

Safety and efficacy of Curcumin versus Diclofenac in Knee Osteoarthritis: a randomized open label parallel arm study

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Abstract

Background: To compare the efficacy and safety of curcumin with diclofenac in the treatment of knee osteoarthritis (OA). **Methods:** In this randomized, open label, parallel, active controlled clinical study, 139 knee OA patients were randomized to receive either curcumin 500 mg (BCM-95®) capsule three times daily or diclofenac 50 mg tablet two times daily for 28 days. Patients underwent assessment at baseline, day 7, day 14 and day 28. Main outcome measure was severity of pain using Visual Analogue Scale (VAS) at day 14 and day 28. Knee injury and osteoarthritis outcome score (KOOS) (at day 14 and day 28), anti-flatulent effect (at day 7), anti-ulcer effect, weight lowering effect, patient and physician's global assessment of therapy at day 28 were included as secondary outcome measures. Safety after treatment was evaluated by recording adverse events and laboratory investigation. **Results:** At day 14 and day 28, patients receiving curcumin showed similar improvement in severity of pain and KOOS scale when compared to diclofenac, and the difference was not statistically significant. At day 7, the patients treated with curcumin experienced significantly greater reduction in number of episodes of flatulence compared with diclofenac ($p < 0.01$). At day 28, weight lowering effect ($p < 0.01$) and anti-ulcer effect ($p < 0.01$) of curcumin were observed. None of the patients required H2 blockers in curcumin group and 19 patients required H2 blockers in diclofenac group (0% vs. 28%, respectively; $p < 0.01$). Adverse effects were significantly less in the curcumin group (13% vs. 38% in diclofenac group; $p < 0.01$). Patient's and physician's global assessment of therapy was similar in both treatment groups. **Conclusion:** Curcumin has similar efficacy to diclofenac, but demonstrated better tolerance among patients with knee OA. Curcumin can be an alternative treatment option in the patients with knee OA who are intolerant to the side effects of NSAIDs. **Trial Registration:** ISRCTN, ISRCTN10074826, Registered 21 November 2017 - Retrospectively registered, <http://www.isrctn.com/ISRCTN10074826>

Background

Knee Osteoarthritis (OA) is one of the most common and fourth leading cause of disability [1]. Symptoms of knee OA normally begin after the age of 40 years, but they can affect younger people after a traumatic injury. It is highly prevalent among obese patients, with the estimated incidence of 10% to 15% in population aged above 60 years [1, 2]. Due to increasing prevalence of obesity and aging population, the prevalence of knee OA is expected to increase [3, 4]. Activity restriction and functional limitations among elderly obese patient with knee OA gradually reduce physical, psychological, and social well-being of patients leading to worsening of their quality of life [5, 6]. Also, it significantly increases the financial burden on patients and families and health care systems. A study conducted by Dominick et al. (2004) among more than 4000 OA patients showed worse quality of life, in most patients especially for item related to poor general health, pain and activity limitation [7].

Pain is one of the key symptoms that drive individuals to seek medical attention, and contributes to functional limitations and reduced quality of life [8-11]. Current recommendations for managing OA consider on relieving pain, improving physical functions and slowing the progress of the underlying disease as important goals of therapy. Usual first line pharmacologic therapy for knee OA is non-steroidal

anti-inflammatory drugs (NSAIDs) which provides effective relief of symptoms in most patients [12, 13]. Pharmacological therapy with NSAIDs offer temporary relief in symptoms but is associated with serious risk after long-term use. Chronic administrations of NSAIDs cause gastroduodenal mucosal erosions in approximately 35–60% of patients, gastric or duodenal ulceration in 10–25% of patients [14]. These events are a consequence of non-selective mechanism of action of traditional NSAIDs [13]. Additionally, elderly patients are at greater risk for gastrointestinal (GI) bleeding secondary to use of NSAIDs [15]. Long-term use of non-opioid analgesics such as acetaminophen and NSAIDs, including cyclo-oxygenase (COX)-2 inhibitors have been found to be associated with enhanced risk for gastrointestinal bleeding, hypertension, congestive heart failure and renal insufficiency [16]. There is need of an effective and safer alternative treatment for patients with knee OA.

Curcumin, a polyphenolic compound derived from dietary spice turmeric (*Curcuma longa*), possesses diverse pharmacologic and biological properties. Curcumin has been used for centuries in traditional Chinese and Ayurvedic medicine for its anti-inflammatory properties [17]. The efficacy of curcumin is shown to be similar to that of ibuprofen for the treatment of knee OA [18]. Study done with curcumin on patients with rheumatoid arthritis demonstrated a significant improvement in the duration of walking time and joint swelling which was almost comparable with phenylbutazone [19]. Pre-clinical studies conducted on rats suggested that curcumin is a gastroprotective agent and acts as a potent anti-ulcer compound, protecting against gastric mucosal injury [20, 21]. A study has shown that curcumin acts as a potent anti-ulcer compound to protect indomethacin (NSAID)-induced gastric ulcer [22]. It inhibits increased acid secretion to prevent ulcer aggravation. Clinical evidence confirmed that curcumin is safe for human use [23-24]. Anti-flatulent and body weight lowering effect was also reported with the use of curcumin in pre-clinical studies [25-26].

