

Dual Release Paracetamol in Osteoarthritis of Knee: A Randomized Controlled Clinical Trial

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ABSTRACT

Background: Paracetamol is recommended as first line agent for pain management in osteoarthritis (OA) by various guidelines. The main problem associated with management of osteoarthritis is long term patient compliance to paracetamol due to its frequent dosing.

Objective: To evaluate the efficacy and safety of Paracetamol 650 mg dual release tablet twice daily (PCM 650 dual release) compared to paracetamol 500mg immediate release tablet thrice daily (PCM 500 IR) in the treatment of Knee OA.

Materials and Methods: In this randomized, open label, parallel, active controlled clinical study, 250 patients of OA knee meeting inclusion criteria were randomized to receive either PCM 650 dual release two times daily or PCM 500 IR three times daily for 6 weeks. Patients were assessed at baseline, 2, 4 and 6 weeks. Primary efficacy measures were severity of pain (Visual Analogue Scale) and Knee injury and osteoarthritis outcome score (KOOS) subscale for pain at week 2, 4 and 6. Other KOOS subscales (symptoms other than pain, function in daily living, function in

sport and recreation, quality of life) and patient's and physicians global assessment of therapy were included as secondary endpoints.

Results: Both treatment groups showed improvement in primary endpoints at each evaluation visit. Patients receiving PCM 650 dual release showed significant improvement of pain in both primary endpoints at each study visit compared to patients receiving PCM 500 IR ($p < 0.001$). PCM 650 dual release was significantly superior to PCM 500 IR for improvement in all KOOS subscales at each study visit ($p < 0.01$).

Less number of patients required additional rescue analgesics in PCM 650 dual release group (16% patients vs 26%, PCM 500 IR; $p > 0.05$). Adverse effects were significantly less in PCM 650 dual release group (6% vs. 14% in PCM 500 IR; $p < 0.05$). Patient's and physician's global assessment of therapy favoured PCM 650 dual release than PCM 500 IR ($p < 0.001$).

Conclusion: Patients with symptomatic OA of the knee showed a greater improvement in pain and functional capacity with PCM 650 dual release than PCM 500 IR with better tolerability.

Keywords: Acetaminophen, Extended release, Immediate release, KOOS, OA knee, VAS

INTRODUCTION

Osteoarthritis (OA) is the common form of inflammatory joint disease or arthritis [1] and it is the most important cause of disability [2]. It leads to significant health and economic burden on the patients. OA is the second most common rheumatological problem and is most frequent joint disease with prevalence of 22% to 39% in India [2].

Paracetamol is one of the most widely used oral analgesics, with a large clinical experience clearly establishing it as the standard analgesic for mild to moderate pain states. Guidelines of Royal College of Physician for OA has suggested that Paracetamol should be considered ahead of COX 2 inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids [3]. Further, it has been stated that paracetamol is preferred choice for the long term treatment of OA and NSAIDs should be prescribed only in the patients not responding to Paracetamol. Paracetamol is also recommended as a first line agent for symptomatic treatment of osteoarthritis (OA) by European league against Rheumatism [4], and American College of Rheumatology [5] owing to its good risk benefit ratio.

To alleviate continuous pain in patients with Knee OA, medications are effective when given regularly. However one of the problems associated with management of OA is compliance to long term use of analgesics. It has been demonstrated that compliance is inversely related to the daily dose frequency. Frequent dosing of paracetamol is necessary because of its short half-life and it can sometimes be perceived as being ineffective when insufficient doses or irregular

dosing schedules are used. It is possible that three to four times daily dosing of paracetamol tablet may lead to the inconvenience and contribute to the failure of individuals to take the recommended dose. As per an observational study by National institute on aging, majority of patients suffering from pain due to OA taking PCM used less than the recommended dose [6]. Altman et al., [7] suggested that OA patients are not always compliant with paracetamol dosed three to four times daily which may lead to an inadequate therapeutic response. Delayed/extended release paracetamol tablets allow reduction in frequency of dosing which may improve compliance and convenience [8].

