

Research Article



Efficacy, Safety and Impact on Quality of Life Indices of Polyherbal Formulation and Paracetamol on in-Patients of Osteoarthritis of Knee: A Comparative Study

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ABSTRACT

Osteoarthritis (OA) is a common painful, debilitating joint disease. Symptomatic pain relief with existing treatments is less than desired. The gap in available therapeutic alternatives may be bridged by drugs from indigenous sources. Thus this study compared the efficacy, safety and impact on quality of life (QOL) indices of a polyherbal formulation (PF) with paracetamol (PCT) in patients of osteoarthritis. This was a randomized control trial between one group receiving PCT 500mg twice a day and other group receiving PF tablets twice a day for 4 weeks. Primary efficacy parameters were improvement of pain score on *Numeric Rating Scale* (NRS), predefined symptom score (PSC) and Quality of life at the end of study. p value <0.05 was considered as statistically significant. 15 patients in PCT and 17 patients in PF group were followed. The mean NRS score at the end of 4 weeks was 7.1 ± 2.3 in PCT group and 5.6 ± 1.8 in PF group ($p=0.0464^*$). The mean PSC at the end of 4 weeks was 18 ± 1.8 in PCT group and 16 ± 2.3 in PF group ($p=0.1010$). The mean QOL score at the end of 4 weeks was 11 ± 2 in PCT group and 13 ± 2.1 in PF group ($p=0.0096^{**}$). 2 patients in PF group complained of dyspepsia and 1 had dizziness. None had adverse events in PCT group ($p=0.2288$). PF is more efficacious in terms of pain reduction and QOL with safety comparable to PCT in knee OA.

Keywords: Osteoarthritis, Polyherbal formulation, Paracetamol.

INTRODUCTION

Osteoarthritis (OA), is a common painful, debilitating joint disease. The mechanisms leading to OA are complex and not yet clear. Patients with ongoing, disabling pain are likely to need both non-pharmacological and pharmacotherapy.¹ Current treatment guidelines^{2,3} recommend paracetamol (PCT) as the initial analgesic of choice but few studies have questioned the efficacy and safety of PCT in patients of OA.⁴⁻⁶ Also symptomatic pain relief with existing treatments is less than desired. Considering the natural history of OA, which requires long term symptomatic pharmacotherapy, and limitations of available therapeutic options, search for an efficacious and safe alternative for this condition ensues. The gap in available therapeutic alternatives may be bridged by drugs from indigenous sources.

A polyherbal formulation (PF) containing extracts of *Boswellia serrata*, *Alpinia galanga*, *Commiphora wightii*, *Glycyrrhiza glabra*, *Tinospora cordifolia* and *Tribulus terrestris*; all of which have anti-inflammatory -analgesic properties and are said to be effective for symptomatic treatment in OA. In addition to analgesic-anti-inflammatory effect, individual components of the polyherbal formulation also have specific antiarthritic properties.⁷

Osteoarthritis causes significant limitations in walking, stair climbing, and squatting that greatly interfere with activities of daily living and recreation. Thus has a significant negative impact on quality of life (QOL).⁸

However not so many studies so far have assessed the impact of treatment OA on QOL indices.

Thus the purpose of this study was to compare polyherbal formulation and paracetamol with respect to their efficacy, safety and impact on QOL indices in patients of OA of knee.

MATERIALS AND METHODS

The study was an open labeled, parallel group, randomized active controlled trial. 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 as per diagnostic criteria laid down by American College of Rheumatology (ACR) 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.

Following recruitment, study participants were randomized to two groups (PCT group patients received tab. 500mg twice daily and PF 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 this was the major symptom for which patients of OA seek medical care.

Parameters used for assessing efficacy include pain intensity score on 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].

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.

Assessment of safety was done by self-report of adverse events by the patients in either group.

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.

A self-designed questionnaire consisting of 6 questions concerned with general health, physical functioning, bodily pain and vitality based on Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (maximum score of 20 for a person at the best of health) was used to assess impact of therapy on the above QOL parameters.

Difference in these scores between the treatment groups from baseline to the end of treatment period was compared.

Also subgroup analysis of QOL questionnaire was done by noting the responses of patients to each point of the QOL questionnaire as to see which of the individual components was actually affected by therapy.

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 and individual responses to points of QOL were 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 PF 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. (Table no.2)

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. 3)

At the end of study there was statistically significant improvement in the QOL score with PF (Table no. 4) and there was more improvement in each QOL component in PF than PCT at the end of therapy.

