Evaluation of the efficacy and safety of JT-2000* in Osteoarthritis: A randomized controlled clinical trial

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[* JT-2000 is marketed as Rumalaya forte]

ABSTRACT
The present study was aimed to evaluate the efficacy and safety of JT-2000, a polyherbal drug, in patients suffering from osteoarthritis (OA) of knee.

This was a randomized placebo-controlled clinical trial conducted among 100 patients of either sex, with clinical and radiological evidence of OA of the knee.

Among the 100 patients, a majority of the patients had OA of the knee with a female preponderance in the study population. Both groups had an equal number of patients with similar treatment symptom scoring. The analysis of blood chemistry parameters was within normal limits for all patients and no significant change was noted at the end of study. At the end of 6-month treatment period, JT-2000 treated group showed highly significant improvement over their pretreatment symptom score when compared to placebo. However, there was no significant improvement in the radiographic images. No patient was withdrawn from the therapy due to any complications nor were they lost to follow up.

This study indicates that in the management of mild-to-moderate OA, JT-2000 is a more effective and safer alternative for long-term use than NSAIDs.

INTRODUCTION
The very term osteoarthritis (OA) is a misnomer, because it implies an inflammatory process. The original use of the term by John Spender in 1886 was as a synonym for rheumatoid arthritis (RA) and not as the disorder is recognized today. The term, however, has been used in the English speaking nations for several generations, and neither the pathology-wise more accurate term “degenerative joint disease” nor the European term “osteoarthrosis” have displaced it. Osteoarthritis has also suffered from a lack of consensus regarding its definition. Different classification schemes for OA have emerged based on putative mechanical and biologic factors of the disorder. The current working definition of OA incorporates these into a working formulation stating “morphologic, biochemical, molecular, and biomechanical changes of both cells and matrix, which lead to softening, fibrillation, ulceration, and loss of articular cartilage, sclerosis, and, eburnation of subchondral bone, osteophytes and
In less comprehensive terms, OA is thus characterized by a deterioration of articular cartilage and formation of new bone at the joint surfaces.

The prevalence of OA is high in the aging population and involves hands and weight-bearing joints such as knees, hips, feet and spine. Osteoarthritis is characterized by joint pain and tenderness, limitation of movements, crepitus, occasional effusion and variable degrees of inflammation without systemic effects.

The etiology of OA is multifactorial and various morphological, biochemical changes result in a softened, ulcerated and malfunctioning articular cartilage. The commonly encountered findings of OA are sclerosis, eburnation of subchondral bone (where bone is converted into a dense smooth substance resembling ivory) and development of osteophytes and subchondral cysts. It has been postulated that age, gender, body weight, repetitive trauma and genetic factors are cardinal risk factors, which play an important role in the natural history of OA. The only symptoms in OA of the knee are pain, and difficulty in movements like getting up from the squatting position, climbing stairs, etc.  

The therapy for OA is aimed at symptom relief and effective therapy combines many of the tools available, including physical measures, medications and surgery. Numerous treatment regimens and NSAIDs have been tried for the management of OA of which articular corticosteroids are the preferred choice. However, available evidence indicates that the use of NSAIDs in OA is causally associated with various short- and long-term adverse effects. Similarly, it was observed that prolonged used of acetaminophen for symptomatic management of OA may result in hepatotoxicity and nephrotoxicity.

JT-2000 is a polyherbal formulation comprising of *Boswellia serrata*, *Commiphora wightii*, *Alpinia galanga*, *Glycyrrhiza glabra*, *Tribulus terrestris* and *Tinospora cordifolia*.

**METHODOLOGY**

**Aim of the study**
The present study was aimed to evaluate the efficacy and safety of JT-2000 in OA.

**Study design**
This was a randomized, placebo-controlled study approved by the Ethics Committee of Era’s Lucknow Medical College, Lucknow, India.

**Inclusion criteria**
One hundred ambulatory patients, between the ages of 50 to 65 years, of either sex, who attended the out-patient clinic of the Department of Orthopedics, Era’s Lucknow Medical College, Lucknow, from October 1, 2002 to December 1, 2003, with clinical and radiological evidence of OA of the of the knees, spine, hands, feet and hip were included in the present study. A written informed consent was obtained from all these patients. Prior to the study, all patients had clinical symptoms of OA of the knees or spine or hands or feet or hip over a
period of 2 years. These patients had radiologic evidence of OA with findings like osteophytes, marginal lipping, narrowing of joint space, sharpened articular margin or sclerosis.

**Exclusion criteria**
Patients with established hypertension, renal, hepatic or cardiac failure, on long-term steroid treatment with biochemical and clinical evidence of rheumatoid arthritis or gout, were excluded from the study.

**Study procedures**
All patients were randomized into two groups (JT-2000 and Placebo) of 50 patients each, with the help of a computer-generated random number allocation program. A detailed medical history of all patients was recorded and symptomatic evaluation was done using the scoring system (sign and symptom score). The two groups were similar with regard to the demographic data, baseline parameters and pain scores. The total symptom score was based on the number of joints involved, degree of pain, joint swelling, stiffness and activity level. The total sign score was based on joint effusion, tenderness, crepitus, range of movements, synovial hypertrophy, muscle wasting and joint deformity.

