PACIFIC JOURNAL OF MEDICAL SCIENCES

{Formerly: Medical Sciences Bulletin}

ISSN: 2072 – 1625

Pac. J. Med. Sci. (PJMS)

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ABSTRACT:

To evaluate the efficacy and tolerability of fixed dose combination of curcumin and piperine in osteoarthritis (OA), a non-randomized, open labeled, non-comparative, single-centric, and post marketing surveillance (PMS) study was conducted in 166 osteoarthritic patients (73 men and 93 women, mean age: 54.5 ± 12.45 years). Each patient was administered a combination of curcumin 500 mg and piperine 5 mg twice daily for 12 weeks. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used as a tool to assess the efficacy of the fixe dose combination during the 12 weeks therapy. At the end of 12 weeks of therapy, WOMAC score improved significantly ($p<0.0001$) from 65.82 ± 18.10 to 25.12 ± 21.26. Also a significant reduction ($p<0.0001$) was found in scores for pain, stiffness and physical function from 15.03 ± 3.74 to 5.83 ± 4.42, 5.43 ± 1.95 to 1.52 ± 1.56 and 45.57 ± 13.72 to 17.76 ± 16.23 respectively at the end of 12 weeks. Combination of Curcumin and Piperine was effective and safe for the management of osteoarthritis in Indian patients.

Keywords: Curcumin, Piperine, Osteoarthritis, NSAID

Submitted May 2017, accepted September 2017

INTRODUCTION:

Osteoarthritis is a common degenerative disorder of the articular cartilage associated with hypertrophic changes in the bone. Risk factors include genetics, gender, past trauma, advancing age, and obesity [1]. The most common symptoms of OA (Osteoarthritis) are pain, stiffness of the joint, crepitation on motion and limitation of joint motion [2].

An imbalance between inflammatory and anti-inflammatory signaling in chondrocytes and synovial cells, with an abnormal activation of cytokine cascades and an overproduction of inflammatory mediators like IL-1β and tumor necrosis factor-alpha which leads to a decrease in collagen synthesis and, by activation of matrix metalloproteinases (MMPs), to a corresponding increase in collagen degradation, with further up-regulation of mediators and effectors like IL-8, IL-

6, prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS) is the major cause of arthritis [3].

During OA there is a loss of cartilage, the subchondral bone becomes thicker, the subchondral trabecular bone mass decreases and new osteophytes are formed. OA affects the entire joint: the cartilage is damaged, the underlying subchondral bone structure is remodeled, and a chronic inflammation of the synovium develops. The progression of OA involves changes in the production and functioning of various cytokines. The cytokines involved may be inflammatory interleukins (IL-1β, IL-6, IL-15, IL-17, and IL-18) and tumour necrosis factor-alpha (TNF-α) or anti-inflammatory interleukins (IL-4, IL-10, and IL-13) [4].

Current standard of care for patients with OA mainly relies on the use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). These treatments have partial efficacy in controlling disease symptoms, and their long-term use has been reported to cause several gastrointestinal, renal and cardiovascular side effects [2].

Traditionally, plants have been used for centuries as a popular method for the treatment of various health disorders [5]. Curcumin is the yellow pigment of turmeric (Curcuma longa L.), the most popular spice in Indian cuisine and a major ingredient of curry powders. Turmeric has a long history of medicinal use, especially to treat inflammation, and many of its traditional uses have been mechanistically validated in cellular systems as well as in animal models of disease. Indeed, with almost 3,000 preclinical investigations, curcumin is one of the best investigated botanical constituents in the biomedical literature [3]. Also, Korea Food and Drug Safety administration has declared turmeric roots as “generally regarded as safe.” Turmeric and curcumin have been found to be safe and tolerable in human clinical trials and systematic reviews [6].