There was a trend towards better grading of health in general in the PF group at the end of therapy as compared to PCT group.(Graph 1) The overall comparison of proportion of patients of two groups at the end of therapy with respect to their physical activity profile showed that less number of patients had their physical activity limited in PF group and this group of patients tends to accomplish more as compared to PCT group. (Graph 2, 3, 4) The pain of OA to some extent interfered with normal activities in patients of both the groups but to a lesser extent in patients of PF group.(Graph 5) Comparing the proportions, graph 6 shows that energy level overall seem to be more positive for PF group as compared to PCT group.

Thus significant increase in total QOL score in patients of PF group seems to be a result of better grading of general health, vitality and lesser limitation of physical activity due to pain leading to better overall accomplishment of daily activities.

Table 1: Comparison of Paracetamol (PCT) and Polyherbal Formulation (PF) with respect to Efficacy Parameters

Parameter		PCT (Mean ± SD) (n=15)	PF (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 Paracetamol (PCT) and Polyherbal Formulation (PF) with respect to their effects on individual symptoms of Knee OA at the end of therapy

Symptom	PCT Improved		Proportion of improved patients (%)	PF Improved		Proportion of improved patients (%)
	Yes	No		Yes	No	
Muscle swelling	2	2	50	5	0	100
Joint swelling	0	7	NIL	2	0	100
Night pain	1	9	10	3	13	18.75
Joint stiffness	3	12	20	8	6	57.14

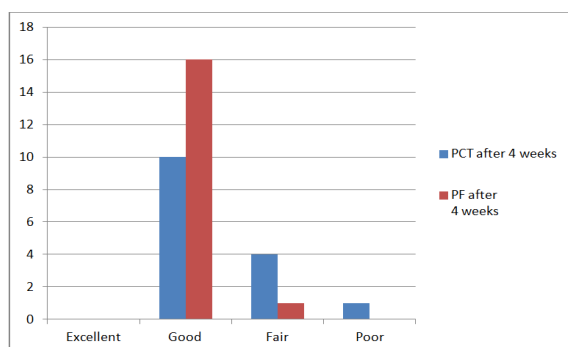
Table 3: Comparison of Safety of Paracetamol (PCT) and Polyherbal Formulation (PF) at the end of 4 weeks of therapy

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

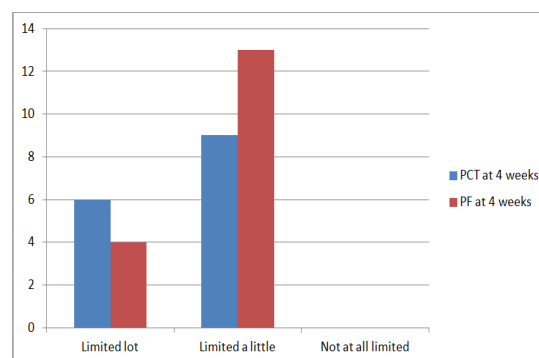
Table 4: Comparison of Paracetamol (PCT) and Polyherbal Formulation (PF) with respect to their impact on Quality of Life (QOL) Parameters

Parameter		PCT (Mean ± SD) (n=15)	PF (Mean ± SD) (n=17)	p value
QOL score	Baseline	10 ± 2	11 ± 2	0.8550
	4 weeks	11 ± 2	13 ± 2.1	0.0096**

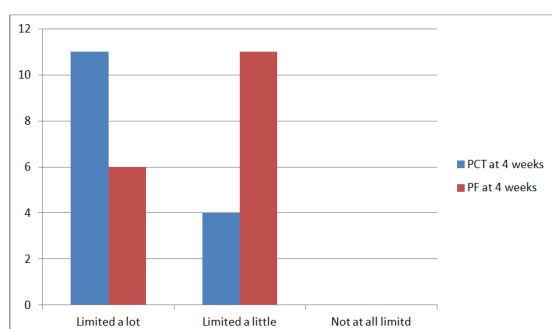
* significant, ** highly significant,



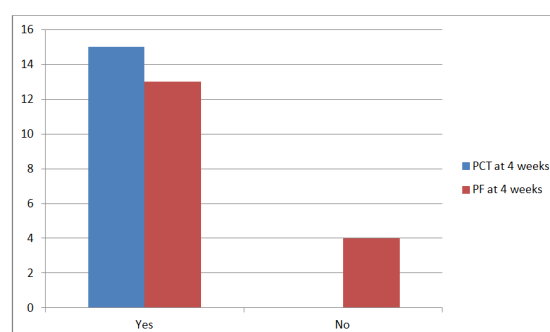
Graph 1: Comparison of Grading of Health by Patients in Paracetamol (PCT) and Polyherbal Formulation (PF) at the end of 4 weeks of Treatment



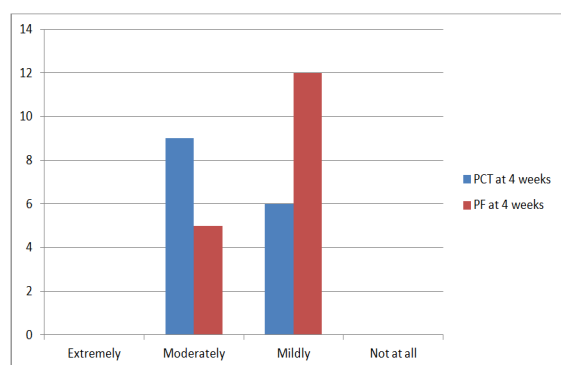
Graph 2: Comparison of Limitation of Daily Activities in Paracetamol (PCT) and Polyherbal Formulation (PF) Group at the end of 4 weeks of Treatment.



