Clinical evaluation of the efficacy of JT-2000* in the management of osteoarthritis: A double-blind placebo-controlled trial

Upadhyay, L. and Tripathi, K.
Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India
and
Kolhapure, S.A., M.D.,
Senior Medical Advisor, R&D Center, The Himalaya Drug Company, Bangalore, Karnataka, India.

[* JT-2000 is marketed as Rumalaya forte]

ABSTRACT
Osteoarthritis (OA), degenerative arthritis is one of the most common forms of arthritis. NSAIDs are the preferred choice for the management of OA. However, the use of NSAIDs in OA is causally associated with various short and long term adverse effects. The present study was aimed to evaluate the efficacy and safety of JT-2000, a polyherbal drug, in patients suffering from OA of knee.

This was a randomized placebo-controlled clinical trial conducted on 100 patients of either sex, with clinical and radiological evidence of OA of the knee. Patients with established hypertension, renal, hepatic or cardiac failure, on long-term steroid treatment, or with evidence of rheumatoid arthritis and gout were excluded from the study. All the patients were randomized into drug and placebo groups of 50 patients each. A detailed medical history of all patients was recorded and symptomatic evaluation was done using the scoring system followed by clinical, radiological and blood chemistry examination. All patients were followed up for 6 months. The predefined primary outcome measure for efficacy was a decrease in the total sign-and-symptom score at the end of 6 months; secondary outcome measures were short- and long-term safety, assessed by incidence of adverse events, patient compliance to therapy and improvement in laboratory parameters. All adverse events predefined as unrelated, possible and probable, reported by the patients, were recorded. Statistical analysis was done according to intention-to-treat principles. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of less than 0.05 was considered significant.

Patients ranged from 20-80 years and there were thrice as many female as males. No significant changes were observed in any of the biochemical parameters in both groups. The reduction in the mean of number of joints involved in the JT-2000 group was highly significant (t=17.32, p<0.0001), while the results were not significant in the placebo group. (t=1.56, p=0.1208). There was a significant reduction in the average swelling score and pain scores and mean secondary muscle weakness score, in the JT-2000 group compared to the placebo group. At the end of 6 months treatment, patients in the JT-2000 group had a significant reduction in difficulty in climbing, compared to the placebo group. In the JT-2000 group, there was a significant...
decrease in subchondral sclerosis, osteophytes, cartilage proliferation, fibrosis, synovial fluid viscosity and crystal deposition at the end of 6 months of treatment. The unaltered blood chemistry, liver and renal function parameters suggested long-term safety of the drug. In this study, there was an excellent relief from pain at the end of the therapy and an overall improvement in quality of life of the JT-2000 group. This study indicates that JT-2000 is a more effective and safer alternative for long-term use in the management of mild to moderate OA than NSAIDs.

INTRODUCTION

Osteoarthritis (OA), or degenerative arthritis is one of the most common forms of arthritis, characterized by the breakdown of the joint's cartilage, leading to chronic disability at older ages. Clinical manifestations of OA range from mild to severe, and affect hands and weight-bearing joints such as knees, hips, feet and spine. Osteoarthritis is characterized by joint pain and tenderness, and limitation of movements, crepitus, occasional effusion and variable degrees of inflammation without systemic effects.

The etiology of OA is multifactorial. Various morphological as well as 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 pain is predominant, often the only symptom in OA of the knee, and causes difficulty in movements like getting up from the squatting position, climbing stairs, etc.

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, ranging from esophagitis, gastritis, mucosal erosions, hemorrhage, peptic ulceration, hematopoietic disturbances, headache, dysmenorrhea, acute and chronic renal failure. Similarly, it was observed that prolonged used of acetaminophen for symptomatic management of OA may result in hepatotoxicity and nephrotoxicity.

The need for safer drugs has lead medical researchers to clinically test several herbal compounds proved effective in experimental animal models. It was observed that *Boswellia serrata*, *Commiphora wightii*, *Alpinia galanga*, *Glycyrrhiza glabra*, *Tribulus terrestris* and *Tinospora cordifolia* exhibited analgesic, antipyretic and anti-inflammatory activities in various in vitro and in vivo studies.

JT-2000 is a polyherbal formulation with extracts 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 clinical efficacy and long-term safety of JT-2000 in patients suffering from OA of knee.

