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Efficacy and Safety of Piroxicam Beta-Cyclodextrin Sachets for Treating Chronic Low Back Pain: A Randomized, Parallel, Active-Controlled Trial

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Background: The clinical effects of the sachet form of piroxicam beta-cyclodextrin have been studied for their efficacy against acute or osteoarthritic pain in Western populations, but studies are sparse for chronic low back pain. We evaluated the effects of the sachet form on local Asian people with chronic backache, compared with conventional piroxicam tablets. **Methods:** Forty-seven eligible patients were randomized into a sachet treatment group (n=24) and a tablet treatment group (n=23). Both groups received dosages of 20 mg per day orally for 28 days. Efficacy was evaluated using a pain score and a disability index. **Results:** The efficacy of the two application methods was compared based on 42 patients included in the per-protocol population. The sachet-form drugs showed greater improvement than tablets in lowering the pain score by 1.93 units. This mode of delivery also showed a greater improvement in the patients' disability index. Sachet application produced 12.5% of adverse incidences versus 19% for tablets, with no statistically significant difference. **Conclusion:** Piroxicam beta-cyclodextrin sachets extended the spectrum of analgesic activity for the treatment of these patients with chronic low back pain and provided a low incidence of side effects.

Key words: piroxicam beta-cyclodextrin; sachets; low back pain; visual analogue scale; Oswestry Disability Index

INTRODUCTION

Low back pain (LBP) is the most common cause of physical disability in the working age population and is one of the most debilitating in terms of reductions in health-related quality of life[1]. The prevalence and lifetime incidence of LBP in cross-sectional studies in the USA and other Western countries range from 12% to 30%, and 49% to 70%, respectively[2]. Chronic LBP is defined as pain lasting for more than three months attributed to degenerative or traumatic conditions of the spine and is the most expensive benign condition in the population younger than 45 years[3-5]. A variety of drug therapies have been proposed for the treatment of LBP. Of these, nonsteroidal anti-inflammatory drugs (NSAIDs) are presently the first choice of treatment, with analgesia resulting from the inhibition of prostaglandin synthesis secondary to tissue injury. Among all classes of NSAIDs, the oxicams inhibit the synthesis of prostaglandins in the spinal cord, where autacoids play a role in hyperalgesic pain pathways[6]. An oxicam, piroxicam, has been widely prescribed for the treatment of LBP, even though gastrointestinal (GI) mucosal injury reduces the incidence of favorable outcomes[7].

Inclusion complexes between guest drugs and cyclodextrins are of current interest for the pharmaceutical industry and are the subject of advanced clinical investigations. The cyclodextrin molecule comprises a highly hydrophilic external part and a less polar cavity capable of including large organic molecules by noncovalent interactions. The therapeutic aim of the industry is to alter the physical and chemical properties of such guest drug molecules and impart beneficial characteristics. There are many advantages of forming a cyclodextrin complex with guest drug molecules, such as better solubility, stability, and bioavailability[8]. Piroxicam, in addition to possessing the properties of an NSAID, is well known to be capable of forming an inclusion complex with beta cyclodextrin.

The formulation in tablet form studied here was of piroxicam complexed with beta-cyclodextrin. This was first developed by Chiesi Farmaceutici, SpA, Parma, Italy[9]. Since then, there have been many pharmacokinetic studies

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on this new formulation of piroxicam beta-cyclodextrin (PBC) in healthy subjects. These studies show that, compared with plain piroxicam, PBC has faster absorption in the GI tract and less gastric intolerance[10-14], enhances the solubility and wettability of piroxicam[15,16], and provides rapid attainment of the peak plasma concentration and reduction of side effects in the GI tract[17,18]. It also proved promising in many studies on inflammation and pain, for example in patients: with acute periodontitis[19]; with chronic rheumatoid arthritis and osteoarthritis[20]; with acute pain from rheumatic disease[21]; with postoperative dental pain[22]; with pain of musculoskeletal origin or of the knee16 and with knee effusion[23], chronic back pain[24], or even migraine[25]. In contrast, one small study demonstrated no difference in pain relief between PBC and plain piroxicam, but there is little doubt about the efficacy and safety of piroxicam for patients with osteoarthritis-induced neckache and LBP[26].

