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Evaluation of Clinical Efficacy And Safety of Herbal Formulation in Patients Suffering From Osteoarthritis of The Knee

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ABSTRACT

Background: The present study was conducted to evaluate the clinical efficacy and safety of herbal formulation in patients suffering from osteoarthritis of the knee. Methodology: It was a prospective, open labeled, randomized active controlled study. The study was conducted in the outpatient Department of Orthopedics in a tertiary care hospital over duration of one year. 15 patients in PCT and 17 in HF group were enrolled. Numeric rating scale and symptom score were used as pain efficacy parameters. Self-reported adverse events were used to assess safety of the drugs and causality assessment was done using Naranjo's scale. Results: NRS score was significantly lower in the HF group as compared to PCT group at the end of therapy (p-0.0464). There was no statistically significant improvement in the symptom score. On comparison, total number of adverse drug events reported in the two groups showed no statistical significance. Conclusion: Herbal formulation offers better symptomatic relief of pain and is well tolerated as PCT in patients of OA of knee.*

KEYWORDS : Herbal formulation, Paracetamol, efficacy, safety

Introduction

Osteoarthritis (OA), is a common painful, progressive, degenerating joint disease. The mechanisms leading to OA are complex and not yet clear. Osteoarthritis causes significant limitations in walking, stair climbing, and squatting that greatly interfere with activities of daily living and recreation.[1] Patients with disabling pain are likely to need both non-pharmacological and pharmacotherapy.[2] Currently American college of rheumatology and NICE treatment guidelines recommend paracetamol (PCT) as the initial analgesic of choice.[3,4] Few studies like Boureau F et al, Towheed T et al and Kamath A. have questioned the efficacy and safety of PCT in patients of OA.[5,6,7] Also there is less desired symptomatic pain relief with existing treatments. Osteoarthritis requires long term symptomatic treatment and there are limitations with available therapeutic options, hence the search for an efficacious and safe alternative for this condition is going on. This gap in the available therapeutic alternatives may be bridged by drugs from indigenous sources.

A herbal formulation (HF) containing extracts of Boswellia serrata, Alpinia galanga, Commiphora wightii, Glycyrrhiza glabra, Tinospora cordifolia and Tribulus terrestris. All these extracts have an anti-inflammatory-analgesic property and are said to be effective for symptomatic treatment in OA. In addition, individual components of the herbal formulation also have specific antiarthritic properties.[8]

Hence the present study was conducted to evaluate and compare herbal formulation and paracetamol with respect to their efficacy and safety in patients of OA of knee.

Materials and Methods:

It was a prospective, open labeled, randomized active controlled study. The study was conducted in the outpatient Department of Orthopedics in a tertiary care hospital over duration of one year. Patients aged between 40-70 years, of either sex, willing to participate in the study, with clinical and radiological evidence of osteoarthritis of knee with a minimal pain score of 4 on numeric rating scale (NRS) at baseline, after taking a well-informed written consent were included in the study. Patients with severe hypertension, evidence of renal, hepatic or cardiac failure, joint pain secondary to metabolic disorders like gout or rheumatoid arthritis, who described their pain as intolerable (NRS=10) at baseline and patients who did not give informed consent were excluded from the study. The study was approved by institutional ethics committee.

After enrollment, patients were randomized to two groups (PCT group patients received tab. 500mg twice daily and HF group patients received one capsule twice daily) by means of computer generated random numbers.

Pain was the primary efficacy parameter of the present study, since it was the major symptom for which patients of OA seek medical care. An 11 point numeric rating scale (NRS) [with 0 indicating no pain to 10 indicating intolerable pain] [9] and total symptom score [components as number of joints involved, swelling, pain, joint malfunction, secondary muscle weakness, interference with routine activity with max total score 26] were used as the pain efficacy parameters. Efficacy assessment of patients was done by intergroup comparison of the differences in total symptom score and pain intensity score at the end of 4 weeks therapy; as compared to baseline.

Self-reported adverse events by the patients in either group were used for safety assessment. Causality assessment of adverse events was made based on Naranjo scale.[10] Overall safety assessment included an inter group comparison of total number of adverse events.

Intra-group comparisons for efficacy parameters as compared to baseline were done by paired t test and intergroup comparisons were done by unpaired t test. Total ADRs were compared by F test. Subgroup analysis of individual symptom improvement was done by tabulating response percentages. P value of less than 0.05 was considered statistically significant. Graph pad prism 5.02 software was used for statistical analysis.

