

# Sublingual Piroxicam in Migraine without Aura

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## Abstract

**Objective:** The aim of the present study was to compare the analgesic efficacy of a single dose of sublingual piroxicam to that of a placebo during acute attacks of migraine without aura.

**Methods:** The drug (N=30) or a placebo (N=30) was administered, on randomisation and double-blind basis, to 60 patients between 18 and 50 years of age suffering from migraine without aura. The patients were instructed to take a single tablet sublingually [corresponding to piroxicam 40mg or placebo] and the severity of the painful symptomatology and associated symptoms were evaluated by this study.

**Results:** The patients treated with sublingual piroxicam showed a significant ( $P<0.05$ ) decrease in pain intensity 15 minutes after ingestion; they went on to show a further reduction in the 24 hours after drug administration. On the contrary, the group treated with placebo showed a significant reduction of symptoms only after seven hours of observation. Associated symptoms disappeared significantly ( $P<0.05$ ) after sublingual piroxicam administration. In 83.3 %, the drug resulted in excellent to good response as compared to only 10 % in the placebo group. No local and systemic side effects were reported with sublingual piroxicam.

**Conclusions:** The present study has demonstrated that for the acute management of migraine without aura sublingual piroxicam showed significant analgesic effect with excellent tolerability.

## Introduction

Migraine is a chronic recurrent complex disorder characterised by stereotypical attacks of headache, focal neurological symptoms or a combination of both. It is the most common headache diagnosis for which patients seek treatment. Migraine is associated with significant disability that results in a marked decrease in a patient's quality of life, as measured by physical, mental, and social health-related instruments. A comprehensive treatment approach to migraine may include non-pharmacologic measures, as well as abortive and prophylactic medications.<sup>1</sup>

Piroxicam is a chemically different non-steroidal anti-inflammatory drug with a long half-life that enables it to be administered once daily. This member of the oxicam series of compounds is now well established in the treatment of rheumatoid arthritis, osteoarthritis, gout, various musculoskeletal disorders and pain of varied etiology. Patient preference and compliance has consistently been higher for piroxicam therapy as compared to several other drugs of this class.<sup>2,3</sup>

The sublingual tablet formulation of piroxicam has been developed for ease of administration. Due to its rapid absorption rate when administered sublingually, this formulation may well be useful in the symptomatic treatment of headache attacks, and migraine in particular.<sup>4</sup>

The aim of the present study, double-blind type versus placebo, was to compare the analgesic efficacy of a single dose of piroxicam sublingual to that of a placebo during attacks of migraine without aura.

## Subjects and Methods

The drug (piroxicam, 40 mg) or a placebo was administered, on randomisation and double blind basis, to 60 patients of both sexes between the ages of 18 and 50 years suffering from migraine without aura [as defined by the diagnostic

criteria of the International Headache Society (IHS) 2004]. The monthly frequency of attack was between 2 to 16, while few of them suffered daily or for more than 15 days in a month. Patients categorised their pain by the different characteristics *viz.* throbbing, dull, penetrating, nagging, blasting, pulling, stinging, gnawing, hammering, etc. factors related to lifestyle, environment and food were labelled as triggering features for the migraine attack (Table 1).

Individuals suffering from moderate to severe migraine pain (patients who could not attend work) or individuals with migraine pain score (VAS > 4) were included in the study. We excluded from the trial, patients with other serious medical conditions and women who were pregnant or lactating. Patients were adequately informed of all the aspects of the study and written informed consent was obtained from them. The study was conducted at Jaslok Hospital and Research Centre in accordance with the declaration of Helsinki and was approved by the Institutional Ethics Committee of Jaslok Hospital and Research Centre. Periodical progress report of the study was also regularly sent to Scientific Advisory Committee of Jaslok Hospital and Research Centre.

At the commencement of a migraine attack, patients from group A were instructed to take one tablet of sublingual piroxicam, 40 mg and those from group B were given a placebo.

The severity of the painful symptomatology was evaluated using the Visual Analogue Scale (VAS): To allow a continuous assessment of pain, VAS uses a 10 cm line labelled at '0' with 'no pain' and '10' with 'very severe pain' (0-2 no pain, 2.1- 4 mild pain, 4.1- 6 moderate pain, 6.1- 8 severe pain and 8.1-10 very severe pain). Assessment of the pain was done on day 1, at 0 mins, 15 mins, 30 mins, 45 mins, 60 mins, 2<sup>nd</sup> hr, 3<sup>rd</sup> hr, 4<sup>th</sup> hr, 5<sup>th</sup> hr, 6<sup>th</sup> hr, 7<sup>th</sup> hr, 8<sup>th</sup> hr and at 24 hrs. Migraine associated symptoms such as nausea; vomiting, photophobia and phonophobia were assessed at baseline and 2 hr and 24 hr after treatment.