It possesses many beneficial effects including anti-inflammatory, antioxidant, anticancer, antimicrobial, hepatoprotective and anti-hyperlipidemic [7]. Curcumin acts as a master switch of inflammation by acting at the level of pro-inflammatory enzymes (cyclooxygenases (COX) and lipoxygenases) and inflammatory transcription factors (nuclear factor-kappaB (NF-kB) and signal transducer and activator of transcription 3 (STAT3)) and their genomic expression [3].

Curcumin’s potent anti-inflammatory properties have led to active research on its use for a variety of inflammatory conditions, including postoperative inflammation, arthritis, uveitis, inflammatory pseudotumors, dyspepsia, irritable

bowel syndrome, inflammatory bowel disease, pancreatitis, and Helicobacter pylori infection [8]. Curcumin is a potent and established anti-inflammatory dietary botanical component that inhibits all mediators of the inflammatory response such as cytokines, chemokines, adhesion molecules and growth factors, as well as other mediators such as cyclooxygenase-2, inducible nitric oxide, tissue factor and epigenetic alterations [9].

The bioavailability of Curcumin is low due to a relatively low intestinal absorption, and rapid metabolism in the liver, followed by elimination through the gall bladder [7]. Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavailability [8].

Piperine, a known inhibitor of hepatic and intestinal glucuronidation, was combined with curcumin and administered in healthy human volunteers. Piperine enhanced the serum concentration, extent of absorption and bioavailability of curcumin in humans with no adverse effects. Concomitant administration of piperine 20 mg produced much higher concentrations from 0.25 to 1 h post drug ($P < 0.01$ at 0.25 and 0.5 h; $P < 0.001$ at 1 h) the increase in bioavailability was 2000% [10].

Piperine significantly inhibits the production of two important proinflammatory mediators IL-6 and PGE2. Inhibition of PGE2 production is important due to its central role in triggering pain. Piperine significantly decreased the IL-1β-stimulated gene expression and production of MMP-1, MMP-13 and COX-2 in human OA chondrocytes. MMP13 collagenases play dominant roles in arthritis because they are the rate-limiting components of the collagen degradation process [11].

METHODS AND MATERIALS:

Design and participants:

This was a non-randomized, open labeled, non-comparative, single-centric, and post marketing surveillance (PMS) study to determine the effectiveness and safety of the fixed dose combination of Curcumin 500 mg and Piperine 5 mg twice daily for 12 weeks.

A total of 166 osteoarthritic patients (73 men and 93 women, mean age: 54.5 ± 12.45 years) reporting to Ortho outpatient department (OPD), were screened for the intensity of knee pain on visual analog scale (VAS). Patients complaining of VAS score > 5 were enrolled in the study.

The study was conducted under supervision at SN Jain Hospital, Solapur (Maharashtra, India).

Postgraduate students posted in OPD administered the questionnaire to each patient and data interpretation was done by clinical pharmacologist.

Patient characteristics:

Inclusion and Exclusion criteria: 166 patients with osteoarthritis who gave their informed consent in the vernacular language were included in the study. Eligible patients were in the age range of 21-80 years and were diagnosed to have osteoarthritis assessed as per WOMAC questionnaire (Western Ontario and McMaster Universities Osteoarthritic Index function subscale). This was a post marketing observation study as the combination was already in use for management of osteoarthritis, hence this study did not warrant clearance from the institutional ethics committee.

The exclusion criteria included patients with any of the several conditions listed as follows: concurrent treatment with any non-steroidal anti-inflammatory drug (NSAID), Disease modifying anti-rheumatic drug (DMARD) or any anti-TNF-a therapy or other antiarthritic therapy, treatment with any investigational agent within 4 weeks of screening and intra-articular or parenteral corticosteroids within 4 weeks prior to the screening visit.

Other criteria for exclusion were as follows: Subjects suffering from cardiovascular disease requiring treatment, diabetes, severe metabolic disease, any oncological condition and any planned surgery during the treatment course or undergone surgery prior to 3 months of enrollment. Females who were pregnant or planning to become pregnant and lactating mothers were excluded from the study.

