was well tolerated. As GS has no effect on cyclooxygenase enzyme and hence on prostaglandins production, there is a lack of significant toxicity with its use (Brief et al., 2001).

No pathological changes in hematology and blood chemistry tests were found. A judgement of good/fair of 85% was recorded by us for GS group while 16% for Placebo group.

REFERENCES


Reginster J.Y., Rita D. and Rovati L.C. et al.