Study design
This study was a randomized placebo-controlled clinical trial approved by the Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

Inclusion criteria
One hundred ambulatory patients, of either sex who attended the out-patient clinic of the Institute of Medical Sciences, Banaras Hindu University, with clinical and radiological evidence of OA of the knee (tibio-femoral joint) were included in the present study. A written informed consent was obtained from all these patients.

All patients had clinical symptoms of OA over a period of 2 years prior to the study and were suffering from moderate to severe knee pain (with or without morning stiffness of <30 minutes duration). These patients had radiological evidence of OA with findings like osteophytes, marginal lipping, narrowing of joint space, sharpened articular margin or sclerosis (damaged, thickened, eburnated subchondral bone or bone cysts).

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 the patients were randomized into two groups of 50 patients each (JT-2000 and placebo) 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 (ESR, WBC, erythrocytes and platelet count), liver function tests (SGOT, SGPT, bilirubin, serum proteins, alkaline phosphatase, prothrombin time), renal function tests (uric acid, urea and creatinine), RA factor and immunoglobulins (IgA, IgM). Radiological 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, received 2 capsules of placebo twice daily for a period of 6 months.

**Follow-up and assessment**
The patients were followed up for 6 months and 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. 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. Any patient suffering from a nontraumatic osteoporotic fragile fracture from third month onwards was taken as treatment failure. 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 unpaired ‘t’ test. Comparison of the two 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 95% confidence limit and a 2-sided $p$ value of less than 0.05 was considered significant.
Observations
In the present study, of the 100 patients included, 99 patients completed the treatment. One patient in the drug group reported vaginal bleeding after 1 month of drug treatment and was excluded from the study.

The ages of the patients ranged from 20-80 years and females outnumbered males in the ratio of 3 : 1 (75 females and 24 males). In the JT-2000 group, 11 (22.45%) were male and 38 (77.55%) were females. In the placebo group, 13 (26%) were male and 37 (74%) were females. The maximum numbers of patients were from the 41-60 years age group (53.06%) (Figure 1).

Analysis of medical history revealed that amongst the JT-2000 group, 8 (16.32%) patients had a history of jaundice, 2 (4.08%), blood transfusion, 1 (2.04%), GI bleeding, 12 (24.49%), hospitalization, and 14 (28.58%) from some medical disorder (unrelated to OA) prior to the onset of OA. In the placebo group, 10 (20.40%) patients had a history of jaundice, 2 (4.08%) blood transfusion, 3 (6.12%), GI bleeding, 11 (22.44%), hospitalization and 16 (32.65%), from some medical disorder (unrelated to OA) prior to the onset of OA (Figure 2).

No significant changes were observed in any of the biochemical parameters in both groups, before and after the treatment. However, the values of WBC, RBC, platelet and ESR, remained elevated in both groups (Table 1).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo group (n=50)</th>
<th>JT-2000 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Hemoglobin (mg%)</td>
<td>11.92 ± 1.89</td>
<td>12.07 ± 1.61**</td>
</tr>
<tr>
<td>Total WBC cells/cumm</td>
<td>8673 ± 1268</td>
<td>8660 ± 1208**</td>
</tr>
<tr>
<td>Total RBC (x 10^5/mm³)</td>
<td>4.93 ± 0.66</td>
<td>4.89 ± 0.63**</td>
</tr>
<tr>
<td>Platelets (x 10^5/mm³)</td>
<td>3.26 ± 0.53</td>
<td>3.27 ± 0.56**</td>
</tr>
<tr>
<td>ESR (mm/first hr)</td>
<td>31.21 ± 9.21</td>
<td>30.23 ± 6.62**</td>
</tr>
<tr>
<td>Bilirubin (mg%)</td>
<td>0.83 ± 0.25</td>
<td>0.78 ± 0.23**</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>25.90 ± 6.46</td>
<td>25.81 ± 5.29**</td>
</tr>
<tr>
<td>Protein (gm%)</td>
<td>7.35 ± 0.91</td>
<td>7.25 ± 0.82**</td>
</tr>
<tr>
<td>BUN (mg%)</td>
<td>12.54 ± 2.66</td>
<td>12.38 ± 2.36**</td>
</tr>
</tbody>
</table>
The reduction in the number of joints involved in the JT-2000 group from an average of 4.08 to 1.02 was highly significant (t=17.32, p<0.0001) while the results were not significant in the placebo group (t=1.56, p=0.1208) (Figure 3). There was a higher more significant reduction in average swelling score in the JT-2000 group (27.4%, 47.8% and 73.6% suppression at the end of 1, 3 and 6 months, respectively) than in the placebo group (6.1%, 15.5% and 20.4% suppression at the end of 1 month, 3 months and 6 months, respectively). Further, the average pain score in the JT-2000 group reduced drastically (24.8%, 40.3% and 74.03% at the end of 1 month, 3 months and 6 months, respectively), as compared to the placebo group. The mean secondary muscle weakness score reduced from 16.8% to 74.7%, in the JT-2000 group, while the placebo group, recorded a decrease from 5% to 18% at the end of 6 months treatment. There was a significant favorable reduction in difficulty in climbing experienced by patients in the JT-2000 group compared to the placebo group (68.6% suppression in the JT-2000 group and 20% in the placebo group), at the end of 6 months treatment (Table 2).