## Statistical Analysis

The changes in the intensity of pain in the two groups of patients (those treated with sublingual piroxicam and those given a placebo) were analyzed by the Mann Whitney 'U' Test. The global physician and patient assessment and the differences

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Received: 10.11.2009; Accepted: 07.12.2010



**Table 1 : Trigger factors of migraine attacks**

Serial No.	Trigger Factors
1	Lifestyle Factors:
i.	Mental stress
ii.	Improper sleep/disturbed sleep
iii.	Travelling
iv.	Hair wash
2	Environmental Factors:
i.	Exposure to light
ii.	Exposure to noise
iii.	Exposure to hot climate
iv.	Exposure to cold climate (air condition)
3	Food Factors:
i.	Fasting
ii.	Chocolates
iii.	Tea/coffee
iv.	Cold-drinks

between the two groups were evaluated with the Chi Square test. Changes in migraine associated symptoms intra- and inter-group were also evaluated by Chi Square test.

## Results

Thirty patients were treated with sublingual piroxicam and thirty were given placebo. All the subjects suffered from migraine without aura. All migraine patients habitually required some sort of drug therapy during attacks. More specifically, 16 patients from piroxicam-treated group (53.3%) and 23 from placebo-treated group (76.6%) had been taking analgesics or a combination of NSAIDs and analgesics. Only 15 subjects (6 from piroxicam group and 9 from placebo group) claimed to have benefited from their previous drug therapy and the remaining subjects claimed to have received no substantial benefit at all from drug use.

The patients in the sublingual piroxicam group had an average starting pain intensity of  $7.47 \pm 1.76$  on the VAS. After 15 minutes a significant reduction ( $P < 0.05$ ) was already observable with a drop to a mean value of  $6.42 \pm 2.19$ . The improvement progressively increased. The average score at 24 hours was measured as  $1.73 \pm 1.85$ , which indicates 'no pain'.

The average starting pain intensity level of the placebo group was also  $7.23 \pm 1.69$  but after 30 minutes it still measured  $7.00 \pm 1.90$  and after 24 hours it dropped only to  $6.43 \pm 2.47$ . The statistically significant drop occurred in this group only after 7 hours ( $P < 0.05$ ). On comparison, the drop in intensity was significantly ( $P < 0.05$ ) more in piroxicam group as compared to placebo. At the end of 24 hrs, the drop was 76.9% in piroxicam group as compared to 11.3% in placebo (Table 2).

70-73.3% of the total cases had intense to severe pain at baseline in both the groups, which was same and the difference was not significant. After treatment, the intensity of pain did not show any change in the placebo group but in the piroxicam group at the end of 2 hrs, the intensity of pain had a significant ( $p < 0.05$ ) drop.

At the end of 24 hrs, 16.7% and 63.3% of total cases from the sublingual piroxicam had mild to no pain respectively as compared to only 13.3% and 6.7% in the placebo group respectively, which was statistically significant ( $p < 0.05$ ). Only 1 (3.3%) case in piroxicam had severe pain while significantly ( $p < 0.05$ ) more cases, 5 (16.7%) and 15 (50%) in the placebo group still complained of intense to severe pain respectively (Table 3).

Migraine associated symptoms like nausea was present at the

**Table 2. Changes in mean pain intensity level after the treatment in both the groups**

Duration in Hours	Mean Pain Intensity	
	Piroxicam group	Placebo group
0 min	$7.47 \pm 1.76$	$7.23 \pm 1.69$
15 min	$6.88 \pm 2.20$	$7.25 \pm 1.69$
30 min	$*6.42 \pm 2.19$	$7.00 \pm 1.90$
45 min	$*6.00 \pm 2.66$	$6.90 \pm 1.95$
60 min	$*5.74 \pm 2.45$	$7.06 \pm 2.00$
2	$*4.74 \pm 2.52$	$6.87 \pm 2.18$
3	$*4.40 \pm 2.51$	$6.75 \pm 2.26$
4	$*3.88 \pm 2.24$	$6.87 \pm 2.34$
5	$*3.34 \pm 2.13$	$6.75 \pm 2.24$
6	$*2.82 \pm 2.02$	$6.72 \pm 2.12$
7	$*2.90 \pm 2.23$	$*6.67 \pm 2.23$
8	$*2.45 \pm 1.84$	$*6.61 \pm 2.26$
24	$*1.73 \pm 1.85$	$*6.43 \pm 2.47$