Table 1. Flow chart of visit schedule Visit Screening

visit	Screening visit	Randomization visit	Evaluation visit	Final visit
Day	-7 to -3	0	14 ± 3	28 ± 3
Visit number	1	2	3	4
Demographic & medical history	present			
Inclusion and exclusion criteria	present	present		
Informed consent signed and given	present			
Pregnancy test for applicable patients	present			present
Physical examinations	present			present
Vital signs	present			present
Laboratory test: White blood cells, red blood cells, liver and renal function tests, etc.	present*			present
Randomization number assigned		present		
Treatment medication given		present	present	
Unused Medication Collection			present	present
Pain evaluation by patients using 10-cm VAS	present	present	present	present
Oswestry Disability Index (ODI)		present	present	present
Global assessment by the investigator(s)				present
Global assessment by the patient				present
Adverse events		present	present	present
Concomitant medications	present	present	present	present
Complete exit form				present
Missing patient				present

* Test results within 7 days before Screening visit were acceptable

Interestingly, formulation of PBC in sachets gives the same absorption rate as tablets; both show considerably faster absorption rates than plain piroxicam. In addition to earlier work in healthy subjects using PBC sachets[27], there have been several studies on patients with varying diseases or conditions[28-30]. However, there has been no study on the treatment of Asian patients with LBP. We therefore aimed to compare the efficacy and safety of PCB sachets with plain piroxicam tablets, in a small local Asian population with chronic LBP.

PATIENTS AND METHODS

Study Design

The study protocol (TSGHIRB, No. 094-05-0053) was approved by the Institutional Review Board of our hospital on July 22, 2005, before recruiting the first patient for formulary listing. The study conformed to the principles of the Declaration of Helsinki and all patients provided written informed consent.

This study was designed as a randomized, parallel, active-controlled trial. The patients were assigned randomly using numbered sealed envelopes to receive either the PBC sachets (Brexin Sachets, Chiesi Farmaceutici) or the piroxicam tablets alone. The PBC sachets and the piroxicam tablets were both given orally at doses of 20 mg once daily for a total of 28 days with four visits required by the study design. These were a screening appointment (Visit 1), a randomization (Visit 2, Day 0), an evaluation (Visit 3, Day 14), and a final visit (Visit 4, Day 28). The flow chart of the visiting schedule is shown in Table 1.

Inclusion criteria for the recruitment of patients with LBP were as follows: age between 20 and 75 years; the presence of LBP for more than three months before entry into the study; a history of conservative treatment or management; the administration of NSAIDs or paracetamol for the treatment of LBP within 28 days before entry into the study; and the capability of discontinuing all other analgesics, NSAIDs, glucocorticoids, benzodiazepines, or other muscle relaxants during the study. Patients also needed to record a subjective pain score of at least 4 cm on a 10 cm visual analogue scale (VAS; 10 = extreme or the worst imaginable pain, 0 = no pain) both at the screening visit and at the baseline day of the trial.

Exclusion criteria included patients with LBP caused by neoplasia, infections, or other visceral diseases (such as pelvic organ, renal, vascular or GI diseases); patients who had received surgery for LBP within six months before entry to the study or who had any history of asthma, urticaria, or allergic reactions after taking aspirin or any other kinds of NSAID. Patients were excluded if they had gastric ulcers, gastritis, dyspepsia, depression, psychosis, alcohol or drug abuse, or with confirmed evidence of impaired hepatic function (alanine aminotransferase or aspartate aminotransferase >2.5 times the upper range of

normal) or renal impairment (serum creatinine >1.5 mg/dl). Patients with systolic blood pressure >160 mmHg or diastolic blood pressure >105 mmHg, severe heart failure, severe blood diseases, or hemorrhagic diathesis were excluded, as were pregnant or lactating women. Finally, we did not include any patients who had participated in an investigational drug trial within 30 days before entering this study.

Protocol and Interventions

Patients satisfying the entry criteria and screened as eligible were randomly assigned to receive either PBC sachets or piroxicam tablets for 28 days. The coding system adopted in our study for reporting any adverse events was COSTART. The results of physical examinations and pregnancy tests at Visits 1 and 4 were recorded.

Analytical Methods and Measurement of Efficacy

Two populations of patients were subjected to statistical analysis. The intention-to-treat (ITT) population comprised all randomized patients who took at least one dose of study medication. The per-protocol (PP) population was a subset of the ITT population; all such patients must have received at least 75% of the total targeted study medication cumulatively with a measurement of its efficacy, and they must not have taken any prohibited medications.