A novel dual release (immediate release + sustained release) formulation of paracetamol has become available in the market. Immediate release of drug will attain the sufficient therapeutic level immediately to achieve the effective analgesia while sustained release of drug over the time will maintain the analgesia for extended period. With dual phase release formulation, same onset with prolonged duration of analgesia compared to immediate release formulations could be achieved which eliminates the need of repeat dosing.

This study was designed to evaluate and compare the efficacy and safety of Paracetamol 650 mg dual release (325 mg IR + 325 mg ER) tablet twice daily and paracetamol 500 mg immediate release tablet three times daily in the treatment of OA of the knee.

MATERIALS AND METHODS

This prospective, randomised, open label, parallel group, active controlled study was conducted at six study centres in India.

Six study centres are-

1. Saptagiri Institute of Medical Science and Research Centre, Bangalore, India.
2. Sri Ramchandra Medical College and Research Institute, Ramchandra Nagar, Porur, Chennai, India.
3. Satellite Orthopaedic Hospital, 302, Vraj Complex, Opp Dhananjay Tower, 100ft Ring Road, Satellite, Ahmedabad, India.
4. St. John's Medical College & Hospital, Sarjapur Road, Bangalore, India.
5. Safdarjung Hospital, New Delhi, India.
6. Siddhi Vinayak Hospital, Kankaria, Maninagar, Ahmedabad, India.

The study protocol was approved by Institutional ethics committees of participating study centres. The study was registered in clinical trial registry India (CTRI) prior to initiation of study (CTRI Reg.No CTRI/2010/091/001178).

The study was conducted in accordance with the good clinical practices (GCP) guidelines as issued by the central drugs standard control organization (CDSCO), Ministry of Health, Government of India and the ethical standards laid down in declaration of Helsinki 1964 and its later amendments; Ethical guidelines for biomedical research on human participants issued by Indian Council of Medical Research (2006), New Delhi.

Patient Population

Patients in the age group of 45 years or older, suffering from symptomatic OA of knee for at least 3 months were screened for eligibility after taking written informed consent. Patient meeting the American College of Rheumatology (ACR) criteria for OA of the knee and having mild to moderate pain (Visual analogue scale score 3 or greater) in disease joint while not taking analgesics were included in the study. Patients taking Paracetamol or NSAIDs were given a washout period of at least 48 hours (or longer depending on the pharmacokinetic of drug) before starting the study drug. Patient who received intraarticular injection of any drug within last 4 week; had history of major trauma or surgery in the study joint in previous 6 months; had acute inflammatory arthritis or pseudogout of the study joint or had radiographic evidence suggestive of other type of arthritis, fibromyalgia or collagen vascular disease; patients who required prescription analgesics, anti-inflammatory agents, myorelaxant drugs, psychotropic agents or any other drug affecting the evaluation of analgesic action, or patient having known hypersensitivity to NSAIDs and or related products were excluded from the study. The patients with medical history of significant impairment of hepatic or renal functions, bronchial asthma, peptic ulceration, bronchitis were also excluded. Pregnant and lactating women and women of child bearing age not practicing or not willing to use contraceptive were not included.

Patients fulfilling the eligibility criteria were enrolled and randomized to receive either Paracetamol 650 mg dual Release Tablet (XYKAA EXTEND 650 mg containing 325 mg IR + 325 mg ER, Manufactured By Troikaa Pharmaceuticals Ltd.) two times daily or Paracetamol 500 mg Tablet (CALPOL 500 mg tablet) three times a day.

Simple randomization sequence distinct for each centre was generated by computerised method before start of the study with equal distribution (allocation ratio 1:1) of the patients in both the treatment groups. Patients were instructed to take the medication orally every 12 hours in PCM 650 dual release group and every 8 hours in PCM 500 IR group for 6 weeks. If patient did not get adequate pain relief even after 30 minutes of taking study medication, patients were allowed to take additional paracetamol 500mg tablet (rescue medication). If the patient required more than 2 tablets of rescue medication per day for 3 or more consecutive days, then he/she were excluded from the study.