By Mann Whitney 'U' Test; Mean Pain Intensity (mean  $\pm$  SD); \* $P < 0.05$  Significant; Betn Group-  $P < 0.05$  Significant

baseline in 76.7% of the piroxicam-treated patients and in 60% of the placebo group. Two hours later it was present in 10% of the first group and had increased to 80% in the second. At the end of 24 hrs 16.7% of the cases had nausea in placebo group as compared to none in the piroxicam group and this difference was statistically significant ( $p < 0.05$ ) (Fig. 1).

Fig. 2 shows that 6.7 – 10.0% of total patients in both groups had vomiting as an associated complaint at the baseline. While vomiting was markedly reduced after two hours in the piroxicam group, the placebo group showed persistence of vomiting in 20% patients, and this disappeared completely only after 24 hours (Fig. 2).

Phonophobia at baseline was present in 83.3% patients of the piroxicam group and in 80% of the patients treated with placebo. Two hours later it was present in only 13.3% of the piroxicam patients while in the placebo group it persisted in 66.7%. By the end of 24 hours 3.3% cases had phonophobia in the piroxicam group, which was significantly ( $p < 0.05$ ) low as compared to 30.0% in the placebo group (Fig. 3).

Photophobia was recorded in 86.7% of the piroxicam group and in 90% of the placebo group. It had dropped to 20% after two hours in the first group, but was still present in 73.3% of the placebo group of patients. Not a single patient had photophobia at the end of 24 hours in both the groups (Fig. 4).

The investigator's global assessment of the efficacy was excellent / good in 83.3% of the piroxicam cases and poor in 86.7% of the placebo group (Table 4). The patients themselves confirmed this judgement; 83.3% of the patients who were on piroxicam treatment considered the treatment received to be either excellent or good while only 10% of the patients given the placebo rated their treatment good (Table 5). Sublingual administration of Piroxicam was well tolerated and no local or systemic side effects were reported.

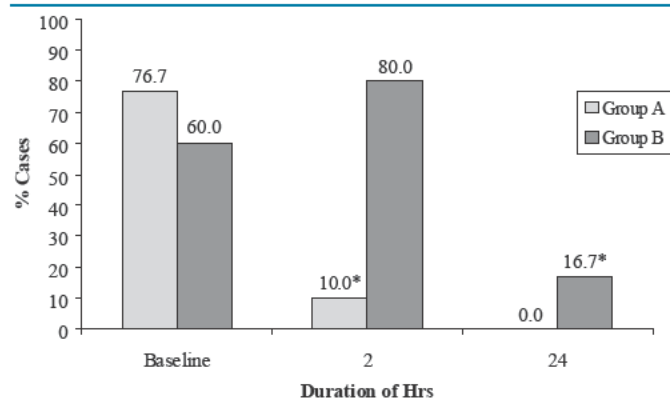
## Discussion

Many different drugs have been proposed for the acute treatment of migraine without aura. Non-steroidal anti-inflammatory drugs, though widely used and reported to be effective, have not been adequately matched to placebo or compared with other drugs of certain efficacy for the relief