Safety evaluations were performed in the ITT population and efficacy analyses were performed in both the ITT and the PP populations. The conclusion of efficacy of the study was made according to the results of the PP analysis. The efficacy endpoint was the net change by Visit 4. Measures included an evaluation of pain compared with the baseline at Visit 2, using the VAS for pain level, the Oswestry Disability Index (ODI), and global assessments by the investigator and by the patients themselves. The ODI, a popular tool for evaluating LBP[31], consists of 10 sections addressing different aspects of function. Each section is scored from 0 to 5, ranging from the least to the greatest disability. The final ODI score was calculated as follows: ODI score = total score/(5×number of questions/sections answered)×100% (rounding the percentage to a whole number). The global assessments by the investigator and by the patient had the same ratings further categorized as significantly improved (grade 4), improved (grade 3), slightly improved (grade 2), no change (grade 1), and worsened (grade 0).

For the safety endpoints, the pretreatment and treatment-emergent adverse events (AEs) of each period were defined as those that occurred before starting any study treatment and those that appeared during treatment. The severity of each AE was categorized as 'mild', 'moderate', or 'severe' and was reported according to treatment groups or physiological measures as appropriate.

Statistical Analysis

Descriptive statistics including means and standard deviations were calculated for continuous variables, and frequency tables were calculated for categorical data. Data were analyzed using either two sample Student's *t* tests or Wilcoxon rank sum tests for continuous variables, and Fisher's exact test for categorical variables to ensure valid comparability between treatment groups. Inferential statistics including estimates of mean and two-sided 95% confidence intervals were calculated. The net changes in laboratory test results and in vital signs from Visits 1 to 4 were analyzed to compare differences between the treatment groups using analysis of covariance (ANCOVA) with treatment effect and baseline as covariates. The ANCOVA model analyzed all net changes in 10 cm VAS and ODI and their corresponding between-group comparisons. Both forms of global assessment were analyzed using the Mantel—Haenszel test. Fisher's exact test was used to analyze the incidences of AEs between treatments. All statistical tests used were two-tailed with α=0.05 and P<0.05 was considered statistically significant.

RESULTS

Study Subjects

Fifty-one patients were screened. Three patients withdrew consent and one was lost to follow-up. The disposition of patients for each treatment is shown in Figure 1. There were 47 patients randomized into this study: 24 in the PBC sachet treatment group and 23 in the piroxicam tablet treatment group. Two patients in the piroxicam tablet group did not take any doses of the study medication and were excluded from the ITT population, leaving 45 patients in the ITT population: 24 in the PBC sachet group and 21 in the piroxicam tablet group.

Three patients in the ITT population (one in the PBC sachet group and two in the piroxicam tablet group) were excluded from the PP population, as they did not follow the required dosing conditions (see Analytical Methods and Measurement of Efficacy). Therefore, the final PP population consisted of 42 patients: 23 in the PBC sachet group and 19 in the piroxicam tablet group.

Subject and Baseline Characteristics

Comparability between the two treatment groups was assessed at the baseline at randomization Visit 2, or at

screening Visit 1 if the measurements or examinations were not taken at the randomization visit. The demographics and baseline characteristics of the 45 ITT patients (age, sex, weight, height, and body mass index) are summarized in Table 2. There were 17/24 men (71%) in the PBC sachet group and 15/21 (71%) in the piroxicam tablet group. No demographic characteristics differed significantly between the two treatment groups.

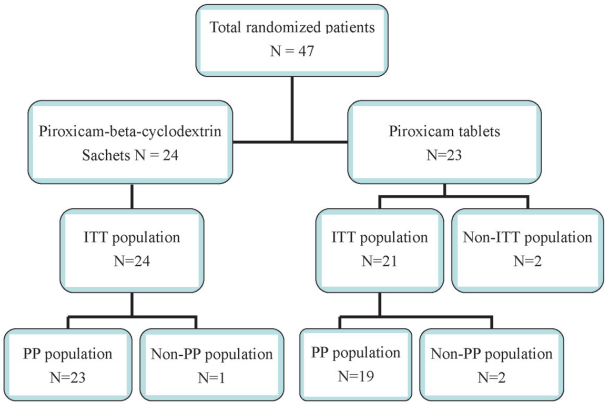

Fig. 1 Clinical trial profile shows the disposition of patients for each treatment. There were 47 (24 in the piroxicam-beta-cyclodextrin sachets treatment group and 23 in the piroxicam tablets treatment group) patients randomized into this study. Except for two patients in the piroxicam tablets group that did not take any dose of study medication and were excluded from the intention-to-treat (ITT) population, there were 45 (24 in the piroxicam-beta-cyclodextrin sachets group and 21 in the piroxicam tablets group) patients included in the ITT population.