However, the poor oral bioavailability of curcumin hampers its therapeutic efficacy which is a major concern. Bioavailability of curcumin can be increased by combining curcuminoids with essential oil of turmeric [27-28]. Availability of curcumin in blood plasma was seven folds higher after consuming curcuminoids and essential oil of turmeric than normal curcumin. Significant level of curcumin was retained even at 8 hours post administration and found to be non-toxic and safe [29-31]. Studies has been conducted on curcuminoid–essential oil complex showing therapeutic efficacy in numerous diseases like major depressive disorders, alzheimer’s disease, rheumatoid arthritis and has potential for widespread application and radioprotective effect in different kinds of cancer [32-38].

Diclofenac is a well-known NSAID with anti-inflammatory, analgesic and antipyretic properties, comparable or superior to other NSAIDs [39]. Curcumin has been extensively used in traditional medicine in India, particularly as an anti-inflammatory agent [40]. The objective of this study was to compare efficacy and safety of curcumin versus diclofenac in patients with knee OA. We also investigated the anti-flatulent and weight lowering effect of curcumin among patients with knee OA and compared it with diclofenac.

Methods

Ethics & participant confidentiality:

This study was conducted according to the Declaration of Helsinki, the ICH-GCP E6 (R1, R2), and ICMR-National Ethical Guidelines for Biomedical and Health Research 2006. The Ethics committee approval was obtained from Krishna Institute of medical sciences, Karad, Maharashtra, India before initiating study (Reference No: kimsu/PhD/11/2010). Prior to any study-related screening procedures, written informed consent was obtained by the principal investigator from each patient before enrolling in the study. The study was registered with the ISRCTN registry (ISRCTN10074826). The participant was only identified by the participant study number and all documents in the study were identified using the initials and participant study number. The patient identification information was handled only by a delegated staff and stored in locked cabinets accessible only to study staff.

Trial Design & Participant selection

This trial was designed as a prospective, randomized, open label, active controlled parallel group study. The randomization sequence was generated by an independent statistician using the Graphpad software with an allocation ratio 1:1. Allocation was concealed using sequentially numbered identical boxes. Patients fulfilling the eligibility criteria were enrolled and randomized to receive either the intervention or the comparator. The pharmacist designated by the investigator dispensed the investigational products.

This study was conducted at City Care Accident Hospital, Parli Vaijnath, Maharashtra, India. All patients (aged 38-65 years) suffering from symptomatic knee OA for at least 3 months with no joint deformities and requiring treatment with anti-inflammatory drugs were screened for eligibility after taking written informed consent. Patient meeting the American College of Rheumatology (ACR) criteria for knee OA (confirmed by X-ray) and having moderate pain (visual analogue scale score 4 or greater) in the knee joint were included in the study. Patients taking analgesics were given a washout period of at least 3-7 days (or longer depending on the pharmacokinetic of drug) before starting the study intervention. The dietary intake of curcumin was restricted. The patients were advised not to change their routine dietary habits and physical activity which can lead to weight gain or loss. Patients with flatulence episodes ranging from 5 to 20 per day were enrolled to evaluate anti-flatulent effect.

Patients who received corticosteroid injection within last 4 weeks; history of active peptic ulcer, gastric ulceration, stomach pain or GI bleeding or bleeding disorders; had secondary osteoarthritis due to syphilis, metabolic bone disorder, acute trauma; patients who required prescription anticoagulants, hydantoin, lithium, steroids, methotrexate and colchicines or concurrent pain relieving medication such as tranquilizers, hypnotics, excessive alcohol or any other drug affecting the evaluation of analgesic action, or patient having known hypersensitivity to diclofenac sodium and turmeric were excluded from the study. Patients with medical history of significant impairment of hepatic or renal functions, cardiac insufficiency, and bronchitis were also excluded. Pregnant and lactating women and women of child bearing age not using or not willing to use contraceptive were not included.

Interventions & Dosage

The intervention used in this clinical trial was curcumin (BCM-95®) 500 mg zero size hard gelatin capsule (Curcugreen® from Arjuna Natural Ltd, India). Each capsule contained curcuminoids and essential oil of turmeric complex (curcumin, demethoxycurcumin, bisdemethoxycurcumin and volatile oils from turmeric rhizome) total not less than 95%, curcuminoids not less than 88% and curcumin not less than 68%.

The comparator used was diclofenac 50 mg uncoated tablet (Diclofenac) manufactured by Lupin Pharmaceuticals)

The dosage was curcumin 500 mg three times daily or diclofenac 50 mg two times daily for 28 days. Patients were also provided with rescue medications paracetamol 500 mg tablet (Calpol - Manufactured by GlaxoSmithKline Pharmaceuticals Ltd) and ranitidine 150 mg tab (Rantac - Manufactured by J B Chemicals & Pharma Ltd).

Assessments

Patients were evaluated at baseline (day 0), week 2 (day 14) and week 4 (day 28). Improvement in the pain intensity on visual analogue scale (VAS) at each evaluation visits was considered as the primary outcome. The visual analog scale is a valid assessment tool. It brought greater sensitivity and greater statistical power to data collection and analysis by allowing a broader range of responses. It removed bias that was introduced by examiner questioning, and it allowed graphic temporal comparisons [41]. Secondary outcomes were: improvement in the pain intensity on Knee injury and osteoarthritis outcome score (KOOS) subscale, anti-flatulent effect, weight lowering effect, patient's global assessment for over all symptom relief and physician's global evaluation of treatment and anti-ulcer effect. The KOOS is a valid, reliable and responsive self-administered instrument used for evaluating short term and long-term follow-up of knee injury including osteoarthritis [42]. The patients were asked to record the number of episodes of flatulence over past 24 hours before administering medication and on day 7. The anti-flatulent effect was assessed by comparing the mean fall in number of episodes of flatulence. The weight lowering effect was assessed by comparing the mean fall in weight on day 28 with baseline weight. Anti-ulcer effect was assessed by recording the number of patients consumed H2 blocker tablets during study period. Requirement of rescue medication throughout the study period was recorded in case report form. Compliance to study medications was checked in each visit. Adverse events (AE) reported or observed during study period were recorded in case report form at each study visit.