**Table 3 : Changes in pain score (as per VAS score) after the treatment in both the groups**

Duration in hours	Piroxicam (N=30)					Placebo (N=30)				
	Intense	Severe	Moderate	Mild	No pain	Intense	Severe	Moderate	Mild	No pain
0 min	12 (40.0)	9 (30.0)	9 (30.0)	0 (00.0)	0 (00.0)	10 (33.3)	12 (40.0)	7 (23.3)	1 (03.3)	0 (00.0)
15 min	9 (30.0)	11 (36.7)	6 (20.0)	4 (13.3)	0 (00.0)	11 (36.7)	11 (36.7)	7 (23.3)	1 (03.3)	0 (00.0)
30 min	6 (20.0)	13 (43.3)	7 (23.3)	2 (06.7)	2 (06.7)	9 (30.0)	12 (40.0)	7 (23.3)	2 (06.7)	0 (00.0)
45 min	7 (23.3)	11 (36.7)	5 (16.7)	4 (13.3)	3 (10.0)	8 (26.7)	13 (43.3)	7 (23.3)	2 (06.7)	0 (00.0)
60 min	5 (16.7)	9 (30.0)	10 (33.3)	4 (13.3)	2 (06.7)	9 (30.0)	11 (36.7)	7 (23.3)	3 (10.0)	0 (00.0)
2	2 (06.7)	6 (20.0)	10 (33.3)	*7 (23.3)	*5 (16.7)	9 (30.0)	11 (36.7)	6 (20.0)	4 (13.3)	0 (00.0)
3	2 (06.7)	4 (13.3)	11 (36.7)	*7 (23.3)	*6 (20.0)	9 (30.0)	12 (40.0)	4 (13.3)	4 (13.3)	1 (03.3)
4	0 (00.0)	4 (13.3)	12 (40.0)	*7 (23.3)	*7 (23.3)	11 (36.7)	10 (33.3)	4 (13.3)	4 (13.3)	1 (03.3)
5	0 (00.0)	4 (13.3)	7 (23.3)	*11 (36.7)	*8 (26.7)	9 (30.0)	13 (43.3)	3 (10.0)	4 (13.3)	1 (03.3)
6	0 (00.0)	2 (06.7)	5 (16.7)	*12 (40.0)	*11 (36.7)	9 (30.0)	11 (36.7)	5 (16.7)	4 (13.3)	1 (03.3)
7	1 (03.3)	2 (06.7)	4 (13.3)	*13 (43.3)	*10 (33.3)	8 (26.7)	12 (40.0)	4 (13.3)	5 (16.7)	1 (03.3)
8	0 (00.0)	2 (06.7)	2 (06.7)	*12 (40.0)	*14 (46.7)	8 (26.7)	11 (36.7)	6 (20.0)	4 (13.3)	1 (03.3)
24	0 (00.0)	1 (03.3)	5 (16.7)	*5 (16.7)	*19 (63.3)	5 (16.7)	15 (50.0)	4 (13.3)	4 (13.3)	2 (06.7)

By Chi-square test; \* P < 0.05 Significant



By Chi-square test

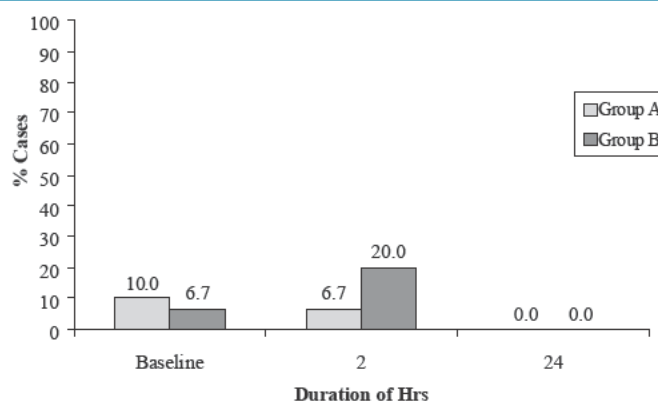
\* P < 0.05 Significant

**Fig. 1 : Changes in proportion of cases with nausea after the treatment**

of migraine symptomatology. Piroxicam is an NSAID with a long half-life and potent analgesic activity similar to that of indomethacin.<sup>5</sup>

The present study, conducted as a double-blind, administered either piroxicam or placebo to patients at the beginning of a migraine attack and then evaluated the analgesic effect and tolerability of the drug as a sublingual formulation.

The patients treated with sublingual piroxicam showed a significant decrease in pain intensity 15 minutes after ingestion; they went on to show a further reduction in the 24 hours after drug administration. On the contrary, the group treated with placebo showed a significant reduction of symptoms only after seven hours of observation and this reduction was most likely spontaneous in nature.