The mean durations of LBP for the PBC sachet group and the piroxicam tablet group were 1.88±2.74 and 1.43 ±2.60 years, respectively. More than 95% of the PBC sachet group patients and more than 80% of the piroxicam tablet group patients had at least one medical history and current abnormality. No statistically significant difference was shown between these two treatment groups in either history or medication use. Table 2 shows the VAS and ODI scores at Visit 2. The PBC sachet treatment group had slightly higher mean VAS and ODI scores (5.10 cm and 34%, respectively) than the piroxicam tablet group (5.03 cm and 31%, respectively). However, there was no statistically significant difference between these two treatment groups for either of the baseline scores. Thus, both treatment groups were statistically similar at the baseline.

Efficacy

Efficacy endpoints were evaluated at Visit 4 and were analyzed for both ITT and PP data sets. The final efficacy of the study was judged according to the results of PP analysis.

One of the efficacy variables was measurement of the net change of the 10 cm VAS for pain from the baseline at Visit 2 to the final Visit 4; the results are shown in Table 3 and Figure 2. Both treatments showed significant net changes, but the PBC sachet group apparently had greater improvement. The net changes were 3.07± 1.56 and 1.80± 1.41 in the ITT and PP populations, respectively ($P = 0.009$ for both groups). Thus, PBC sachets had a stronger effect in lowering the VAS score than the piroxicam tablets.

Table 2 Demographic characteristics and baseline scores of visual analogue scale (VAS) and the Oswestry Disability Index (ODI) in the intention-to-treat (ITT) population

Demographic characteristics	PBC sachets group (N=24) (Mean ± SD)	Piroxicam tab group (N = 21) (Mean ± SD)	Total (N = 45) (Mean ± SD)	*P* value
Age (years)	34.25 ± 14.27	34.29 ± 16.74	34.27 ± 15.29	0.623[a]
Gender (Male : Female)	17 : 7	15 : 6	32 : 13	1.000[b]
Weight (kg)	64.88 ± 8.68	68.45 ± 10.59	66.54 ± 9.67	0.220[c]
Height (cm)	167.52 ± 8.35	169.83 ± 9.48	168.60 ± 8.87	0.389[c]
Body mass index (kg/m^2)	23.12 ± 2.63	23.74 ± 3.55	23.41 ± 3.07	0.918[a]
VAS scores (cm)	5.10 ± 0.75	5.03 ± 0.84	5.06 ± 0.78	0.608[a]
ODI score (%)	33.78 ± 12.67	31.02 ± 10.41	32.49 ± 11.62	0.432[c]

a: Wilcoxon rank sum test
b: Fisher's exact test
c: Two sample t-test
PBC, Piroxicam-beta-cyclodextrin

Another efficacy variable was the net change in ODI scores from the randomization Visit 2 to the final Visit 4; results for the ITT and PP populations are shown in Table 4 and Figure 3. The net changes in these two groups were 18.05±14.73 (P = 0.030) and 8.90 ± 9.51 (P = 0.031), respectively. Thus, the PBC sachet group had a greater improvement in the ODI score at both visits.

Table 3 Net changes of visual analogue scale (VAS) score (cm) from baseline to the final visit in the intention-to-treat (ITT) and the per-protocol (PP) populations

Statistics	PBC sachets group	Piroxicam tab group	Difference [95% CI][a]	*P* valueb
ITT population				
N	24	21		
Mean ± SD	3.07 ± 1.56	1.80 ± 1.41	1.237 [0.328; 2.147]	0.009
LS_Mean [95% CI][b]	3.054 [2.427; 3.682]	1.817 [1.160; 2.474]		
PP population				
N	23	19		
Mean ± SD	3.07 ± 1.56	1.75 ± 1.48	1.296 [0.344; 2.247]	0.009
LS_Mean [95% CI][b]	3.058 [2.427; 3.682]	1.762 [1.058; 2.466]		

a: PBC minus Piroxicam
b: ANCOVA with treatment effect and covariate of baseline
PBC, Piroxicam-beta-cyclodextrin