Assessments

Patients were evaluated for efficacy at week 2, week 4 and week 6 after start of the study treatment. Primary endpoints were pain intensity on VAS and KOOS subscale assessment for Pain at each evaluation visits. Secondary endpoints were KOOS subscales other than pain (Other symptoms, functions daily living, functions in sports and recreation and knee related quality of life), Patient's global assessment for over all symptom relief and physician's global evaluation of treatment. Requirement of rescue medication throughout the study period was recorded in case report form. Adverse events (AE) reported /observed during study period were recorded in case report form at each study visit.

STATISTICAL ANALYSIS

To detect a clinically significant difference of 1cm in VAS score for severity of pain (with an SD of 2.2 cm) [9] between both the groups and to achieve the power of 80% with a type I error rate of $\alpha=0.05$ (2-tailed), a sample size of at least 103 patients per group was required. Considering dropout rate of approximately 20 %, total sample size required will be 250 patients (125 patients in each group).

After statistical analysis, quantitative data are presented as mean \pm SD for continuous variables or descriptively for categorical variables. Quantitative data of both the treatment groups were analyzed by unpaired t-test or Mann Whitney test based on the distribution of data. Chi-square test or fisher exact test was used to compare the categorical data of both the treatment groups. P value of less than 0.05 was considered as statistically significant difference between both the treatment groups. All statistical analysis was performed using software STATISTICA, Version 11 by StatSoft Inc. (2012)

RESULTS

Out of total 272 patients screened, 250 patients met the inclusion criteria and enrolled in the study. All 250 patients completed the study and were subjected to statistical analysis [Table/Fig-1]. Both treatment groups were comparable in terms of demographic characteristics i.e. age, weight, height and gender [Table/Fig-2]. Clinical assessment of pain on VAS and KOOS subscale at the start of the trial (baseline) was similar between both treatment groups [Table/Fig-3 and 4].

