Durg Corner

Effectiveness and Safety of Nefopam in Indian Patients with Acute Traumatic Pain

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Purpose : Nefopam is a non-narcotic, centrally acting analgesic agent commonly used as an adjuvant for postoperative pain. Considering the paucity of clinical evidence for nefopam in traumatic pain in the Indian setting, this study was conducted to assess the effectiveness and safety of nefopam hydrochloride in Indian patients presenting with acute traumatic pain.

Methods : This open-label, multicenter, single-arm study was conducted at 7 centers across India. Patients with acute traumatic pain (visual analog scale [VAS] score ≥6cm), receiving nefopam 30mg tablets, thrice a day for 5 days, were enrolled. Medical records were collected on Day 1 (baseline). Effectiveness (VAS score, physician's global assessment [PGA] of pain) and safety were assessed at follow-up (Day 2), Day 4, and Day 6.

Findings : A total of 113 patients were enrolled (55 males and 58 females). The mean standard deviation (SD) age of the enrolled population was 44.7 (13.01) years. A significant (P<0.001) reduction in pain intensity (as measured by VAS) at 24 hours. By the end of the treatment, 94 (83.2%) patients reported significant pain relief. PGA scale scores revealed 42 patients with moderately better and a slight but noticeable change in the pain and 38 patients with definite improvement in the pain. Three (2.7%) patients reported Adverse Drug Reactions (ADRs) which included anorectal swelling, dyschezia, hyperchlorhydria, proctalgia, dizziness, headache, dysuria and blisters.

Implications : Nefopam was well tolerated and provided effective analgesia in Indian patients with acute traumatic pain.

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Key words **: Nefopam, traumatic pain, acute pain, nonsteroidal anti-inflammatory drugs, effectiveness, safety.**

Pain is defined as 'an unpleasant sensory and emotional experience relating to actual or potential tissue damage' as per the International Association for the Study of Pain[1]. There are two subtypes of pain: (1) 'nociceptive pain,' which is caused by injury to tissues other than nerves and may be somatic or visceral, and (2) 'neuropathic pain,' which is caused by damage to sensory nerves either peripheral or central. Both these pain types often coexist, particularly during traumatic injuries. It is increasingly recognized that acute and chronic pain, rather than being separate entities, are part of a continuum. Corroborative evidences reported that approximately 58% of poly-trauma victims complain of persistent pain up to 2 years post-injury[2]. This is often an outcome of a surgical procedure performed following a major trauma.

Editor's Comment :

- Despite its available in the Indian market for several years, limited clinical evidence is available on the effectiveness and safety of nefopam in Indian patients with acute traumatic pain
- In this multicenter, open-label, single-arm study conducted across 7 centers in India, patients with acute traumatic pain were administered with 30 mg nefopam thrice daily and followed up for 5 days
- Significant reduction in pain intensity as measured by the visual analog scale was observed at 24 hours after treatment
- Nefopam was generally well tolerated with a low incidence of adverse drug reactions

The primary goals of acute pain management include effective analgesia while promoting the resolution of the underlying causes of pain[3]. In general, most commonly used drugs for acute pain control are Non-steroidal Anti-inflammatory Drugs (NSAIDs) and opiates. However, NSAIDs possess side effects like allergic reactions, gastrointestinal bleeding, perforation, renal dysfunction, and platelet aggregation, while opiates induce dizziness, nausea, vomiting, constipation, pruritis, and respiratory depression[4]. In addition to the side effects, monotherapy alone may

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have limited analgesic potency. Therefore, it has been suggested that analgesic drug combination may be useful to improve analgesia and limit side effects. For a multimodal approach, very few non-narcotic analgesics are available[5].

Nefopam is a non-narcotic analgesic, which is chemically distinct and pharmacologically unrelated to any presently known analgesic[6]. It acts by inhibiting 5-hydroxytryptamine and noradrenaline uptake and reduces the presynaptic release of glutamate associated with pain. Nefopam also interferes with postsynaptic N-methyl-D- aspartate (NMDA) receptors[7,8]. It has the advantage of not affecting platelet aggregation without acausing a depressive effecton the central nervous system[9,10].

Despite its availability for many years, clinical data on the effectiveness and safety of nefopam for acute traumatic pain are scarce. In most previous studies evaluating the analgesic effects of nefopam,it was found to be an effective adjuvant in relieving postoperative pain in patients who underwent orthopedic surgery, cardiac surgery, or experienced other traumatic conditions[11-14]. Other safety studies reported nefopam to be well tolerated, without causing respiratory depression or having an effect on platelet function[10,15]. More recent evidence highlighted significant morphine-sparing effect and additive or synergistic potential of nefopam when used along with other NSAIDs[5,16,17].

Nevertheless, there is paucity of clinical evidence on the use of nefopam in traumatic pain in the Indian setting. Therefore, this study was conducted to assess the effectiveness and safety of nefopam hydrochloride in Indian patients presenting with acute traumatic pain.