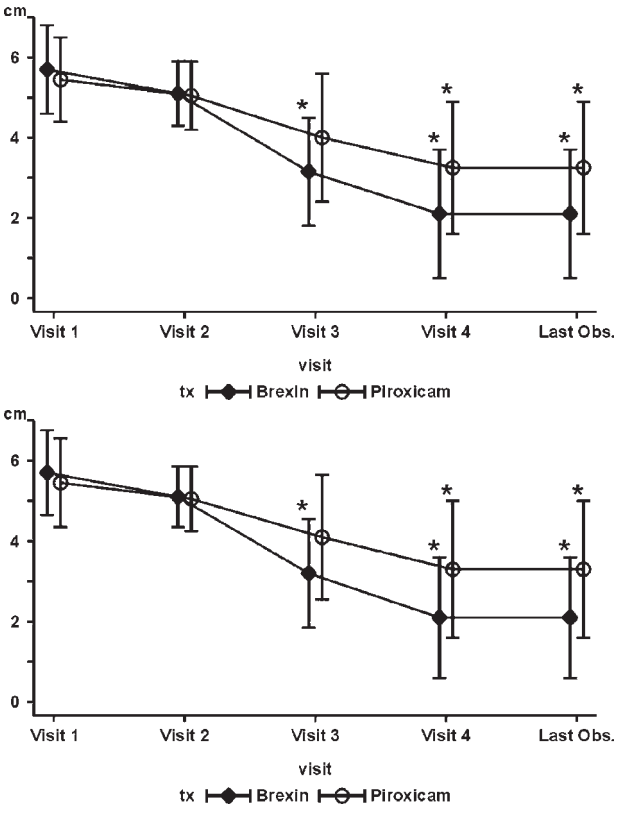

Fig. 2 The VAS score (mean±SD) recorded at visit days in the intention-to-treat (ITT, upper) and the per-protocol (PP, lower) populations showing that piroxicam-beta-cyclodextrin sachets had a stronger effect in lowering down the VAS score than the piroxicam tablets. Significant difference from baseline (P < 0.05)

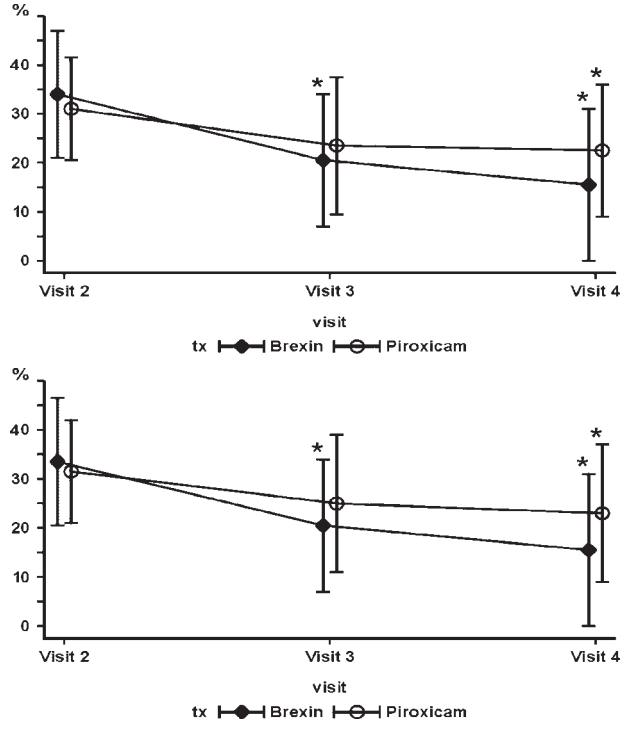

Fig. 3 The ODI score (mean ± SD) recorded at visit days in the intention-to-treat (ITT, upper) and the per-protocol (PP, lower) populations showing that the piroxicam-beta-cyclodextrin sachets treatment group had greater improvements of ODI score in both visits. However, only the difference in the net changes between treatment from the Visit 2 to the final visit (Visit 4, Day 28) was statistically significant in both of ITT and PP populations. Significant difference from Visit 2 (P < 0.05)

Table 4 Net changes of ODI from baseline to the final visit in the intention-to-treat (ITT) and the per-protocol (PP) populations