Statistical Analysis:

Sample size calculation was performed using software PS Power and Sample Size Calculations (version no.3). Based on a power of 80% and a Type I error rate of $\alpha = 0.05$ (2-tailed), a sample size of 65 participants per group was required to detect an estimated difference of 1.24 in the mean pain scores between the treatment arms with standard deviation (SD) of 2.5. Assuming dropout rate of 5%, a total sample size of 69 participants per treatment group was considered sufficient in this study. All statistical analyses were performed on intention-to-treat basis with last observation carried forward method. Normality was tested for the data using Shapiro-wilk test. Paired t-test or unpaired t-test, was used for

normally distributed data and Wilcoxon-signed rank test or Mann Whitney test was used for the non-normally distributed data to compare the continuous data within groups and between groups respectively and Chi-square or Fishers exact test was used to compare the categorical data of study groups. For comparing VAS score between the groups independent t-test was used as the scores were not on one of the extremes. A comparison of two treatments (curcumin & diclofenac) with the perfect analgesic was also done and the correlation coefficient was determined. P-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS version 24.

Results

Patient disposition and characteristics:

160 patients were screened and 149 patients were enrolled in the study. A total of 139 patients (curcumin : 70; diclofenac : 69) completed the study and were subjected to statistical analysis. Drop-outs included four patients from curcumin group and six from diclofenac group [Figure 1]. Both treatment groups were comparable in terms of demographic characteristics i.e. age, weight, height and gender. Clinical assessment of pain on VAS and KOOS subscale at the start of the trial (baseline) was similar between both treatment groups. Overall, demographic and baseline characteristics between both the treatment group was similar before the start of study treatment [Table 1].

Table 1: Demographic and baseline characteristics in patients with knee OA

Patient characteristic	Curcumin	Diclofenac
	(N = 70)	(N = 69)
Age (years)	53.09 ± 4.17	52.14 ± 3.76
Gender (M/F)	M = 45; F = 25	M = 48; F = 21
Weight (Kg)	61.37 ± 5.46	63.51 ± 5.19
Duration of knee osteoarthritis (months)	7.40 ± 3.53	7.45 ± 3.15
Baseline pain intensity on Visual analogue scale (VAS)	7.84 ± 0.63	7.81 ± 0.73

Values are expressed in Mean ± SD except for gender variable (presented as number of patients in each category). Visual analogue scale (0 to 10 where 0 indicates “No pain” and 10 indicates “Worst possible pain”

Efficacy results:

Both treatment groups showed significant reduction in VAS scores on day 28 from their base lines ($p < 0.01$). However, there was no significant difference in reduction in pain intensity between the groups. The number of patients having more than 50% improvement in VAS score were 66 in curcumin and 67 in diclofenac group. This difference was not statistically significant ($p = 0.68$) [Table 2].

Table 2: Comparison of pain as determined by VAS in patients with knee OA

Visit	Curcumin (N = 70)	Diclofenac (N = 69)	p value
Baseline	7.84 ± 0.63	7.81 ± 0.73	0.79t
Day 14	4.69 ± 0.79	4.58 ± 0.60	0.38t
Day 28	2.20 ± 0.81	2.20 ± 0.61	0.98t
Change at day 14	-3.16 ± 0.79	-3.23 ± 0.91	0.61t
Change at day 28	-5.93 ± 0.99	-5.61 ± 0.88	0.82t
p value	p < 0.01wc	p < 0.01wc	
VAS Reduction % ≤ 50	N = 4	N = 2	p = 0.68f
VAS Reduction % > 50	N = 66	N = 67	

Values are expressed in Mean ± SD. wc = Wilcoxon signed rank test, t = Independent T-test. f = Fisher Exact test, N = number of patients in each group. p < 0.05 considered as statistically significant difference. Visual analogue scale (0 to 10 where 0 indicates “No pain” and 10 indicates “Worst possible pain”). Change in mean score at day 14 and day 28 is calculated from baseline VAS score.

In our study, pain relief for diclofenac and curcumin are well below the “perfect analgesic” (slope = 1) and above “no treatment” (slope = 0) graph and the contribution of slope change due to the initial pain score is nil and statistically not significant (p = 0.79) [Figure 2].

Both treatment groups showed continuous improvement in scores in all 5 subscales of KOOS at each treatment visit from baseline and the difference at the end of the study was statistically significant (p < 0.01). Patients receiving curcumin showed similar improvement in KOOS scores in all subscales as compared to diclofenac at the end of study, as difference was not statistically significant [Table 3].