Efficacy Variables

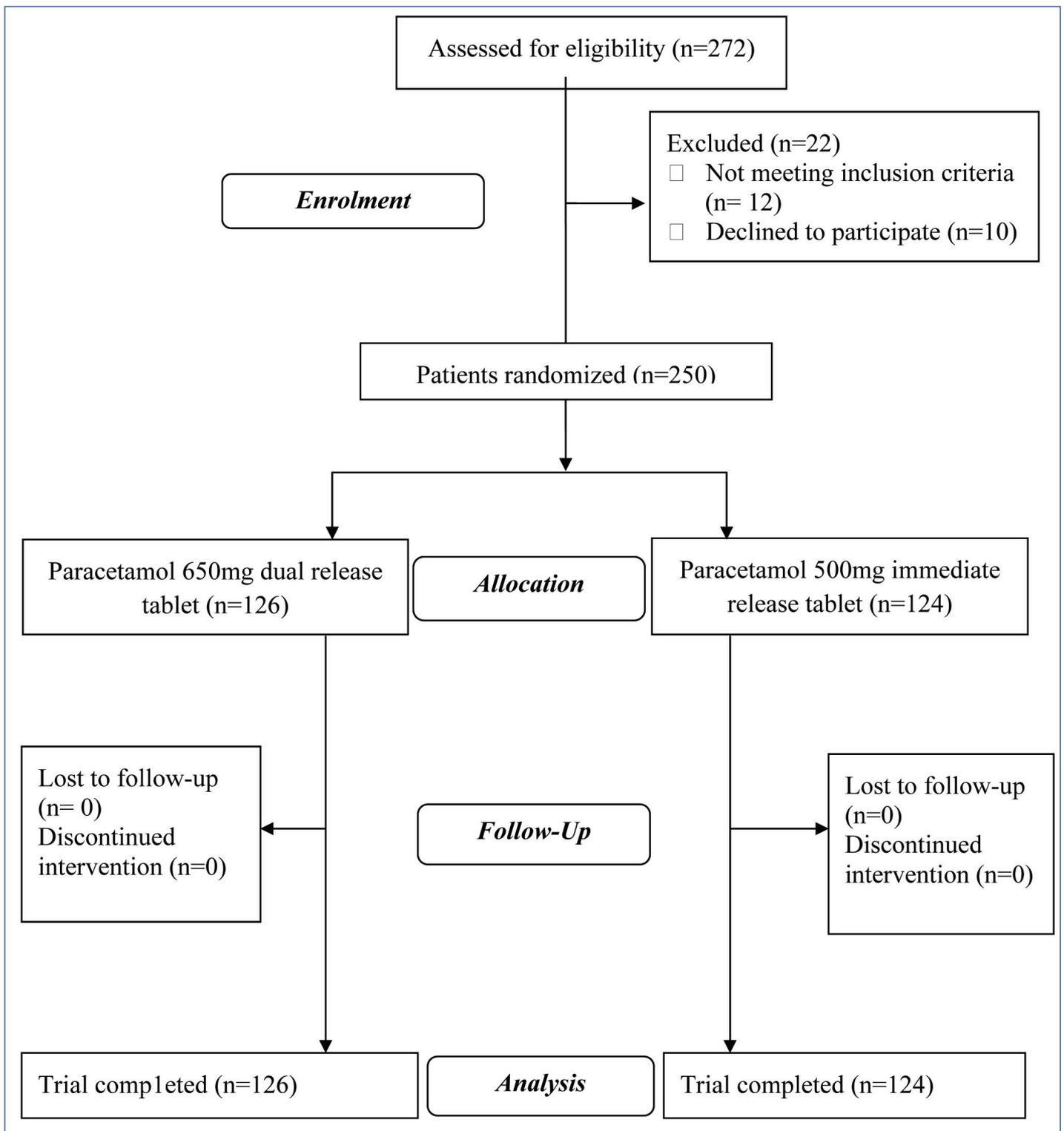
Both treatment groups showed consistent decline in pain intensity on VAS at each study visit from baseline. However, patients treated with PCM 650 dual release experienced significantly greater reduction in pain intensity compared to those treated with PCM 500 IR at each study visit on week 2, 4 and 6 ($p < 0.0001$) [Table/Fig-3].

Both treatment groups showed persistent improvement of score in all 5 subscales of KOOS at each study visit from baseline. However, patients receiving PCM 650 dual release reported significantly greater improvement in KOOS score of all 5 subscales than those receiving PCM 500 IR ($p < 0.01$); difference between both groups were more significant at week 6 compared to week 2 or 4 [Table/Fig-4].

Global assessments of treatment by patient and physician [Table/Fig-5] based on overall efficacy and safety was significantly favourable towards PCM 650 dual release twice daily compared to PCM 500 IR thrice daily ($p < 0.0001$). Although not statistically significant, need for rescue medication was less in PCM 650 dual release group (21 patients; 16%) compared to PCM 500 IR group (32 patients; 26%).

Safety Variables

Overall, 5.5% patients receiving PCM 650 dual release and 13.7% patients receiving PCM 500 IR reported adverse event; all reported



[Table/Fig-1]: Flow chart of patients through trial

adverse events were mild to moderate in severity. No serious adverse event had been reported in either group [Table/Fig-6].

DISCUSSION

Pharmacological treatment of osteoarthritis of knee includes paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and COX 2 inhibitors. However long-term therapy with NSAIDs is associated with dose dependent risk for GI bleeding [10] and dose dependent increased risk of cardiovascular events even with the nonselective NSAIDs [11]. Paracetamol is recommended as a first line agent for symptomatic treatment of osteoarthritis (OA) by various guidelines [5, 12]. Due to short duration of action paracetamol needs to be given 3 to 4 times daily. Frequent dosing schedule is associated with poor compliance [13] in management of diseases

like OA, requiring long term treatment. Sustained release formulation can reduce the frequency of dosing but it will have slower onset of action. A novel dual layered dual release paracetamol formulation (325 mg IR+ 325 mg ER) with reduced frequency of administration may improve compliance. This study was designed to evaluate efficacy and safety of PCM 650 dual release twice daily formulation with immediate release conventional PCM 500 mg tablet given as thrice daily in patient of knee OA.