Statistics	PBC sachets group	Piroxicam tab group	Difference [95% CI][a]	*P* value[b]
ITT population				
N	24 21	21		
Mean ± SD	18.05 ± 14.73	8.90 ± 9.51		
LS_Mean [95% CI][b]	17.704 [12.574; 22.835]	9.296 [3.791; 14.801]	8.408 [0.863; 15.952]	0.030
PP population				
N	23 19	19		
Mean ± SD	18.05 ± 14.73	8.78 ± 10.02	8.772 [0.832; 16.712]	0.031
LS_Mean [95% CI][b]	17.829 [12.575; 23.084]	9.057 [3.116; 14.998]		

a: PBC minus Piroxicam
b: ANCOVA with treatment effect and covariate of baseline
PBC, Piroxicam-beta-cyclodextrin

Global assessment was made by both the investigators and the patients at the final Visit 4. The analysis for the ITT population is shown in Table 5. The PBC sachet group had more 'improved' and 'significantly improved' patients (91% estimated by the investigators and 65% by patients) than the piroxicam tablet group (33% estimated by the investigators and 28% by the patients). A similar trend can be seen in the results for the PP population.

Adverse Events

There was one pretreatment AE in the piroxicam tablet treatment group. This was mild and was unrelated to the trial treatment. There were 11 treatment-emergent AEs (four in the PBC sachet group and seven in piroxicam tablet group), reported by three patients (12.5%) in the PBC sachet group and four (19%) in the piroxicam tablet group. All these treatment-emergent AEs were diagnosed as mild. Seven of these events (two in the PBC sachet group and five in the piroxicam tablet group) were attributed to factors that might be related to treatment; the remaining four AEs were unrelated. Of the seven AEs (in three patients) possibly related to treatment, four were classified using COSTART as 'body as a whole', two as 'digestive system', and one as 'nervous system'. For these three patients, one in the piroxicam group had a 'digestive system' AE, which led to the reduction of trial drug dosage. Later, this patient had simultaneous AEs covering 'digestive system' and 'body as a whole', which led to the termination of treatment. One patient in the piroxicam tablet group had two 'body as a whole' AEs (stomachache), which did not affect the treatment dose; one patient in the PBC sachet group had a 'body as a whole' AE (headache) and one 'nervous system' AE (dizziness), both of which led to the termination of treatment. All these patients with AEs recovered. The P value for comparing the incidence rate between subjects who did and did not experience AEs was 0.422. None of the mean net changes in these test results was significant in the PBC sachet treatment group. The results indicated that PBC sachets were at least as safe as the piroxicam tablets when considering the incidence of AEs and physical examination results.

Table 5 Statistical analysis of global assessment in the intention-to-treat (ITT) population

Category	PBC sachet group	Piroxicam tab group	*P* value
By Investigators			
Worsen	0 (0.0%)	0 (0.0%)	<.001
No changed	1 (4.3%)	6 (33.3%)	
Slightly improved	1 (4.3%)	6 (33.3%)	
Improved	8 (34.8%)	5 (27.8%)	
Significantly improved	13 (56.5%)	1 (5.6%)	
Total	23 (100.0%)	18 (100.0%)	
By Patients			
Worsen	0 (0.0%)	0 (0.0%)	0.005
No changed	1 (4.3%)	8 (44.4%)	
Slightly improved	7 (30.4%)	5 (27.8%)	
Improved	6 (26.1%)	2 (11.1%)	
Significantly improved	9 (39.1%)	3 (16.7%)	
Total	23 (100.0%)	18 (100.0%)	

Statistical significance was assessed by using Mantel-Haenszel test. PBC, Piroxicam-beta-cyclodextrin

Vital signs consisting of blood pressure, pulse rate, and body temperature were monitored at the baseline and at Visit 4. The analysis of net changes from the baseline to the final visit of vital signs as well as hematology- and laboratory-related test results are shown in Table 6. The mean diastolic blood pressure in the piroxicam tablet group and the mean systolic blood pressure in the PBC sachet group decreased significantly from baseline. However, the net

Table 6 Net changes of vital signs and hematological and biochemical profiles in the intention-to-treat (ITT) population