Table 3: Assessment of KOOS subscale in patients with knee OA

KOOS subscale*	Visit	Curcumin (N = 70)	Diclofenac (N = 69)	p valuem
Pain	Baseline	53.29 ± 5.70	53.15 ± 4.24	0.89
	Day 14	72.70 ± 4.89	73.69 ± 3.97	0.56
	Day 28	88.77 ± 5.62	90.38 ± 3.61	0.07
	Change at day 14	19.40 ± 2.89	20.55 ± 3.22	0.25
	Change at day 28	35.48 ± 4.07	37.23 ± 2.05	0.15
	p valuewc	< 0.01	< 0.01	
Symptoms	Baseline	55.77 ± 6.00	55.87 ± 5.97	0.66
	Day 14	61.58 ± 5.65	61.93 ± 5.47	0.88
	Day 28	67.95 ± 5.86	69.13 ± 5.50	0.82
	Change at day 14	5.82 ± 3.81	6.06 ± 3.36	0.83
	Change at day 28	12.19 ± 5.28	13.26 ± 4.44	0.94
	p valuewc	< 0.01	< 0.01	
Function in daily living	Baseline	58.45 ± 4.96	61.26 ± 5.24	0.21
	Day 14	77.67 ± 5.90	80.54 ± 6.10	0.05
	Day 28	94.58 ± 6.58	96.23 ± 2.71	0.49
	Change at day 14	19.22 ± 2.99	19.275 ± 2.38	0.55
	Change at day 28	36.13 ± 3.61	34.971 ± 5.05	0.34
	p valuewc	< 0.01	< 0.01	
Function in sport and recreation	Baseline	44.86 ± 8.47	48.55 ± 7.58	< 0.01
	Day 14	68.43 ± 5.81	71.88 ± 5.01	< 0.01
	Day 28	89.14 ± 6.43	91.88 ± 4.38	< 0.01
	Change at day 14	23.57 ± 4.27	23.33 ± 4.34	0.63
	Change at day 28	44.28 ± 6.44	43.33 ± 6.22	0.15
	p valuewc	< 0.01	< 0.01	

Quality of life	Baseline	42.95 ± 5.31	41.91 ± 6.88	0.06
	Day 14	59.64 ± 6.08	59.15 ± 7.73	0.58
	Day 28	73.57 ± 7.46	72.26 ± 8.61	0.64
	Change at day 14	16.70 ± 8.22	17.23 ± 8.44	0.62
	Change at day 28	30.63 ± 10.16	30.35 ± 10.02	0.60
	p value ^{wc}	< 0.01	< 0.01	

*Higher score indicated better improvement.

Values are expressed in Mean ± SD. wc=Wilcoxon signed rank test (within the group), m=Mann-Whitney test (between the group), N = number of patients in each group. p < 0.05 considered as statistical significant difference. KOOS scale (0 to 100 where 0 indicates “Extreme Problem” and 100 indicate “No Problem”). Change in mean score at day 14 and day 28 is calculated from baseline KOOS score for each subscale.

The number of episodes of flatulence between both the treatment groups at baseline were comparable. Patients who were treated with curcumin experienced significantly greater reduction in number of episodes of flatulence from baseline compared to patients treated with diclofenac (p < 0.01) (Table 4). The patients who were treated with curcumin experienced significantly greater reduction in body weight from baseline (p < 0.01) compared to patient treated with diclofenac (p = 0.22). The difference in anti-flatulent effect and weight loss in patients between the groups were statistically significant (p < 0.01) [Table 4].

Table 4: Comparison of anti-flatulent and weight lowering activity

Visit	Curcumin (N = 70)	Diclofenac (N= 69)	p value ^m
Anti-flatulent activity	N = 25	N = 25	-
At baseline	12.04 ± 2.17	11.32 ± 2.21	0.29
Day 7	2.32 ± 1.11	10.8 ± 2.1	< 0.01
Weight lowering activity	N = 70	N = 69	-
At baseline	61.37 ± 5.46	63.51 ± 5.19	0.02
Day 28	60.36 ± 5.19	63.39 ± 5.21	< 0.01
Change from baseline (at day 28)	1.01 ± 0.81	0.12 ± 0.70	< 0.01
p-value of weight lowering activity^{wc}	p < 0.01	p = 0.22	

Values are expressed in Mean \pm SD. Data were analyzed by wc = Wilcoxon signed rank test and m = Mann-Whitney test. N= number of patients in each group. p < 0.05 considered as statistical significant difference.

Global assessments of treatment by patient and physician based on overall efficacy and safety was similar towards both the treatment (curcumin and diclofenac) [Table 5]. The need for rescue medication (paracetamol) was numerically higher in curcumin group (15 patients; 21 %) compared to diclofenac group (12 patients; 17 %), however, the difference was not statistically significant (p = 0.67). None of the patients required H2 Blockers in curcumin group when compared to diclofenac group (0 % vs. 28 %, respectively; p < 0.01), this indicates anti-ulcer effect of curcumin.

Table 5: Global assessment by Physicians and Patients after study drug treatment

Global Assessment Rating	Physician's global assessment	Patient's global assessment		
	Curcumin (N=70) n (%)	Diclofenac (N=69) n (%)	Curcumin (N=70) n (%)	Diclofenac (N=69) n (%)
Excellent	10 (14)	10 (14)	11 (16)	12 (17)
Good	56 (80)	54 (78)	54 (77)	52 (75)
Fair	1 (1)	1 (1)	2 (3)	1 (1)
Poor	3 (4)	4 (6)	3 (4)	4 (6)
p- value	> 0.05	> 0.05		

Values are expressed as absolute number of patients (percentage) in each category. Data were analyzed by Chi-Square test. N = Total number of patients in each treatment group. p < 0.05 considered as statistical significant difference. n = number of patients in each category.