This study demonstrated that PCM 650 dual release administered twice daily for up to 6 weeks in patients with OA knee was superior to PCM 500 IR administered thrice daily for both primary end points (Pain intensity score on VAS and KOOS subscale score for pain) at each evaluation visits, indicating better pain relief with dual layered dual release PCM 650 mg. This can be attributed to similar onset

Parameters	PCM 650 dual release (n=126)	PCM 500 IR (n=124)	p-value
Age (years)	54.80 ± 8.85	54.80 ± 8.729	1.00*
Weight (kg)	64.52 ± 10.09	63.93 ± 9.15	0.78*
Height (cm)	158.69 ± 8.71	159.89 ± 7.59	0.24 †
Gender (Male/Female)	39/87	28/96	0.13 ‡

[Table/Fig-2]: Demographic characteristics

Values are expressed as Mean ± SD. n = number of patients in each treatment group. Data analyzed by *Mann-Whitney test, † Unpaired T test and ‡ Chi-square test. PCM- Paracetamol; IR- Immediate release

Visits	PCM 650 dual release (n=126)	PCM 500 IR (n=124)	p-value
Baseline	7.43 ± 1.26	7.08 ± 1.29	0.05
Week 2 (Visit 1)	5.43 ± 1.32	6.09 ± 1.36	<0.0001
Week 4 (Visit 2)	3.97 ± 1.41	5.20 ± 1.67	<0.0001
Week 6 (Visit 3)	2.65 ± 1.32	4.44 ± 2.11	<0.0001

[Table/Fig-3]: Pain intensity score on Visual analogue scale (VAS)

Values are expressed as Mean ± SD. n = number of patients in each treatment group. Data were analyzed by Mann-Whitney test. PCM- Paracetamol; IR- Immediate release

KOOS subscale*	Visits	PCM 650 dual release (n=126)	PCM 500 IR (n=124)	p-value
Pain	Baseline	44.24 ± 14.12	41.66 ± 13.53	0.39
	Week 2	59.14 ± 11.67	49.75 ± 13.30	<0.001
	Week 4	69.17 ± 11.08	55.82 ± 16.53	<0.001
	Week 6	79.43 ± 14.138	60.32 ± 22.456	<0.001
Other symptoms	Baseline	46.85 ± 14.42	45.01 ± 15.28	0.50
	Week 2	57.00 ± 10.19	52.93 ± 12.52	0.01
	Week 4	63.35 ± 9.35	58.38 ± 12.94	0.001
	Week 6	70.43 ± 13.136	62.6 ± 17.95	0.0001
Function in daily living	Baseline	43.75 ± 12.96	42.08 ± 13.23	0.90
	Week 2	58.55 ± 10.80	49.71 ± 13.37	< 0.001
	Week 4	67.63 ± 11.60	56.99 ± 15.85	< 0.001
	Week 6	78.73 ± 14.76	62.06 ± 20.85	< 0.001
Function in sport and recreation	Baseline	30.63 ± 19.00	29.11 ± 21.030	0.57
	Week 2	44.72 ± 21.48	36.97 ± 23.80	<0.01
	Week 4	53.21 ± 25.65	42.37 ± 25.45	< 0.001
	Week 6	62.46 ± 30.68	47.90 ± 30.45	0.0001
Quality of life	Baseline	39.58 ± 14.053	35.83 ± 15.61	0.10
	Week 2	52.18 ± 11.10	43.04 ± 12.45	<0.001
	Week 4	62.89 ± 11.77	47.88 ± 17.96	<0.001
	Week 6	73.21 ± 16.50	52.97 ± 23.55	<0.001