Parameters	PBC sachets group		Piroxicam tab group		Difference [95% CI][a]	*P* value[b]
	Mean ± SD	LS_Mean [95% CI][b]	Mean ± SD	LS_Mean [95% CI][b]		
Diastolic BP (mmHg)	3.00 ± 11.77	3.193 [-6.02; 6.989]	6.60 ± 9.37	6.378 [2.307; 10.448]	-3.184 [-8.751; 2.383]	0.255
Systolic BP (mmHg)	3.04 ± 9.51)	3.549 [0.239; 6.859]	3.15 ± 8.63	2.569 [-0.983; 6.120]	0.980 [-3.980; 5.851]	0.686
Pulse rate (beats/min)	-0.22 ± 12.05	-0.403 [-4.560; 3.755]	-4.55 ± 8.74	-4.337 [-8.796; 0.122]	3.934 [-2.166; 10.035]	0.200
Body temperature (°C)	0.17 ± 0.75	0.119 [-0.141; 0.380]	-0.10 ± 0.81	-0.042 [-0.322; 0.237]	0.162 [-0.021; 0.545]	0.399
White blood cells (10^3/uL)	-0.06 ± 1.16	-0.085 [-0.594; 0.424]	-0.90 ± 1.88	-0.867 [-1.414; -0.321]	0.783 [0.036; 1.529]	0.040
Red blood cells (10^6/uL)	0.12 ± 0.29	0.100 [-0.008; 0.209]	0.04 ± 0.26	0.066 [-0.050; 0.182]	0.034 [-0.125; 0.194]	0.665
Hemoglobin (g/dL)	0.32 ± 0.92	0.342 [-0.032; 0.716]	0.44 ± 1.06	0.412 [0.011; 0.813]	-0.070 [-0.619; 0.479]	0.798
Hematocrit (%)	0.94 ± 2.77	0.969 [-0.075; 2.012]	0.85 ± 2.81	0.821 [-0.298; 1.940]	0.147 [-1.383; 1.678]	0.847
Platelet counts (10^3/uL)	-5.30 ± 25.25	-5.224 [-18.53; 8.084]	-3.30 ± 43.96	-3.393 [-17.66; 10.878]	-1.831 [-21.34; 17.682]	0.851
Porthrombin time (sec)	0.06 ± 0.52	-0.008 [-0.201; 0.186]	0.05 ± 0.41	0.124 [-0.085; 0.333]	-0.131 [-0.427; 0.164]	0.375
Partial thromboplastin time (sec)	0.22 ± 2.08	0.441 [-0.166; 1.049]	0.33 ± 1.13	0.072 [-0.580; 0.725]	0.369 [-0.536; 1.274]	0.415
Asparate aminotransferase (U/L)	3.13 ± 10.00	2.230 [-2.194; 6.654]	-1.50 ± 15.48	-0.465 [-5.212; 4.282]	2.695 [-3.821; 9.211]	0.408
Alanine aminotransferase (U/L)	2.83 ± 12.37	1.165 [-2.440; 4.770]	-1.00 ± 10.57	0.910 [-2.962; 4.782]	0.255 [-5.101; 5.612]	0.924
BUN (mg/dL)	-0.48 ± 3.17	-0.310 [-2.022; 1.402]	-1.25 ± 6.26	-1.444 [-3.280; 0.393]	1.134 [-1.380; 3.647]	0.367
Creatinine (mg/dL)	-0.03 ± 0.12	-0.026 [-0.073; 0.022]	0.04 ± 0.13	0.025 [-0.027; 0.076]	-0.050 [-0.121; 0.020]	0.157
Total bilirubin mg/dL)	-0.03 ± 0.41	-0.034 [-0.199; 0.131]	-0.01 ± 0.37	-0.001 [-0.178; 0.176]	-0.033 [-0.276; 0.210]	0.784

a: PBC minus Piroxicam
b: ANCOVA with treatment effect and covariate of baseline
BP, blood pressure
PBC, Piroxicam-beta-cyclodextrin
AST, asparate aminotransferase
ALT, alanine aminotransferase

changes were insignificant. With respect to white blood cell (WBC) count and hemoglobin level, there was a significant increase in the former and a significant reduction in the latter in the piroxicam tablet group. There were also significant mean net change differences between these two groups in WBC counts. Except for those mentioned above, none of the changes in vital signs or laboratory tests was significant between test groups. None of the mean net changes in test results was significant in the PBC tablet group.