Safety variables

Overall, 13% of patients receiving curcumin and 38 % of patients receiving diclofenac reported at least one adverse event and this difference was statistically significant (p < 0.01). All reported adverse events were mild and transient. The most common adverse effects were nausea, diarrhea, abdominal pain/acidity and flatulence. Incidence of each adverse effect was significantly less in the curcumin group compared to the diclofenac group. Relative risk of all adverse events except nausea and diarrhea in curcumin group was reduced to less than 10% which was clinically significant. Relative risk of nausea and diarrhea was only reduced to 80% and 60% respectively. Relative risk was calculated by comparing the curcumin group and diclofenac group [Table 6]. Analysis of laboratory values did not reveal any significant adverse outcomes [Table 7].

Table 6: Summary of adverse reactions in each treatment group

Adverse reactions	Curcumina (N=70) n (%)	Diclofenacb (N=69) n (%)	RR	RRLB	RRUB	NNT
Total number of patients experienced AEs*	9 (13%)	26 (38%)				
Dyspepsia	0	6 (8.7%)	0.08**	0	1.3	12
Nausea	6 (9%)	7 (10.14%)	0.8	0.3	2.4	64
Vomiting	0	7(10.14%)	0.07**	0	1.1	10
Diarrhoea	5 (7%)	8 (11.6%)	0.6	0.2	1.8	23
Constipation	0	6 (8.7%)	0.08**	0	1.3	12
Abdominal pain /acidity	0	19 (27.53%)	0.03**	0	0.4***	4
Flatulence	0	9 (13.04%)	0.05**	0	0.9***	8
Upper respiratory Tract Infection	0	5 (7.25%)	0.09**	0	1.6	14

*p < 0.01 for Curcumin vs. Diclofenac

Values are expressed as absolute number of patients (percentage) in each category.

N = Total number of patients in each treatment group. n = number of patients in each category. a= Treatment group, b = Control Group, RR: Relative Risk, RRLB : Relative risk Lower boundary, RRUB: Relative risk upper boundary, NNT: Number Needed to Treat

** Clinically Significant AE (RR < 0.5),

*** Statistically significant AE (95% CI does not include1)

Table 7: Laboratory-based evaluations of safety

Laboratory Parameter	Curcumin (N=70)	Diclofenac (N=69)	p-value#				
	Before treatment	After treatment	p-value*	Before treatment	After treatment	p-value*	
Haemoglobin (gm/dl)	14.67 ± 0.37	14.67 ± 0.36	0.29	14.67±0.35	14.74 ± 0.37	0.03	0.37
R.B.C. Count (million/cu.mm)	5.01 ± 0.32	5.06 ± 0.31	0.06	5.06±0.34	5.12 ± 0.36	0.02	0.29
Total WBC Count (/cmm)	7577.14 ± 1723.26	7841.43 ± 1512.60	0.14	7633.33 ± 1841.09	7682.61 ± 1603.76	0.70	0.59
Red Cell Absolute Values							
Packed Cell Volume %	44.79 ± 2.72	45.06 ± 2.51	0.51	44.86 ± 2.88	45.38 ± 2.77	<0.01	0.40
Mean Corpuscular Volume (cubic micron)	80.56 ± 3.13	80.91 ± 2.91	0.14	81.20 ± 3.47	81.50 ± 3.45	0.06	0.46
Mean Corpuscular Hemoglobin (picogram)	29.02 ± 1.34	29.23 ± 1.23	0.06	29.17 ± 1.52	29.29 ± 1.39	0.17	0.82
Mean corpuscular Hb Con.(g/dl)	33.62 ± 0.89	33.66 ± 0.82	0.69	33.68 ± 0.97	33.74 ± 0.97	0.15	0.42
Differential Count							
Neutrophils %	48.67 ± 4.84	49.08 ± 4.72	0.58	48.85 ± 4.45	49.81 ± 4.68	0.03	0.43
Lymphocytes %	28.58 ± 5.24	28.99 ± 5.09	0.50	28.30 ± 4.74	29.19 ± 4.86	0.06	0.80
Eosinophil %	3.57 ± 0.58	3.39 ± 0.55	0.10	3.61 ± 0.57	3.52 ± 0.58	0.48	0.15
Monocytes %	3.96 ± 0.91	4.06 ± 0.80	0.50	4.03 ± 0.74	4.09 ± 0.80	0.70	0.81
Basophils %	0	0	-	0	0	-	-
Peripheral smear examination							
Platelets (/cmm)	269757.1 ± 55561.02	268514.3 ± 57049.62	0.72	286942 ± 49707.34	279956.5 ± 60135.25	0.37	0.30

ESR (/hr)	13.06 ± 2.90	12.86 ± 2.59	0.59	12.88 ± 2.83	12.93 ± 2.82	0.78	0.82
Biochemistry							
Serum Creatinine (mg/dl)	0.88 ± 0.27	0.91 ± 0.26	0.36	0.93 ± 0.30	0.96 ± 0.30	0.05	0.41
SGPT IU/L	22.71 ± 5.26	23.6 ± 4.75	0.42	25 ± 4.81	23.71 ± 5.45	0.13	0.98
SGOT IU/L	23.6 ± 4.17	23.79 ± 3.51	0.76t	25.12 ± 4.19	24.15 ± 4.04	0.12	0.71

Data expressed as Mean ± SD.