Results:

Results of the present study show that, score on NRS was significantly lower in the HF group as compared to PCT group at the end of therapy. (Table no. 1) Although there was no statistically significant improvement in the symptom score, each component of the symptom score like stiffness, swelling and pain reduced to a greater extent in PF group as compared to PCT group.

In PCT group no adverse events were reported whereas totally 3 (2 dyspepsia and 1 dizziness) adverse events were reported in PF group. After doing causality assessment using Naranjo's scale, it was found that ADRs reported belonged to possible category. Comparison of total number of adverse drug events in the two groups showed no statistical significance. (Table no. 2)

Discussion:

The pathophysiology of OA is complex. Many inflammatory mediators are involved in the gradual pathological progress of OA.

In the present study, HF was found to have higher efficacy as compared to PCT at the end of the 4 weeks of therapy. The results of the present study are in concordance with the previous studies in terms of efficacy. Two studies Chandanwale et. al.[11] and Srivastava N et. al.[12] have also found that PF containing same ingredients were associated with significant improvement of symptoms like pain, swelling, joint malfunction and mobility in patients of osteoarthritis. The components of the HF interrupt the pathophysiology of OA in a complex fashion. Boswellia serrata inhibits 5-LOX, glycosaminoglycan degradation and also inhibits complement pathway, decreases WBC infiltration into joints.[13] Alpinia galanga inhibits release of IL1, TNFα and also COX-2. Glycyrrhiza glabra may play a role in activation of descending inhibitory pain pathways.[14] Tinospora cardiofolia inhibits complement activation by inhibiting C3 convertase. Commiphora wightii have anti-inflammatory and antioxidant activity, also inhibit lipid peroxidation and oxidative damage and in previous studies has been found to reduce pain stiffness and joint mobility in patients of OA of knee.[15] Collectively, HF differs from NSAIDS and PCT because of its multi-modal action on mediators of inflammation. Leukotrienes and complements not are not affected by NSAIDS and PCT, but are affected by components of HF and thus may be superior to NSAIDS and PCT in controlling pain of OA.[15] This may explain the higher efficacy of HF in controlling pain of OA of knee over PCT.

A meta-analysis of RCT by Zhang W et.al has stated that PCT failed to relieve pain and stiffness in patients of OA and similar results were found in our study.[16]

In the present study, comparison of total number of ADRs in the two groups showed no statistical significance. Similarly, studies conducted by Chandanwale and Srivastava N et. al. did not show clinically significant ADRs with polyherbal formulation with similar ingredients and compliance was excellent.[11,12]

In an article by Kamath A.[7] stated that increasing doses of paracetamol was associated with increase in cardiovascular (fatal/nonfatal myocardial infarction, stroke, heart failure), gastro-intestinal (upper and lower), and renal adverse events. Based on these studies, attempts to decrease daily dose of PCT have been made and present study utilized lower dose of PCT. Thus in present study, patients received PCT 500mg twice daily and did not report any adverse events at this dose.

Conclusion:

From the present study it can be concluded that herbal formulation offers better symptomatic relief of pain and is well tolerated as PCT in patients of OA of knee. However, considering the results and conclusions have to interpreted with due considerations to the limitations of the study like its limited sample size and short duration. Thus, larger studies with longer duration of therapy need to be carried out in future to establish the exact role of Herbal formulation in treatment of OA of knee.

Table 1: Comparison of paracetamol (PCT) and polyherbal formulation (PF) with respect to efficacy parameters

Parameter		PCT (Mean ± SD) (n=15)	HF (Mean ± SD) (n=17)	p value
NRS	Baseline	7.2 ± 2.3	6.9 ± 2	0.6833
	4 weeks	7.1 ± 2.3	5.6 ± 1.8	0.0464*
Symptom score	Baseline	18 ± 1.8	18 ± 1.8	0.9455
	4 weeks	18 ± 2.3	16 ± 2.3	0.1010

*** significant, ** highly significant,**

Table 2: Comparison of safety of paracetamol (PCT) and polyherbal formulation (PF) at the end of 4 weeks of therapy

Symptom	PCT (n=15)	HF (n=17)	p value
Dyspepsia	NIL	2	0.2288
Dizziness	NIL	1	
Total ADEs	0	3	

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