An open clinical study to evaluate the safety and efficacy of Turmeric capsules in patients with Osteoarthritis of knee

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ABSTRACT

Osteoarthritis is a chronic, progressive disability involving both weight-bearing and non weight-bearing joints. Currently available treatment options for osteoarthritis are associated with numerous short and long term adverse effects and these drugs are associated with an increased morbidity in older patients. This study was planned to evaluate the efficacy and safety of Turmeric Capsules in the treatment of Osteoarthritis of knee.

The study was an open, non-comparative clinical trial and enrolled 100 patients of either sex aged between 18 years to 60 years and suffering from Osteoarthritis of knee. Patients suffering from severe systemic comorbid illness, which necessitated the use of other medications, were excluded from the study. Informed written consent was obtained from all included patients.

These patients underwent physical examination after a detailed history regarding their disease. In all patients, a thorough systemic examination was done, which was followed by local examination of the knee and other joints affected by osteoarthritis. All enrolled patients underwent hematological and biochemical investigation at entry and at the end of the study. Patients received Turmeric capsule at a dose of 1 capsule per day for 1 month and were examined on a weekly basis till the end of the study. The predefined primary endpoint was a decrease in the disease progression as evident by the reduction in the sign and symptom scores at the end of 4 weeks. The predefined secondary endpoints were incidence of adverse events and overall compliance to the drug therapy. Statistical analysis was carried out using GraphPad Prism, Version 4.03.

This study observed a significant reduction in the mean score for number of involved joints and joint malfunction from the 1st week onwards till the end of the study. Similarly mean scores for difficulty in climbing steps and secondary muscle wasting decreased significantly at the end of 1, 2, 3 and 4 weeks, when compared to their respective baseline values. There were no clinically significant adverse reactions; either reported or observed during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported. Therefore, it may be concluded that Turmeric capsule is effective and safe in the management of osteoarthritis.

Key Words: *Turmeric, Osteoarthritis, Clinical trial*

INTRODUCTION

Osteoarthritis is defined by the American College of Rheumatology as a heterogenous group of conditions that leads to joint symptoms and signs, which are associated with defective integrity of articular cartilage in addition to related changes in the underlying bone at the joint margins. It is a common, age related, heterogenous group of disorders characterized pathologically by focal areas of loss of articular cartilage in synovial joints, associated with varying degrees of osteophyte formation, subchondral bone change and synovitis. Joint damage is caused by a mixture of systemic factors that predispose to the disease and local mechanical factors that dictate its distribution and severity. Acute and chronic insult, including normal wear and tear, age, obesity and joint injury may initiate an imbalance between matrix synthesis and matrix degradation in healthy cartilage that promotes chondroid loss and prevents cartilage self-repair.[1,2]

The osteoarthritis (OA) is considered a disease of the cartilage, but more recent evidence suggests that subchondral bone is also involved in the pathogenesis, of both disease initiation and progression. For example, increased local bone turnover, decreased bone mineral content and stiffness, and decreased trabecular numbers have been observed in osteoarthritic subchondral bone structure compared with normal bone.[3,4]

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Specially Contributed to "The Antiseptic"
Vol. 108 No. 8 & P : 383 - 386

The Duncan-Hartley guinea pig model is a widely used spontaneous model of osteoarthritis progression.[5] Several recent osteoarthritis studies have evaluated the model for the effects of antiresorptive agents like biphosphonates. In a study guinea pig osteoarthritis model, the pyridinyl bisphosphonate residronate was shown to show disease progression, as measured by the size and severity of cartilage lesions and the size of osteophyte, by up to 40%.[6]

The cardinal feature of osteoarthritis is the osteoarthritic lesion in the cartilage that disrupts the chondrocyte-matrix association; alters metabolic responses in the chondrocytes to contribute to the functional breakdown of the joint's cartilage, leading to constant friction between the bones. Clinically, OA manifests as pain in the joint (during or after use), discomfort in the joint (before or during use), swelling and stiffness in the joint (particularly after using the joint). There may be associated loss of flexibility of the joint, intraosseous increase in vascular pressure, periosteal proliferation, subchondral fracture and evidence of sclerosis, ligament laxity, muscle spasm and synovitis.

The diagnosis of osteoarthritis is arrived through a detailed clinical history, physical and radiological examination of the joint, and if required, aspiration of synovial fluid to confirm diagnosis. About 60% of patients have suggestive radiological signs, while only a third of them may have actual symptoms.