*p value (within the group) by Wilcoxon Signed Rank test

#p value (between the groups) (after treatment) by Mann Whitney test

t=Paired t-test

Discussion

This study demonstrated that curcumin has a similar pain relief effect on patients with knee OA compared to diclofenac. For KOOS subscales of symptoms, functions in daily living, functions in sports and recreation and knee related quality of life, curcumin showed comparable improvement to diclofenac. Overall, curcumin showed similar improvement in pain, stiffness, and symptoms, functions of daily living, sports or recreational activities and quality of life that have been attributed to its ability to inhibit COX-2, which results in the suppression of prostaglandin synthesis. Furthermore, curcumin has been shown to suppress several pro-inflammatory cytokines and mediators of their release such as tumour necrosis factor (TNF-alpha), interleukin (IL)-1, IL-8 and nitric oxides synthase (NOS).

Poor bioavailability is the major drawback of free curcumin. In the meta-analysis of data from clinical trials with curcumin supplementation, it was reported that reduction in pain severity did not reach statistical significance with respect to treatment duration. The results of subgroup analysis confirmed that bioavailable optimized preparations increased the analgesic effect of curcuminoids [43]. Beneficial results obtained in our study are possibly due to the combination of curcuminoids and essential oil of turmeric present in curcumin capsules which increased the bioavailability.

Permeability of curcumin is increased by turmerones which acts by inhibiting p-glycoprotein [44]. Inflammation associated colon carcinogenesis was prevented by the synergistic combination of curcumin and turmerones [45]. The superiority of curcuminoids with essential oil of turmeric with turmerones was reported in many research papers. Anti-inflammatory and synergic potential of curcuminoid essential oil of turmeric complex showed superior protection from dextran sodium sulfate (DSS)-induced colitis than curcumin alone [46]. A study done on same composition (BCM-95®) with

Boswellia serrata reduced pain-related symptoms in patients with osteoarthritis and was effective in treating knee osteoarthritis than celecoxib (NSAID) [47-48]. Research on the same composition showed significantly better results in active rheumatoid arthritis when compared to diclofenac sodium [35].

Weight loss can be considered beneficial in the treatment for knee OA, it has been reported that weight reduction of 10% results in improved function by 28% in patients with knee OA [49]. In the study, significant body weight reduction from baseline was shown in the patients treated with curcumin (1.65 % weight reduction in curcumin group and 0.19% weight reduction in diclofenac group). Similar effect from curcumin has been reported by Asma Ejaz et al [26]. Curcumin suppresses angiogenesis in adipose tissue together with its effect on lipid metabolism in adipocytes may contribute to lower body fat and body weight gain. Curcumin induces apoptosis by suppressing the differentiation of preadipocytes to adipocytes. Adipokine- induced angiogenesis of human endothelial cells is also inhibited by suppressing the expression of vascular endothelial growth factor- α . Curcumin increase the activation of AMP-activated protein kinase (AMPK) in adipocytes. Phosphorylation of the α -subunit of AMPK and suppressing the expression of aminocyclopropane carboxylic acid activates AMPK in adipocytes. Beneficial effect of curcumin in obesity is obtained by increasing the fatty acid oxidation in adipocytes and thus produce beneficial effects in obesity [50]. Hence, the weight reduction caused by curcumin can be beneficial in the treatment for knee osteoarthritis especially in obese patients.

In our study, the patients treated with curcumin experienced fewer GI related side effects compared with patients treated with diclofenac. Fewer GI related side effects may be due to potent anti-ulcer action or protection against gastric mucosal injury by curcumin. The mechanism of anti-ulcer activity of curcumin has also been well understood. Neutrophils, lymphocytes and monocytes/ macrophages at the inflammatory site in stomach is primarily activated by the local inflammatory cytokine IL6. This initiates different oxidative bursts of toxic metabolites and lysosomal enzymes which are responsible for local tissue damage in peptic ulcer disease. The severity and duration of inflammation, particularly in its acute phase, can be predicted more precisely by the proinflammatory IL6 than TNF α . Curcumin exhibits its anti-ulcer activity by inhibiting IL6 secretion and also by affecting oxidative stress by its total antioxidant capacity [51]. According to another study, curcumin protects gastric damage by efficient removal of H₂O₂ and H₂O₂-derived SOH by preventing peroxidase inactivation by NSAID [22]. There is also evidence of possible involvement of glutathione in the curcumin-mediated gastroprotection [21].

Patients treated with curcumin experienced significantly greater reduction in the number of episodes of flatulence from baseline compared to patient treated with diclofenac. The effect of curcumin on intestinal gas formation has been demonstrated in vitro and in vivo experiments [52]. Thus, the reduction in number of episodes of flatulence may be associated with anti-flatulent effect of curcumin.

The visual analogue scale (VAS) is most commonly used to assess pain intensity. It is reliable, valid, sensitive to change, and easy to administer for measuring pain severity [53]. In clinical trials measuring pain relief is preferred to pain severity as it is not dependent on initial pain severity, equality of the change in different parts of scale and variation in the patient's expression. The effectiveness of any particular

treatment can be accurately measured by the pain relief which is the change between pain score after treatment and initial pain score [54]. As long as all data points are in between the 'no treatment' and 'perfect analgesic', a steeper line is directly proportional to better treatment efficacy. The effect of the slope variation and its effect on the mis-interpretation of the results are already reported [55]. A significant difference in the initial pain score can misguide the interpretation of the result. In our study, there is no chance for mis-interpretation of the results. Pain relief for diclofenac and curcumin are well below the “perfect analgesic” (slope =1) and above “no treatment” (slope=0) graph. The contribution of slope change due to the initial pain score is nil and statistically not significant ($p = 0.79$). The slope variation obtained in the study results indicates the treatment effect of both the groups.