RESULTS:

Evaluation of Signs/Symptoms of Osteoarthritis:

The WOMAC questionnaire was applied to describe and rate the symptoms of OA. The status of OA signs/symptoms was evaluated by the investigator together with the patient at the time of inclusion and at all visits.

Statistical Analysis:

WOMAC score was evaluated using the analysis of variance (One Way ANOVA using Dunnett's multiple comparisons test). Mean WOMAC scores are presented in Tables 1 and 2. Scores for pain dropped significantly ($p<0.0001$) following Conjoint administration from 15.03 ± 3.74 to 5.83 ± 4.42. Also, a significant reduction in pain score was seen at week 8 when compared with baseline from 15.03 ± 3.74 to 8.54 ± 4.35 ($p<0.0001$). The scores for stiffness

in the treatment group were reduced significantly from 5.43 ± 1.95 to 1.52 ± 1.56 ($p<0.0001$) after 12 weeks of treatment. Also, a significant reduction in stiffness score was seen at week 8 when compared with baseline from 5.43 ± 1.95 to 2.7 ± 1.86 ($p<0.0001$). The scores for physical function in the treatment group were significantly reduced, from 45.57 ± 13.72 to 17.76 ± 16.23 during the course of the study ($p<0.0001$). Also, a significant reduction in physical function was seen at week 8 when compared with baseline from 45.57 ± 13.72 to 26.15 ± 14.99 ($p<0.0001$). The mean total WOMAC score reduced significantly ($p<0.0001$) from baseline from 65.82 ± 18.10 to 25.12 ± 21.26 at the end of 12 weeks of therapy as shown in Figure 1. In addition, a significant reduction in WOMAC score was seen at week 8 when compared with baseline from 65.82 ± 18.10 to 37.3 ± 20.14 ($p<0.001$). Comparison of change in WOMAC score between the group and with baseline also yielded significant reductions ($p<0.0001$) in the treatment group. WOMAC score were evaluated using the analysis of variance (One Way ANOVA using Tukey's multiple comparisons test). Change in mean WOMAC scores within the group are presented in Table 3. Tolerability of the fixed dose combination of curcumin and piperine was reported as excellent by the participants to investigators except for 2% patients who reported gastrointestinal side effect, such as heart burn which was of mild intensity and resolved during the course of treatment without discontinuation of therapy.

Table 1 Change of Mean WOMAC Scores after 4, 8 and 12 Weeks of Treatment

	Treatment group			
WOMAC Parameters	**Baseline (Mean ± SD)**	**4 Week (Mean ± SD)**	**8 Week (Mean ± SD)**	**12 Week (Mean ± SD)**
Pain	15.03 ± 3.74	11.95 ± 3.85	8.54 ± 4.35	5.83 ± 4.42
Stiffness	5.43 ± 1.95	4 ± 1.89	2.7 ± 1.86	1.52 ± 1.56
Physical Functions	45.57 ± 13.72	34.6 ± 14.05	26.15 ± 14.99	17.76 ± 16.23
Total	65.82 ± 18.10	50.54 ± 18.45	37.3 ± 20.14	25.12 ± 21.26

Table 2: Change of Mean WOMAC Scores as compared with Baseline

Dunnett's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Adjusted P Value
BL vs. W4	15.28	10.23 to 20.33	<0.0001
BL vs. W8	28.45	23.4 to 33.5	<0.0001
BL vs. W12	40.7	35.66 to 45.75	<0.0001