Graph 3: Comparison of Limitation of Climbing Stairs in both Paracetamol (PCT) and Polyherbal Formulation (PF) Groups at Baseline and the end of Therapy.



Graph 4: Comparison of Paracetamol (PCT) and Polyherbal Formulation (PF) Groups at the end of 4 weeks of Treatment with respect to overall Accomplishment. (Accomplished less than you would like: YES or NO)



Graph 5: Comparison of Interference of Pain with Normal Activities in Patients of both Paracetamol (PCT) and Polyherbal Formulation (PF) Groups at the end of 4 weeks of Treatment

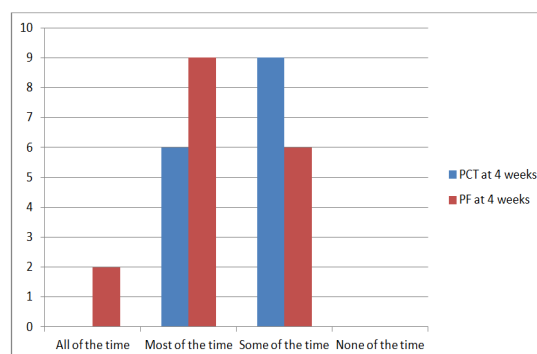
DISCUSSION

Various constituents of the PF intercept pathophysiology of OA in a complex fashion. Boswelliaserrata inhibits 5-LOX and glycosaminoglycan degradation. It also inhibits complement pathway, decreases WBC infiltration into joints and restores integrity of blood vessels.¹¹ Alpiniagalanga inhibits release of IL1, TNF α and also COX-2. Glycyrrhizaglabra increases brain serotonin levels and may play a role in activation of descending inhibitory pathways of pain.¹² Tinosporacardiofolia inhibits complement activation by inhibiting C3 convertase. Commiphorawightii 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.¹³ To put it in a nut shell, PF differs from NSAIDs and PCT in its multifaceted action on mediators of inflammation. Leukotrienes and complements are not affected by NSAIDs and PCT, but are subdued by components of PF and may thus be superior to NSAIDs and PCT in controlling pain of OA.¹³ This may explain the higher efficacy of PF in controlling pain of OA of knee. The results of the present study are in concordance with the previous studies in terms of efficacy. Two studies Chandanwale¹⁴ and Srivastava N¹⁵ 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.

A meta-analysis of RCT¹⁶ has stated that PCT failed to relieve pain and stiffness in patients of OA and similar results were found in our study.

In other studies conducted by Chandanwale and Srivastava N. PF with similar ingredients did not show clinically significant ADRs and compliance was excellent.

In an article by Kamath A.⁶ stated that increasing doses of paracetamol was associated with increase in cardiovascular (fatal/nonfatal myocardial infarction, stroke, heart failure), gastrointestinal (upper and lower), and renal adverse events. These safety data were



Graph 6: Comparison of Energy level in Patients of both Paracetamol (PCT) and Polyherbal Formulation (PF) Groups at the end of 4 weeks of Treatment

assessed based on observational studies with long-term follow-up ranging from 30 days to 20 years.

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.

The significant improvement in quality of life and also in each component with PF can be attributed to its analgesic and anti-inflammatory property which affected the pain intensity more.

Thus, better efficacy of PF in OA leading to overall improvement in their day to day activity profile. Alternative explanations could be increased brain serotonin level by glycyrrhizaglabra producing mild antidepressant and mood elevating actions that leads to better accomplishment and positively affect vitality in patients of OA.¹⁴ No such additional actions have been noted by PCT which was reflected as a poor impact on QOL at the end of treatment in this group.

Not many studies have compared the effect of pharmacotherapy of treatment of OA on QOL indices. No head to head comparisons of PCT with PF for QOL parameters were available on literature search.

From the present study it can be concluded that PF offers better symptomatic relief of pain and is equally well tolerated as PCT in patients of OA of knee. Polyherbal formulation also differs from PCT in terms of additional benefits to the patient in the form of a better quality of life. However, considering the results and conclusions have to be 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 PF in treatment of OA of knee.

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