### Table 2: Effect of JT-2000 treatment (placebo and drug) on symptomatic relief of osteoarthritis patients (values are mean ± SEM)

<table>
<thead>
<tr>
<th>Symptomatic parameters</th>
<th>Placebo group (n=50)</th>
<th>JT-2000 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After 6 months</td>
</tr>
<tr>
<td>No. of joints involved</td>
<td>4.44 ± 0.34</td>
<td>3.72 ± 0.31</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>3.62 ± 0.10</td>
<td>2.88 ± 0.11</td>
</tr>
<tr>
<td>Joint pain</td>
<td>3.67 ± 0.07</td>
<td>3.02 ± 0.07</td>
</tr>
<tr>
<td>Joint malfunction</td>
<td>2.54 ± 0.17</td>
<td>1.86 ± 0.13</td>
</tr>
<tr>
<td>Secondary muscle weakness</td>
<td>3.68 ± 0.08</td>
<td>3.00 ± 0.07</td>
</tr>
<tr>
<td>Difficulty in climbing steps</td>
<td>3.90 ± 0.05</td>
<td>3.10 ± 0.07</td>
</tr>
</tbody>
</table>

### Table 3: Effect of JT-2000 treatment (placebo and drug) on bone, cartilage and synovium of knee joints in patients of osteoarthritis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo group (n=50)</th>
<th>JT-2000 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After 6 months</td>
</tr>
<tr>
<td>Bone Subchondral sclerosis</td>
<td>1.88 ± 0.48</td>
<td>1.76 ± 0.48 NS</td>
</tr>
<tr>
<td>Trabecular hypertrophy/thickening</td>
<td>2.80 ± 0.45</td>
<td>2.74 ± 0.49 NS</td>
</tr>
<tr>
<td>Osteophyte</td>
<td>3.40 ± 0.69</td>
<td>3.32 ± 0.68</td>
</tr>
<tr>
<td>Fracture/s</td>
<td>2.22 ± 0.46</td>
<td>2.26 ± 0.56 NS</td>
</tr>
<tr>
<td>Cartilage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cratering</td>
<td>2.18 ± 0.44</td>
<td>2.14 ± 0.40 NS</td>
</tr>
<tr>
<td>Cartilage proliferation</td>
<td>2.84 ± 0.47</td>
<td>2.78 ± 0.51 NS</td>
</tr>
<tr>
<td>Calcified cartilage layer</td>
<td>2.82 ± 0.39</td>
<td>2.76 ± 0.43 NS</td>
</tr>
<tr>
<td>Cartilage and peri</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>2.32 ± 0.47</td>
<td>2.26 ± 0.53 NS</td>
</tr>
<tr>
<td>Hypertrophy of tendons</td>
<td>2.90 ± 0.36</td>
<td>2.86 ± 0.35 NS</td>
</tr>
</tbody>
</table>
In the JT-2000 group, there was a significant decrease in subchondral sclerosis \( (p<0.001) \), osteophytes \( (p<0.001) \), cartilage proliferation \( (p<0.001) \), fibrosis \( (p<0.001) \), synovial fluid viscosity \( (p<0.001) \) and synovial fluid crystal deposition \( (p<0.001) \) at the end of 6 months of treatment as compared to radiological findings before treatment. However, in the same group, there was no radiologically significant improvement in trabecular hypertrophy and thickening, bone fractures, cratering of cartilage, calcification of cartilage layer and hypertrophy of tendons. There was no significant change in radiological evaluation parameters in the placebo group at the end of 6 months treatment (Table 3).