Treatment includes symptomatic therapy for pain, stiffness and swelling. The therapy is directed to modify the joint structure leading to retardation and reversal or prevention of the disease process. The drug treatment options available for osteoarthrosis include topical and systemic analgesics, anti-inflammatory agents (mainly NSAIDs) and intra-articular injections of corticosteroids or hyaluronic acid.

Cyclo-oxyegenase enzyme inhibitors (nonselective, preferably selective and specifically selective) are widely used in the management of OA, but the present evidence does not suggest their efficacy in preventing disease progression. Furthermore, the usage of NSAIDs is linked with numerous short and long term adverse effects and these drugs are associated with an increased morbidity in older patients. An intra-articular injection of corticosteroid or hyaluronic acid offers analgesia for 4-6 months but is associated with an increased risk of intra-articular infections.

This study was planned to evaluate the efficacy and safety of Turmeric Capsules in the treatment of Osteoarthritis of knee.

Aim of the study

This study was planned to evaluate the clinical efficacy and safety (short- and long-term) of Turmeric Capsules in the treatment of Osteoarthritis of knee.

Study design

The study was an open, non-comparative trial conducted as per the ethical guidelines of Declaration of Helsinki and Good Clinical Practices. The study protocol, CRFs, regulatory documents, product related information and informed consent form were submitted to the Institutional Ethics Committee and were approved by the same.

MATERIALS AND METHODS

Inclusion criteria

One hundred patients of either sex aged between 18 years to 60 years and suffering from Osteoarthritis of knee (clinical and radiological evidence of osteoarthritis of knee, moderate to severe knee pain and with or without morning stiffness of <30 minutes duration) were included in the study.

Exclusion criteria

Patients suffering from severe systemic illness, which necessitated use of other medications, were excluded from the study. Patients with established hypertension, renal, hepatic or cardiac failure, on long-term steroid treatment, with biochemical and clinical evidence of rheumatoid arthritis or gout, women having likelihood of pregnancy, pregnant and lactating women were also excluded from the study.

Study procedures

This study was an open, prospective, non-comparative clinical trial conducted at Department of Orthopaedics, Olatpur Hospital, Cuttack, India. One hundred patients with confirmed clinical diagnosis of osteoarthritis of knee were selected for the clinical trial. Patients were detailed the nature of the study and were included in the study after signing the informed consent document.

These patients underwent physical examination after a detailed history regarding their disease. In all patients, a thorough systemic examination was done, which was followed by local examination of the knee and other joints affected by osteoarthritis. All enrolled patients underwent hematological and biochemical investigation at entry and at the end of the study. Patients received Turmeric capsule at a dose of 1 capsule per day for 1 month and were examined on a weekly basis till the end of the study. Assessment was done on the basis of number of involved joints, degree of pain, joint swelling, and level of joint activity (e.g. difficulty in climbing steps), joint malfunction, and secondary muscle wasting.

All adverse events, either reported or observed by patients/parents/guardians were recorded in the CRF with information about severity, onset, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as "*Unrelated*" (a reaction that does not follow a reasonable temporal

sequence from the time of administration of the drug), "*Possible*" (follows a known response pattern to the suspected drug, but could have been produced by the patient's 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 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.

Follow-up and monitoring

The patients were examined on a weekly basis for a period of 1 month. The symptoms were assessed on the basis of the scores ie, 0-nil, 1-mild, 2-moderate, 3- severe. Adverse effects, as volunteered by the patients, were recorded in the case record forms.

Primary and secondary end points

The predefined primary efficacy endpoint was a decrease in the disease progression as evident by the reduction in the sign and symptom scores at the end of 4 weeks. The predefined secondary endpoints were incidences of adverse events (short- and long-term) and overall compliance to the drug therapy.

Statistical analysis

Statistical analysis was performed by repeated measures of ANOVA using Friedmann's test followed by Dunnett's multiple comparison posthoc test was done to analyse the scores. The values were expressed as Mean ± SD. Statistical analysis was carried out using using GraphPad Prism, Version 4.03 for windows, Graphpad Software, San Diego, California, USA. The minimum level of significance was fixed at 99% confidence limit and a 2-sided '*p*' value of <0.0001 was considered significant. All values were expressed as Mean ± SEM.

RESULTS

Hundred consecutive patients were enrolled into the trial with mean age of 48.40 ± 4.16. Thirty three male patients and 67 female patients had participated of which 16 patients were smokers, 19 were alcoholics and 44 patients were vegetarians (Table 1).