[Table/Fig-4]: Assessment of KOOS subscale

Values are expressed as Mean ± SD. n = number of patients in each treatment group. Data were analyzed by Mann-Whitney test. PCM- Paracetamol; IR- Immediate release; KOOS- Knee injury and Osteoarthritis Outcome Score *Higher score indicated better improvement

but longer duration of action of PCM 650 dual release compared to conventional immediate release paracetamol 500 mg tablet. Previous studies have established the efficacy and safety of sustained-release paracetamol in managing OA pain [8]. KOOS subscales for other symptoms, functions in daily living, functions in sports and recreation and knee related quality of life also showed significantly greater improvement in patients receiving PCM 650 dual release than those receiving PCM 500 IR. Apart from pain relief, treatments with PCM 650 dual release also resulted in significant improvement in functional mobility and overall quality of life in patients of OA

Global Assessment	Patient's global assessment		Physician's global assessment	
	PCM 650 dual release (n=126) (%)	PCM 500 IR (n=124) (%)	PCM 650 dual release (n=126) (%)	PCM 500 IR (n=124) (%)
Excellent	44 (34.9)	7 (5.6)	40 (31.7)	8 (6.5)
Good	74 (58.7)	46 (37.1)	71 (56.3)	47 (37.9)
Fair	8 (6.3)	39 (31.5)	15 (11.9)	36 (29.0)
Poor	0	32 (25.8)	0	33 (26.6)
p-value	<0.0001		<0.0001	

[Table/Fig-5]: Patient's and physician's global assessment of treatment at the end of the trial (%) Values are expressed in absolute number of patients. n = number of patients in each treatment group; Data were analyzed by chi square test. PCM- Paracetamol; IR- Immediate release

Adverse event	PCM 650 dual release (n=126)	PCM 500 IR (n=124)	p value
GI discomfort	2	10	
Morning stiffness	5	2	
Pelvic pain	-	4	
Diarrhea	-	1	
Total	7	17	0.03

[Table/Fig-6]: Number of patients with reported adverse events

Values are expressed in absolute number of patients. n = number of patients in each treatment group; P value was analyzed by chi square test. PCM- Paracetamol; IR- Immediate release

knee. Our results were consistent with previous published study suggested that patients treated with sustained-release paracetamol experienced significant improvement in all parameters of the WOMAC for pain, stiffness and performing activities [8].

Less number of patients required additional rescue analgesics while receiving PCM 650 dual release compared to PCM 500 IR depicting more stable pain control with extended release tablet. Significantly less number of patients in PCM 650 dual release group reported adverse events compared with PCM 500 IR. This favourable safety profile in PCM 650 dual release group may be due to lower daily dose (1300 mg vs 1500 mg) and lesser peak plasma concentration compared to PCM 500 IR.

Patient's and physician's global evaluation of treatments also favoured PCM 650 dual release compared to PCM 500 IR, which reflects the better acceptability of PCM 650 dual release among patients of OA knee. Our results are consistent with the published study reported that patients' global assessment of response to treatment and satisfaction with treatment, both significantly favoured sustained-release over standard paracetamol [6]. Our findings suggest that the dual release 650 mg paracetamol two times daily is equally effective to immediate release paracetamol 500 three times daily. This reduction of daily frequency may add to convenience to patient and improve compliance to the therapy.

CONCLUSION

In conclusion, this results show that novel dual release PCM 650 mg taken twice daily was statistically and therapeutically more effective, safe and convenient than PCM 500 IR taken thrice daily in patients with knee pain due to OA. PCM 650 dual release could be a better alternative treatment option in symptomatic management of knee osteoarthritis as it decreases dosing frequency which may improve patient compliance with better long term efficacy and safety.

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FINANCIAL OR OTHER COMPETING INTERESTS: The study is sponsored by Troikaa Pharmaceuticals Ltd. and author 7, 8 and 9 are full time employee of the organization

Date of Submission: **Jan 02, 2014**
Date of Peer Review: **Mar 25, 2014**
Date of Acceptance: **Mar 25, 2014**
Date of Publishing: **Nov 20, 2014**