Materials and Methods

This open label, multicentric, observational study was conducted from July 2019 to September 2019 across 7 centers in India (Mumbai [2 centers], Coimbatore, Alibag, Bhopal [2 centers] and Vidisha). A total of 113 in- and out-patients with acute traumatic pain of moderate severity (Visual Analog Scale [VAS] score ≥6cm) as assessed by the investigator were enrolled. The study cohort were prescribed with nefopam tablets, 30 mg TID (Nefosar™, Abbott India Ltd) for 5 days. Patients prescribed with other analgesics (up to 7 days prior to baseline), pregnant or lactating women, or patients with cognitive impairment, alcohol abuse, or psychiatric illness were excluded from the study. The total study duration was 6 days, wherein the demographic, baseline and safety data were collected at Visit 1 (Day 1), via telephonic/ in-patient follow-up Day 2 and on Days 4 and 6.

The primary study endpoint was the mean change in pain intensity at 24 hours from baseline using theVAS score. VAS is a self-assessment scale eliciting pain severity on a 10-cm horizontal scale (where 0 = no pain and 10 = worst possible pain). The secondary endpoints comprised of proportion of patients exhibiting clinically significant pain relief (10-cm VAS) at Day 4 and Day 6 of the study. In addition, Physician's Global Assessment (PGA) pain scale (a standardized 7-point scale) was employed to assess the effectiveness to relieve pain and tolerability of the study drug at Day 6. Furthermore, patients with adverse drug reactions (ADRs) and those requiring rescue medications during study period were recorded.

This study was performed in conformity with the principles of the Declaration of Helsinki, International Council for Harmonization-Good Clinical Practices (ICH-GCP) guidelines, Indian Council of Medical Research, Indian GCP guidelines. The study protocol was approved by the independent ethics committees of all participating centers and informed consent was obtained from all patients before data collection.

Statistical analysis :

Continuous variables were summarized descriptively as mean (standard deviation [SD]). Categorical data was summarized as numbers and percentages. A pair-wise t-test was performed at 5% level of significance and the corresponding p-value was obtained to determine significant change in VAS score from baseline. Statistical analysis was done using SAS software (version 9.4,SAS Institute, Cary, NC, US).

Obeservations

Demographic and baseline characteristics :

The study cohort of 113 patients comprised of 55 male and 58 female patients. The mean (SD)age of study cohort was 44.7 (13.01) years. Most patients were educated and belonged to the upper middle class per the Kuppuswamy classification (Table 1).

Vital signs (body temperature, pulse rate, respiration rate, systolic and diastolic blood pressure) recorded throughout the study were within the normal range. However, physical examination reported clinically significant abnormality in cardiovascular and musculoskeletal body systems in 10 (12.8%) and 20 (25.6%) patients, respectively, on Day 2 in 9 (25.7%) and 12 (34.3%) patients, respectively, on Day 4, and in 8 (23.5%) and 6 (17.6%) patients, respectively, on Day 6.

Effectiveness of nefopam :

At baseline, the mean (SD) pain intensity of the study cohort was 8.2 (0.95), which significantly ($P<0.0001$) reduced to 6.7 (1.49), 5.4 (1.90), and 4.6 (2.32) after 24 hours, 3 days, and 5 days of nefopam treatment, respectively (Table 2). As assessed by VAS score, more than 70% patients reported significant pain relief on Day 4 (83 [73.5%]) and Day 6 (94 [83.2%]; Table 3).

Table 1 — Demographics and baseline characteristics

Parameter	Statistics/Category, n (%) [1]	Overall (N=113)
Age (years)		
	Mean (SD)	44.7 (13.01)
	Median	45.0
Gender, n (%)		
	Female	58(51.3)
	Male	55(48.7)
Education		
	Graduate or postgraduate	33(29.2)
	Intermediate or post-high school diploma	24(21.2)
	High school certificate	17(15.0)
	Profession or honors	15(13.3)
	Middle school certificate	12(10.6)
	Illiterate	6(5.3)
	Primary school certificate	6(5.3)
Occupation		
	Skilled worker	58(51.3)
	Unemployed	33(29.2)
	Clerical/shop owner	8(7.1)
	Semi-profession	6(5.3)
	Unskilled worker	5(4.4)
	Profession	3(2.7)
Kuppuswamy classification for socioeconomic status		
	<5:Lower class	1(0.9)
	5-10:Upper-lower class	10(8.8)
	11-15:Lower middle class	31(27.4)
	16-25:Upper middle class	66(58.4)
	26-29:Upper class	5(4.4)

Pain severity by PGA scale indicated 42 (37.2%) patients with moderately better and a slight but noticeable change in pain, 38 (33.6%) patients with definite improvement in pain, and 18 (15.9%) patients with considerable improvement in pain (Fig 1).

Of total 113 patients, 7 patients were given rescue medications, which included analgesics in 6 patients) and anti-inflammatory/antirheumatic products in 1 patient).

Safety of nefopam :

Three (2.7%) patients reported ADRs, which included anorectal swelling, dyschezia, hyperchlorhydria, proctalgia, dizziness, headache, dysuria and blisters. All the events were of Grade 1 with mild intensity and were resolved during the study period.