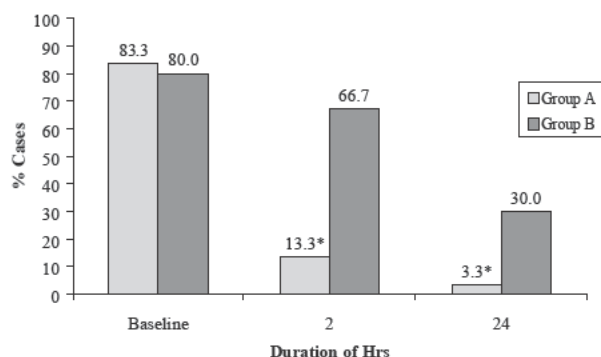
By Chi-square test

P > 0.05 Significant

**Fig. 2 : Changes in proportion of cases with vomiting after the treatment**

It is interesting to note that timely treatment with this new formulation of piroxicam also brought about reduction in the accompanying symptomatology of a migraine attack (nausea, vomiting, phonophobia and photophobia). The gradual disappearance of these symptoms was parallel to that of the pain. It seems that timely ingestion, via "effective" routes which guarantee adequate plasma levels of the drug, are necessary to arrest the neurotransmitter or neuropeptidergic events which determine the occurrence of pain and the associated phenomena of migraine attacks.

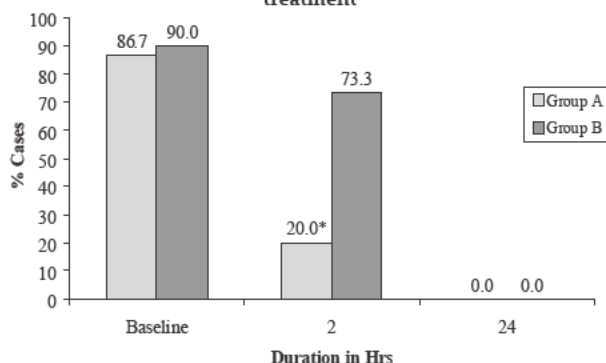
The present study, by demonstrating an almost uniform and overwhelmingly positive patient response, opens up another different and less utilised option for the treatment of acute migraine.



By Chi-square test

\* P < 0.05 Significant

Fig. 3 : Changes in proportion of cases with phonophobia after the treatment



By Chi-square test

\* P < 0.05 Significant

Fig. 4 : Changes in proportion of cases with photophobia after the treatment

A sublingually administered drug is intended to be absorbed across the oral mucosa avoiding gastrointestinal hepatic degradation prior to entry into systemic circulation. Sublingual tablets get absorbed quickly and avoid first pass metabolism. Hence, sublingual dosage form is considered more effective than oral dosage form. Further, sublingual dosage form has less adverse effect as compared to the oral form which often shows adverse effects like nausea, vomiting, gastritis, heart burn, diarrhoea, etc. Other advantages of clinical interest which may be associated with this quick- dissolving formulation of piroxicam include: (i) ease of use, which may improve patient compliance (ii) self administration, which renders it useful in hospital and particularly in general practice and (iii) once daily administration which leads to better patient compliance.

The efficacy and tolerability of the sublingual formulation has been endorsed in several clinical studies in patients with pain of varied etiologies including post surgical pain,<sup>6,7</sup> renal colic,<sup>5</sup> acute recurrent osteoarthritis,<sup>8,9</sup> acute low back pain<sup>10</sup> and dysmenorrhoea<sup>11</sup>. These studies have compared the efficacy and tolerability of sublingual piroxicam with diclofenac sodium,<sup>5</sup> naproxen<sup>6,9</sup> and aspirin.<sup>7</sup>

In this study no patient reported any local or systemic adverse event till the end of treatment.

## Conclusion

The improvement in headache symptoms and accompanying autonomic phenomena seems to indicate that timely ingestion of piroxicam, via an "effective" sublingual route which assures better plasma levels of the drug, is necessary to acquire rapid

Table 4 : Overall global assessment of treatment by physician

Assessment	Piroxicam group		Placebo group	
	No.	%	No.	%
Excellent	18	*60.0	01	03.3
Good	07	*23.3	02	06.7
Fair	03	*10.0	01	03.3
Poor	02	*06.7	26	86.7
No. of Pts	30	100.0	30	100.0

By Chi-square test; \*P < 0.05 Significant

Table 5 : Overall global assessment of treatment by patient

Assessment	Piroxicam group		Placebo group	
	No.	%	No.	%
Excellent	13	*43.3	01	03.3
Good	12	*40.0	02	06.7
Fair	03	*10.0	01	03.3
Poor	02	*06.7	26	86.7
No. of Pts	30	100.0	30	100.0

By Chi-square test; \* P < 0.05 Significant

analgesic effect with excellent tolerability. For the moment however, the present preliminary study, by demonstrating an almost uniform and overwhelmingly positive patient response, call for multicentric studies to verify the reported findings in the treatment of migraine without aura.

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