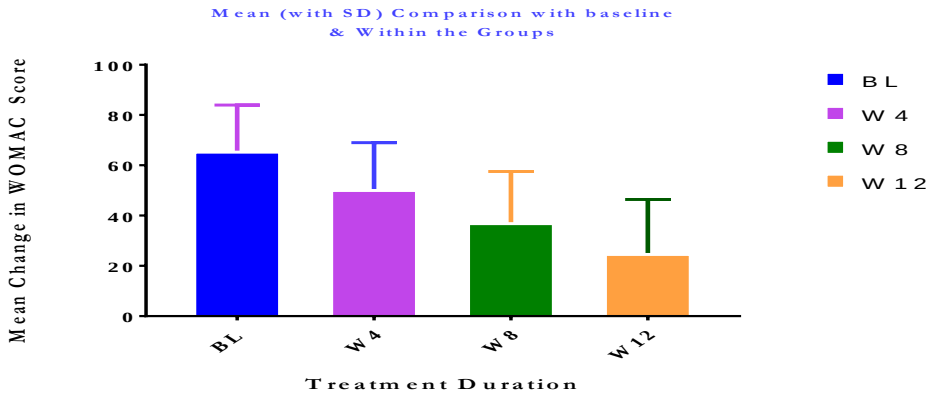

Figure 1: Comparison of WOMAC Score (Mean ± SD) at baseline and follow-up visits

Table 3 Change of Mean WOMAC Scores compared within the group

Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Adjusted P Value
W4 vs. W8	13.17	7.652 to 18.7	<0.0001
W4 vs. W12	25.43	19.9 to 30.95	<0.0001
W8 vs. W12	12.25	6.73 to 17.78	<0.0001

DISCUSSION:

Herbal therapies with anti-inflammatory properties and minimum side effects are needed for the treatment of arthritis, including rheumatoid arthritis and osteoarthritis [6]. Pain and osteoarthritis symptoms are known to limit social interactions, and any improvement in these conditions is likely to have a socio-emotional effect. The first evidence for the safety and superiority of curcumin treatment in patients with active rheumatoid arthritis was shown in one pilot clinical study, which evaluated curcumin alone,

diclofenac sodium alone, and their combination, wherein significantly greater improvement was shown by the curcumin group than by the diclofenac sodium group [9]. Nakagawa et al conducted a randomized, double blind, placebo-controlled, prospective clinical study of the efficacy of Theracurmin, a highly bioavailable form of curcumin, in patients with osteoarthritis wherein Theracurmin was significantly effective in decreasing pain and NSAID necessity with no major adverse events [12]. Curcumin has been reported to be effective in alleviating chronic pain in different experimental models, including neuropathic pain, one of the most difficult forms of pain to treat. In an animal model of formalin-induced orofacial pain, curcumin was found to potentiate a subanalgaesic dose (0.2 mg/kg) of diclofenac [9].

In this study significant results were obtained for the efficacy endpoint (WOMAC score) evaluated at week 4, week 8 and week 12. Thus, after 12 weeks of continuous use of Conjoint twice daily, the WOMAC score for OA symptoms decreased by >40%. The significant decrease of all WOMAC items suggests that the clinical improvements observed have a clear mechanistic basis that validates the efficacy of curcumin on joint. Curcumin targets the multiple mechanisms involved in the progression of arthritis and its symptoms. Piperine controls the important inflammatory mediators involved in the pain generation and proteins which degrades cartilage. Also coadministration of piperine enhances the bioavailability of curcumin.

The limitations of the studies were (i) small sample size consisting of 166 subjects, (ii) open label study and (iii) no direct comparison with NSAIDs to determine the effectiveness of Curcumin over existing therapy. However the study provides sufficient evidence to support larger clinical trials that could eventually lead to its acceptance as a standard therapy for many forms of arthritis and possibly other inflammatory conditions.

CONCLUSION:

Osteoarthritis is an age related disorder. The existing therapy has its own limitations of side effects like gastric bleeding or therapy may not be safe in renally compromised patients or at times even the long term therapy may lead to renal impairment. Twelve weeks fixed dose combination of curcumin 500 mg and piperine 5 mg has shown significant reduction in scores for pain, stiffness and physical function. Thus combination of Curcumin and Piperine warrants further investigation as an effective and safe option for the management of osteoarthritis in Indian patients.

ACKNOWLEDGEMENT

Author acknowledges the immense help received from the scholars whose articles are cited and included in references of this manuscript and to the participating investigators for extending their help in data support. The author was also thankful to Ms. Kanchan Choudhary M-Pharm (Pharmacology) for extending her help in performing statistical analysis and writing the manuscript.

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