Discussion

Nefopam is a racemic mixture of its two enantiomers and is a centrally acting non-narcotic analgesic. Having completed more than 60 years in the Indian market and in the absence of data among the Indian milieu, it was imperative to analyze the accumulating evidences on outcomes of nefopam for acute traumatic pain in the real-world setting.

In this observational study, 113 patients with acute traumatic pain arising from different tissue injuries prescribed with nefopam were enrolled. Employing the standard and validated 10 cm VAS, a significant reduction in pain was observed after 24 hours of nefopam treatment (30 mg, TID) in patients with moderately severe acute traumatic pain. Continuing treatment with nefopam up to 5 days resulted in about 83% patients reporting significant pain reduction. These findings are corroborated by the observations of the PGA scale, wherein ~87% of patients experienced change in pain intensity and felt moderately better. A retrospective chart review among trauma patients who received nefopam at the emergency department of Korea University Medical Center had also reported significant pain reduction on a numerical rating scale after 30 min from baseline[18]. Evidence thus supports the effectiveness of nefopam as a potent analgesic in patients with acute traumatic pain.

Furthermore, 3 out of 113 enrolled patients reported ADRs with nefopam administration, a few of which are known effects of nefopam[19,20]. Interestingly all the 8

Table 2 — *Visual analog scale scores*

Visit/Follow up,	(N=113)	Change from Baseline	*P* value
Visit 1 (Day 1) :			
Mean (SD)	8.2 (0.95)	-	
Median (95% CI)	8.0(7.98, 8.34)	-	
Follow-up (Day 2) :			
Mean (SD)	6.7 (1.49)	-1.5 (1.54)	<0.0001
Median (95% CI)	7.0(6.42, 6.98)	-1.0(-1.75,-1.17)	
Visit 2 (Day 4) :			
Mean (SD)	5.4 (1.90)	-2.8 (2.13)	<0.0001
Median (95% CI)	6.0(5.03,5.74)	-2.00(-3.17,-2.38)	
Visit 3 (Day 6 + 1day) :			
Mean (SD)	4.6 (2.32)	-3.6 (2.57)	<0.0001
Median (95% CI)	6.0(4.12, 4.99)	-3.00(-4.09,-3.13)	

CI, confidence interval; SD, standard deviation

Table 3 — Summary of pain relief

Patients, n (%)	Overall (N=113)	CI*
Visit 1 (Day 1) :		
Has the patient discontinued the treatment?		
Yes	0	
No	113 (100.0)	
Visit 2 (Day 4) :		
Significant pain relief based on VAS		
Yes	83 (73.5)	64.32-81.32
Has the patient discontinued the treatment?		
Yes	3 (2.7)	
No	110 (97.3)	
Visit 3 (Day 6) :		
Significant pain relief based on Visual analog scale scores (cm)		
Yes	94 (83.2)	74.99-89.56
Has the patient discontinued the treatment?		
Yes	1 (0.9)	
No	112 (99.1)	

'Significant pain relief' is defined as at least 1.4 cm decrease in pain intensity from reported on VAS
*95% CI of the percentage value was calculated by Clopper–Pearson method.
CI, confidence interval; VAS, visual analog scale

events such as anorectal swelling, dyschezia, hyperchlorhydria, proctalgia, dizziness, headache, dysuria and blisters were of mild intensity and resolved within the study period.

A study limitation is that our observations are largely based on the reduction of VAS score. Considering that the severity of pain is highly subjective and variable among patients, differences with the accuracy of results are likely to occur. However, the conclusions are based on cumulative assessment of observations reported by patients (VAS score) as well as the physicians (PGA score). Therefore, likelihood of a larger deviation in the study observations is minimal.

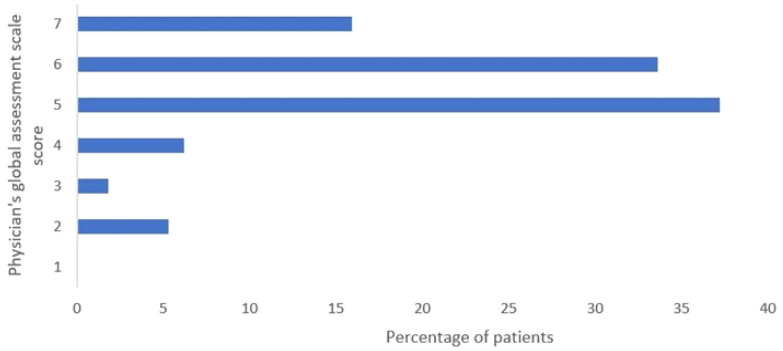

Fig 1 — Physician's global assessment of pain

Score 1 = no change; 2 = almost the same, hardly any change at all; 3 = a little better, but no noticeable change; 4 = somewhat better, but the change has not made any real difference; 5 = moderately better and a slight but noticeable change; 6 = better and a definite improvement that has made a real and worthwhile difference; 7 = great deal better and a considerable improvement that has made all the difference.

In conclusion, the results indicate that nefopam provides effective analgesia by virtue of its ability to reduce pain significantly after 24 hours,and up to 5 days of treatment. Nefopam was also found to be tolerable in these patients with acute traumatic pain. Further studies are warranted on the use of nefopam in patients with trauma and in larger population cohorts.

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