A complete systemic and joint examination was also performed. Blood chemistry investigations included complete hemogram, liver function tests, renal function tests, RA factor and immunoglobulins. Radiologic examination of the affected joints was carried out for osteophytes, subchondral sclerosis, trabecular hypertrophy, thickening, fracture, cratering, cartilage proliferation, calcified cartilage layer, fibrosis, hypertrophy of tendons, wasting of muscles, crystal deposition and viscosity of synovial fluid.

The study group received 2 capsules of JT-2000 and the placebo group, 2 capsules of placebo each twice daily for a period of 6 months.

**Follow-up and assessment**
The patients were followed up for 6 months and a symptomatic evaluation was recorded after completion of each month. A complete clinical, biochemical and radiographical evaluation was carried out at the end of the 3rd and 6th months.

**Primary and secondary outcome measures**
The predefined primary outcome measure for efficacy was a decrease in the total sign and symptom score at the end of 6 months and the clinical evaluation done by assessment of free mobility of the joint/s without causing joint discomfort or pain. Secondary outcome measures were short- and long-term safety assessed by incidence of adverse events, patient compliance to therapy and improvement in laboratory parameters.
Adverse events
All adverse events reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication were predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), “Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patients clinical state or other modes of therapy administered to the patient), and “Probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Statistical analysis
Statistical analysis was done according to intention-to-treat principles. The reduction in pain and swelling scores were evaluated to differentiate between the two treatment groups by the unpaired ‘t’ test. Comparison of the 2 groups for baseline comparability of different parameters by unpaired ‘t’ test was done. Changes in various parameters from baseline values after the 3rd and 6th months were evaluated by paired ‘t’ test. The minimum level of significance was fixed at a 95% confidence limit and a 2-sided p value of less than 0.05 was considered significant.

RESULTS
Out of 100 enrolled patients, a majority, 71, had OA of the knee and 14 had OA of the spine, 10 had OA of the hand and 5 had OA of the foot (Figure 1). There were 20 patients in the age group of 50-55 years, 30 between 56-60 years and 50 patients between 61-65 years (Table 1). There was a female preponderance in the study population (56 females, and 44 males) (Table 2).

<p>| Table 1: Agewise distribution of cases |</p>
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of cases</th>
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<tbody>
<tr>
<td>50-55</td>
<td>20</td>
</tr>
<tr>
<td>56-60</td>
<td>30</td>
</tr>
<tr>
<td>61-65</td>
<td>50</td>
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<p>| Table 2: Sexwise distribution of cases |</p>
<table>
<thead>
<tr>
<th>Sex</th>
<th>No. of cases</th>
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<tbody>
<tr>
<td>Male</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>56</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 1: No. of patients by involvement of joints in osteoarthritis

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No. of patients by involvement of joints in osteoarthritis

Knee
Spine
Hand
Foot

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Both the groups had an equal number of patients, and were similar with regard to pre-treatment symptom score (33 patients with score below 20, 17 patients with score above 20).

The analysis of blood chemistry parameters was within normal limits for all patients. No significant change was noted at the end of study.

The pre-treatment symptom score evaluation showed that 66 patients had a score of <20, and 34 patients had a score between 21 and 26 (Table 3). At the end of the 6 month treatment period, 46 (92%) patients in the JT 2000 group showed highly significant improvement in their pre-treatment symptom score, whereas only 5 (10%) of placebo group showed improvement (Figure 2).

All patients displayed osteoarthritis in the radiologic records before starting treatment.

None of the patients were withdrawn from the therapy due to any complication nor were any of them lost to follow-up.

### DISCUSSION

Osteoarthritis is a leading cause of chronic disability in the aging population. NSAIDs are preferred drugs for management of OA, but this prolonged use may lead to serious adverse effects.\(^{11-13}\) Herbal medications have been used in the past for the effective management of several chronic diseases and to find a safe remedy for OA.\(^{24}\)

In the present study, it was observed that there were more female than male patients, confirming that OA is more common in females than males. The unaltered blood chemistry, liver and renal function parameters after therapy suggest long-term safety of the drug in management of OA.

The excellent symptomatic relief observed with JT-2000, might be due to a synergistic action of its ingredients. Boswellic acid, which is the principle ingredient of *Boswellia serrata*, blocks the synthesis of pro-inflammatory chemomediators and also reduces glycosaminoglycan degradation, essential to prevent articular damage.\(^{18-27}\)

*Commiphora wightii* has a dose-dependent anti-inflammatory activity and helps to control inflammation and pain in OA patients.\(^{28-30}\)
*Alpinia galanga* has been shown to induce biphasic activity in membrane stabilization, which may be one of the possible contributory mechanisms for the anti-inflammatory activity observed in the present study.\(^{31}\)

*Glycyrrhiza glabra* exhibits anti-inflammatory activity and it has been suggested that the anti-inflammatory action may be due to terpinoids like glycyrrbin and glycyrrhetinic acids. These active ingredients of *Glycyrrhiza glabra* bind to glucocorticoid receptors. The anti-inflammatory activity of *Glycyrrhiza glabra* has been explained by its cortisol-like effect.\(^{21,32}\)

In this study, there was an excellent relief from pain at the end of the therapy and an overall improvement in quality of life was seen in the JT-2000 group. The absence of any adverse events, any alterations in the blood parameters indicate the long-term safety of JT-2000.

**CONCLUSION**

This study indicates that JT-2000 is effective and safe for long-term use in the management of OA.

**ACKNOWLEDGEMENT**

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**REFERENCES**