In estimating pain relief, it may not be appropriate simply to compare only the scores before and after treatment, because the magnitude of this difference is limited by the placement of the initial mark [56]. Quantal method measures pain relief based on proportion of patients achieving defined degree of pain relief. Such a method is not suitable for testing drugs which produce moderate pain relief and a more sensitive method is required. Assessment of pain severity based on the percentage change from the initial level and a minimum cut off of 50% in pain relief greatly improves the sensitivity of pain measurement scales [55]. In our study, both curcumin and diclofenac group had almost equal proportion ($n = 66$ and $n = 67$ respectively) of patients who had more than 50% reduction in VAS scores from baseline levels with p value 0.68

Significantly fewer patients in the curcumin group reported adverse events compared with the diclofenac group. None of the patients in the curcumin group required H2 blockers. The favorable safety profile in curcumin group was observed due to its gastro-protective and anti-ulcer effect, which may be an alternative to the GI side effect of NSAIDs. Overall assessment of efficacy and safety of treatment by patient and physician was similar for both groups.

Limitations of the study

Open label study design without a placebo controlled group was one of the limitations of the study. The treatment duration of 28 days may not be sufficient to assess long term efficacy and prevention of progression of disease as evidenced by structural damage in OA patients. Hence a long term study is warranted with curcumin in OA patients. Though validated scales were used, the efficacy of curcumin in the treatment of OA was not based on objective measures but on subjective measurement of pain which is another limitation of the study.

Conclusion

Our findings suggest that the curcumin three times daily has similar efficacy, but better safety profile to diclofenac two times daily among patients with knee OA. Our study results suggest that the curcumin with increased bioavailability (BCM-95®) can be a good alternative treatment option in the patients of knee OA, who are intolerant to the side effects of NSAIDs.

List Of Abbreviations

ACR American College of Rheumatology

AE Adverse events

AMPK AMP-activated protein kinase

COX Cyclo-oxygenase

GI Gastrointestinal

IL Interleukin

KOOS Knee injury and osteoarthritis outcome score

NOS Nitric oxides synthase

NSAIDs Non-steroidal anti-inflammatory drugs

OA Osteoarthritis

TNF α . Tumour necrosis factor-alpha

VAS Visual analog score

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and got approved by Institutional Ethics Committee, Krishna Institute of Medical sciences, Karad, Maharashtra, India before initiating study (Reference No: kimsu/PhD/11/2010). Prior to any study-related screening procedures, written informed consent was obtained by the principal investigator from each patient before enrolling in the study.

Consent for publication

Not Applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

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Author's contribution

DS made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data.

CK involved in drafting the manuscript, revising it critically for important intellectual content and gave final approval of the version to be published.

PG involved in drafting the manuscript, revising it critically for important intellectual content.

SK agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors read and approved the final manuscript.