**DISCUSSION**

Osteoarthritis is a leading cause of chronic disability in the aging population. The risk of disability attributable to OA of the knee is greater than risk of any other medical condition among the aged\(^1\). NSAIDs are preferred drugs for management of OA, but the prolonged use of these medications may lead to serious adverse effects\(^{13-15,17,26}\). Herbal medications have been used in the past for the effective management of several chronic diseases and to find a safe remedy for OA\(^{27}\).

In the present study, it was observed that the maximum number of patients were in the age group of 41-60 years, which confirms that osteoarthritis widely affects an increasingly aging population. Further, the male to female ratio of these patients was 1:3, which confirmed that OA is more compared in females than males.

The unaltered blood chemistry, liver and renal function parameters suggest long-term safety of the drug in management of OA.

The remarkable reduction in the number of joints involved, improvement in joint malformation and secondary muscular weakness after drug treatment, may be attributable to the synergistic effects of different ingredients of the drug. The reduction in difficulties faced by patients during routine activities (like climbing steps) is an important outcome of the pharmacodynamic actions of the drug. Similarly, radiological improvements are indicative of the potency of the drug.

A significant reduction of pain and inflammation in osteoarthritis patients after JT-2000 treatment, may be attributed to different herbal extracts possessing anti-inflammatory and analgesic properties.

Boswellic acid, which is the principle ingredient of *Boswellia serrata*, is known to block the synthesis of pro-inflammatory chemomediators like 5-Lipooxygenase (including 5-hydroxy-
eicosa tetraenoic acid) and leukotriene\textsuperscript{2,7}. Further, *Boswellia serrata* also reduces glycosaminoglycan degradation, which is essential to prevent articular damage\textsuperscript{28-30}. Menon and Kar have reported potent sedative and analgesic effects for *Boswellia serrata*\textsuperscript{20}. Thus, *Boswellia serrata* may reduce the inflammation of OA patients by reducing the degradation of glycosaminoglycans.

The alcoholic extract of *Commiphora wightii* regulates inflammation and obesity in rats\textsuperscript{31}. A dose-dependent anti-inflammatory activity by *Commiphora wightii* resin was also observed\textsuperscript{32}. Thus, it appears that *Commiphora wightii* actively participates in reducing the inflammation and associated pain of OA patients.

Inflammation is a complex phenomenon and anti-inflammatory drugs exert their effect through different modes of action. When leucocytes phagocytize an inflammatory agent, anti-inflammatory drugs release lysosomal hydrolase, which damage the surrounding tissues\textsuperscript{33}. Further anti-inflammatory drugs have been shown to stabilize lysosome, which may account for one of the major mechanisms of action\textsuperscript{34}. It was observed that *Alpinia galanga*, along with other ingredients, induced biphasic activity in membrane stabilization, which may be one of the possible contributory mechanisms for the anti-inflammatory activity observed in the present study\textsuperscript{34}.

*Glycyrrhiza glabra*, another ingredient possesses anti-inflammatory and anti-allergic activity. The anti-inflammatory action might be due to the presence of terpinoids, i.e., Glycyrrbin and Glycyrrhetic acids\textsuperscript{35}. These active ingredients of *Glycyrrhiza glabra* bind to glucocorticoid receptors, and the anti-inflammatory activity of *Glycyrrhiza glabra* has been explained by its cortisol-like effect\textsuperscript{23}.

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. Though the exact mode of action of JT-2000 remains elusive so far, it appears that its active ingredients works synergistically as an anti-inflammatory to reduce inflammation and pain among OA patients.

**CONCLUSION**

Osteoarthritis is the common cause of morbidity in the aging population worldwide. Joint pain, joint malfunction and restricted mobility lead to considerable compromise in quality of life. Current drug therapies (NSAIDs) have their own limitations due to the numerous adverse effects and are therefore of questionable advocacy for long-term use in management of OA. Furthermore, the chronic nature of the OA itself demands a long-term drug therapy for years.

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