DISCUSSION

In a prospective, randomized, single-blinded case-controlled trial, Manzini et al.[28] reported that PBC sachets exerted more rapid analgesic effects in patients with osteoarthritic pain than piroxicam tablets. In addition to the good effects and gastric tolerance shown by both groups, they found a statistically significant difference in pain reduction between the use of PBC sachets and piroxicam tablets during the 24 h treatment. However, there was a similar level of residual spontaneous pain for both groups at the end of the treatment period. Our results reported here are similar to theirs in terms of the numbers of patient enrolled and GI tolerability. However, our results for pain reduction showed obvious improvements in the efficacy of PBC sachets, in contrast to their results. Based on the statistical results, we postulate that the PBC sachets might exhibit better therapeutic effects on chronic pain than on the acute pain resulting from osteoarticular inflammation. The PBC sachets yielded greater improvement than piroxicam tablets in all efficacy results for the treatment of chronic LBP in our study; thus, PBC sachets produce better continuous pain relief than does plain piroxicam.

In a comparison of the efficacy and tolerability between PBC sachets and plain piroxicam tablets in the treatment of osteoarthritis, D'Ercole et al.[30] demonstrated a significant difference between treatment groups. They concluded in favor of the PBC sachets in terms of pain relief responses on active movement on the seventh day and functional impairment on the 14th day of treatment. However, in our study, the duration of drug treatment was longer and there was still effective pain relief by the 28th day.

In terms of clinical studies on pain, Manzini et al.[28] studied the effects of PBC sachets in a group of patients with osteoarthritic pain, but did not mention the duration of pain. Michelacci et al.[29] studied the effects of PBC sachets on 24 patients with postsurgical pain and D'Ercole et al.30 studied a group of patients with chronic osteoarthritic pain. However, they did not study any patients with LBP. Compared with other studies on Western populations, our study performed on local Asian people showed no ethnic difference in pain relief or in dosage.

We found here that the few AE events were transient and easily tolerable for the patients and did not affect their

usual daily activities. The mean diastolic blood pressure in the piroxicam tablet group and the mean systolic blood pressure in the PBC sachet group decreased by statistically significant levels compared with baseline, but the net changes were slight, harmless, and insignificant. The slight change in blood pressure might have contributed to the additional benefits of significant pain relief. These results suggest that PBC sachets are possibly safer than piroxicam tablets alone, and at least as safe when considering vital signs, the incidence of AEs, laboratory examinations, and biochemistry results.

PBC sachets may cause less GI injury than piroxicam tablets by reducing the contact time with the GI mucosa, but to date only a trend for this effect has been demonstrated[15,28,30]. Considering these previous results, our study reinforces the idea that PBC sachets are effective and safe.

There is growing concern about the ethical issues associated with the use of placebo controls in clinical trials and the need to avoid the risks of symptom deterioration or delayed recovery[32]. Clearly, one of the limitations of our study was that it was open-labeled, unblinded, and lacked placebo control. However, a significant change from baseline value was seen for most endpoints for the PBC sachet group and treatment differences were detected. Another limitation was that both methods of drug delivery used here had their limitations because of the subjectivity of the recordings, resulting in a large range of variation and reduced sensitivity. These findings warrant a large-scale clinical trial to explore further the relationship between PBC sachets and other analgesics.

There have been many studies to identify factors associated with poor compliance to drug therapy. Generally, the etiology of poor adherence is multifactorial, and factors such as personality traits, sociodemographic factors, psychological distress (depression or anxiety), self-efficacy, health beliefs, and intentions can all predict adherence. Therefore, patients will self-titrate dosages based on feeling better, perceptions of side effects or treatment effectiveness, regimen complexity, and cost. Patients might misunderstand dosage, frequency, or other aspects of the regimen; they might forget information or have dementia or cognitive problems. Erratic adherence, due for instance to being too busy or overloaded, running out of medication, problems in getting refills, and changes in schedules or routines, is also a major problem. Fortunately, our patients showed high adherence because our study complied with the principles of a good therapeutic regimen, that is, being simple, easy to follow, and of short duration, lacking disruptions to lifestyle, and being clearly linked to reductions in symptoms or pain[33-35].

In conclusion, PBC sachets retain the potent anti-inflammatory activity of piroxicam tablets alone and extend the spectrum of analgesic activity for the treatment of chronic LBP with a low incidence of side effects.

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