All the patients completed the study protocol. The Turmeric capsules produced a significant improvement in symptoms associated with osteoarthritis. There was significant reduction in the mean number of involved joints score from 2.24±0.09 at entry to 2.18±0.10, 1.84±0.12, 1.40±0.08 and 0.48±0.10 at the end of 1 week, 2 weeks, 3 weeks and 4 weeks of treatment respectively, with significance of $p<0.0001$ at 4 weeks as compared to baseline values. Significant reduction was also observed in joint pain from 2.42±1.10 at entry to 1.86±0.08, 1.48±0.10 and 0.62±0.12 at the end of 1 week, 02 weeks and 4 weeks of treatment respectively, with significance of $p<0.0001$ at 4 weeks as compared to baseline values. There was significant reduction in the mean score for joint malfunction from the 1st week onwards till the end of the study. Similarly mean scores for difficulty in climbing steps and secondary muscle wasting decreased at the end of 1, 2, 3 and 4 weeks with a significance of $p<0.0001$ as compared to their baseline values (Table 2).

There were no clinically significant changes in any of the hematological and biochemical parameters. There were no clinically significant adverse reactions, either reported or observed during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported.

DISCUSSION

Osteoarthritis is a chronic, progressive disability affecting the elderly (involving both weight-bearing and non weight-bearing joints). It is one of the most common forms of arthritis encountered in clinical practice, which affects an increasing aging population. Osteoarthritis is a major cause of morbidity, disability and impaired quality of life especially among the elderly. The etiology of osteoarthrosis is multifactorial, and is influenced by age, sex, genetic and biomechanical factors. The association between repetitive joint trauma (sports, work-related, or accidental) and osteoarthritis is well documented. The long-term use of NSAIDs in its management has been shown to be associated with serious adverse effects[7-11]. Herbal formulations have been proven an effective, safe alternative to NSAIDs.

Turmeric is a medicinal plant extensively used in Ayurveda, possesses anti-inflammatory, apoptotic activities and supports healthy joint function. Curcumin is the major active constituent of turmeric and has been reported to possess anti inflammatory activity. The other constituents of turmeric namely curcuminoids and essential oils also possess biological activity.[12] Curcumin has multiple modes of action. It inhibits prostaglandin synthesis, it has a strong stabilizing effect on lysosomal membranes, and it has an inhibitory action on leukotrienes.[13]

This study observed significant reduction in the mean symptom score for number of involved joints, joint pain and swelling, difficulty in climbing steps and secondary muscle wasting. There were no clinically significant adverse reactions (either reported by patients, or observed by the investigators), and the overall compliance to the treatment was excellent.

CONCLUSION

Osteoarthritis is a chronic, progressive disability involving both weight-bearing and non weight-

TABLES:

Table 1: Demographic data of patients on entry (n=100)

Parameter	Turmeric Capsule
Age in years (mean ± SD)	48.40 ± 4.16
Weight in Kg (mean ± SD)	55 ± 14.50
Sex ratio/ M:F	33:67
H/o smoking	16
H/o alcohol consumption	19
Diet (veg/nonveg)	44/56

Table 2: Effect of Turmeric capsule on clinical parameters of Osteoarthritis

Time point	No. of involved joints	Joint pain	Joint swelling	Difficulty in climbing steps	Joint malfunction	Secondary muscle wasting
Baseline	2.24±0.09	2.42±1.10	2.62±1.14	3.28±0.12	3.38±0.18	3.14±0.14
1st week	2.18±0.10	1.86±0.08	1.68±1.10	3.02±0.06	2.92±0.14	2.80±0.09
2nd week	1.84±0.12	1.48±0.10	1.32±0.80	2.28±0.10	1.40±0.12	1.84±0.14
3rd week	1.40±0.08	1.26±0.12	1.20±1.10	1.60±0.12	1.18±0.06	1.30±0.10
4th week	0.48±0.10*	0.62±0.12*	0.52±0.08*	0.84±0.10*	0.80±1.10*	0.74±0.12*
*p<0.0001 as compared to the baseline values						

bearing joints. Currently available treatment options for osteoarthritis are associated with numerous short and long term adverse effects and these drugs are associated with an increased morbidity in older patients. This study observed a significant reduction in the mean number of joints involved, and in the mean score for joint pain, joint swelling, difficulty in climbing steps, joint malfunction, and secondary muscle wasting in patients treated with turmeric capsules. Also, there were no clinically significant changes in any of the hematological and biochemical parameters. There were no clinically significant adverse reactions during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported. Therefore, it may be concluded that Turmeric capsule is effective and safe in the management of osteoarthritis.

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