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Figures

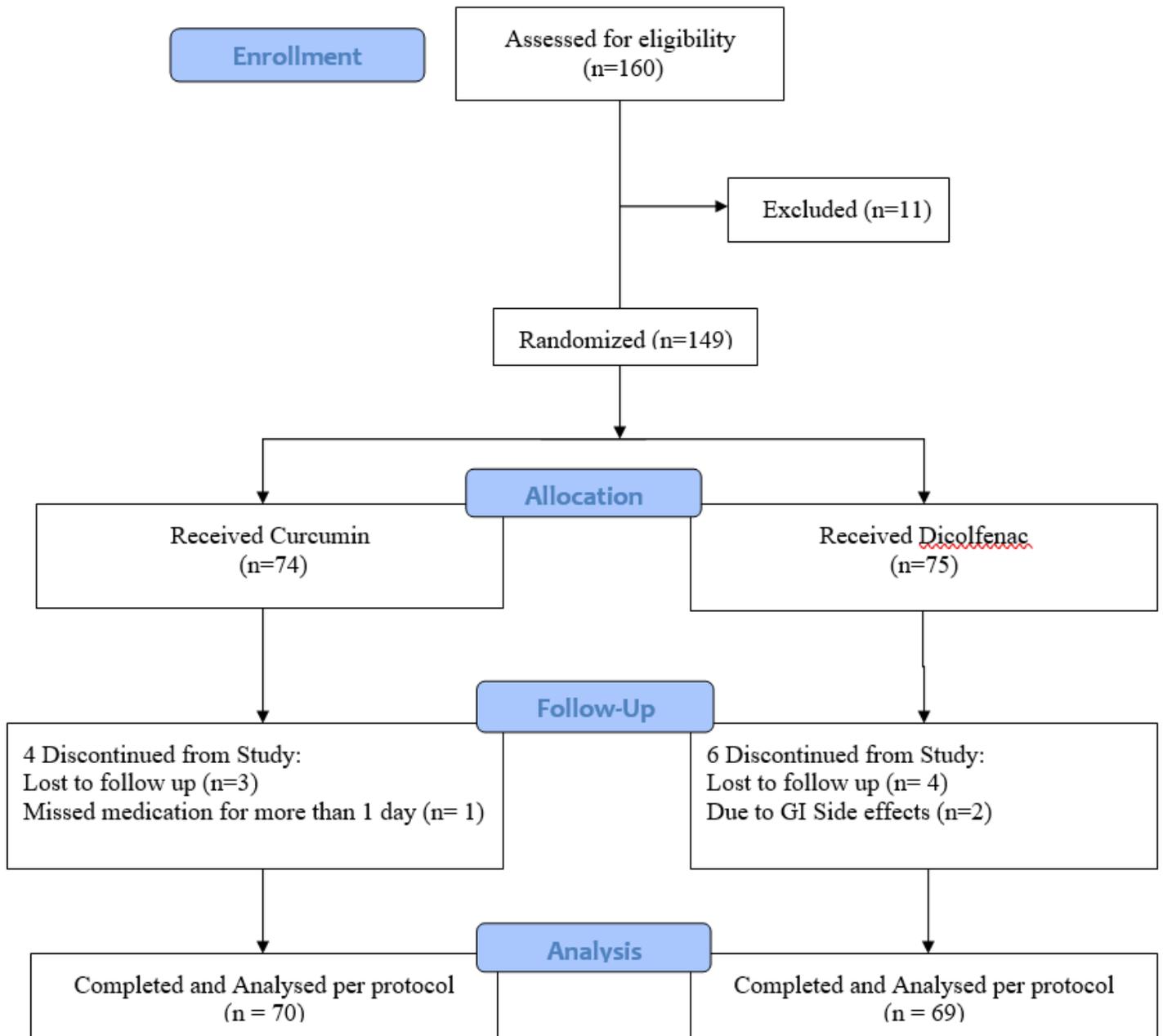


Figure 1

Participants flow diagram

VAS Score

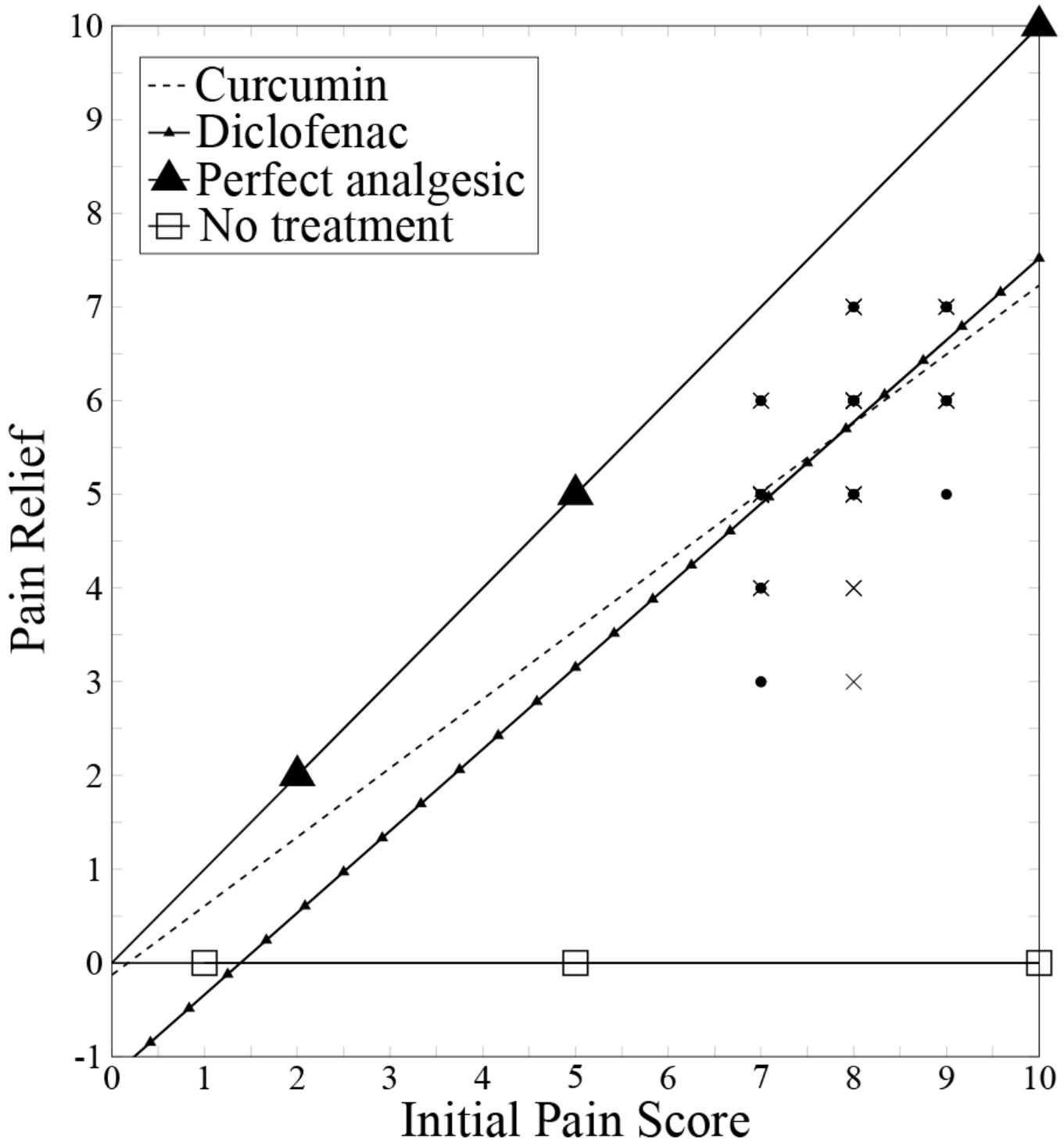


Figure 2

Visual Analogue Scale (VAS plot): Relationship between pain relief measured by subtraction and initial pain score for curcumin and diclofenac drugs. Correlation Coefficient - Curcumin: 0.5; Diclofenac: 0.73