The Journal of Medical Research

Research Article

JMR 2020; 6(6): 282-285
November- December
ISSN: 2395-7565

www.medicinearticle.com
Received: 08-10-2020
Accepted: 07-11-2020

Comparison of oral and intravenous nefopam for fracture pain in Emergencies, Antananarivo

Aurelia Rakotondrainibe*[1], Angelot F. Randrianarisoa[1], Nicole R. C. Rakotoarison[1]

[1] Faculté de Médecine d'Antananarivo, Université d'Antananarivo, Madagascar

Abstract

Background: Pain management of fractures in emergency room requires multimodal analgesia including nefopam. Oral or parenteral administration of this molecule can be performed. **Aim of the study:** The main aim of the study was to compare the efficiency of oral and intravenous nefopam in traumatic fracture pain, in emergency unit. **Methods:** A prospective, comparative, randomized study was conducted in Emergency Department of the Hospital University of J.R. Andrianavalona. This study was conducted in two groups (oral and intravenous groups) of patients presenting fracture pain, over a period of six months. The primary endpoint was the analgesic efficiency. Comparison and correlation tests were used (SigmaPlot® 10.0). **Results:** The study population was aged 29 [18 - 70] years, mostly men (sex ratio: 6.3). Oral nefopam significantly decreased the pain by 1.5 to 2 points. The decrease in pain intensity with oral nefopam was significant from 20th minute to 90th minute ($p<0.05$). Acetaminophen was associated with nefopam in 98% after the 20th minute. Tachycardia, dizziness and dry mouth were observed. Fewer adverse effects were observed with oral nefopam. **Conclusion**: Oral nefopam seems to be more efficient comparing to intravenous nefopam in fracture pain management in emergency room. This practice should be implemented in emergency multimodal analgesia by its ease and efficiency of use.

Keywords: Adverse effects, Analgesia, Emergency, Fracture, Nefopam, Pain.

INTRODUCTION

Developed as fenazocine in the 1960s, nefopam is used in many countries, as a non-opioid, non-steroidal, centrally acting analgesic drug, to treat moderate to severe acute pain [1, 2]. Nefopam can be orally and intravenously administered with same effectiveness [2-5]. Parenteral nefopam is more used in multimodal management of pain and adverse effects are more reported [2, 6]. Oral nefopam may be use with dose of 90-180 mg/day, in three to six times [1].

Fractures and fracture pain are the most common and costly problem caused by bone injury [4]. The management of fracture pain (FP) remains one of the main management in emergency unit. It is an ethical duty for all health personnel, particularly for emergency physicians who need to have targeted invasive treatments [7-9]. Whatever the type of fracture (open or closed, simple or complex, displaced or not), it can cause intense pain from the start of the fracture process until the end of the consolidation process. Besides the fracture itself, this FP can be linked to many other factors and can vary in intensity and duration [4, 7]. Currently, its management begins from the initial consultation until the discharge order. In order to fight against FP, several drugs can be used, including nefopam, in multimodal analgesia [1, 10-12].

The use of nefopam is common in emergency and other departments; however some precautions should be taken due to its adverse effects [5, 13]. The few articles - despite the current oral use of nefopam - motivated us to realize this study witch aim is to compare the effectiveness of oral and intraveinous nefopam in traumatic fracture pain. This aim arose from the hypothesis that oral nefopam would be as effective as intravenous nefopam.

MATERIALS AND METHODS

A prospective, comparative, randomized single-blind study, over a period of six months, from August 2016 to January 2017, was carried out in the Emergency Room (ER) of the Joseph Ravoahangy Andrianavalona University Hospital Center (Centre Hospitalier Universitaire J.R. Andrianavalona [CHU JRA]).

Before including any patient, informed consent was obtained. approval from the Anesthesia-Intensive Care-Emergency Department was obtained before the beginning of the study. The inclusion criteria were conscious patients, aged over 15 years, with a traumatic fracture, admitted to the emergency room. Besides, analgesia with nefopam was done (orally or intravenously), at the hospital admission, with assessment of the "nefopam-analgesia" during the first 20 minutes. Were excluded, the patients in whom a discontinuation or a change in the administration of the nefopam was done.

***Corresponding author:**
Dr. Aurelia Rakotondrainibe
Faculté de Médecine d'Antananarivo, Université d'Antananarivo, Madagascar
Email:
aaurelia.rakotondrainibe[at]gmail.com

Also, exclusion of patients was done if there was an addition of other pain relievers during the first 20 minutes after administration of nefopam. The primary endpoint was the analgesic efficiency of nefopam; the secondary endpoint, the side effects of nefopam.

Randomization was performed for protocol assignment. Nefopam has been administered either intravenously or orally. The use of sugar with a teaspoon was added for oral administration. Intravenous nefopam was done by 20 minutes-direct infusion. The patients were divided into two groups: **(i) "O GROUP"**: oral nefopam 20 mg combined with sugar in a teaspoon without renewal and **(ii) "IV GROUP"**: 20 mg of intravenous nefopam also without renewal. In case of moderate pain or higher [evaluated with Numerical Pain Rating Scale (NPRS)] greater than 3, acetaminophen was added 20 minutes after administration of nefopam.

The studied parameters were age, gender, American Society of Anesthesiologists (ASA) physical status, characteristics of the trauma (traffic, public, domestic, school, sports, work, civil liability accidents), the type of fracture (simple or not, displaced or not, open or closed). The clinical parameters studied were the arterial blood pressure [systolic arterial blood pressure (SBP), diastolic arterial blood pressure (DBP) and mean arterial blood pressure (MBP)], the heart rate (HR), the respiratory rate (FR)) and the intensity of pain according to NPRS. Data on analgesia were studied (the quality of the analgesia, the use of other molecules, including acetaminophen, morphine and the use of immobilization or restraints of the fracture).The nefopam-related adverse effects were also investigated (drowsiness, nausea / vomiting, dry mouth, tachycardia / palpitations, urinary retention).

Statistics

The results were expressed as the median with [minimum – maximum] for the continuous data and in frequency for the categorical variables. Comparison (Mann Whitney test) and correlation (Spearman test) tests were carried out (SigmaPlot® 10.0). A p-value less than 0.05 was considered significant.

RESULTS

During the study period, 60 patients were included. After randomization, two groups of 30 patients were determined. One "IV GROUP" patient was withdrawn from the study due to the administration of oral nefopam, one hour after intravenous nefopam administration. Hence, 59 patients were selected and divided in "O GROUP" (30 patients) and "IV GROUP" (29 patients).

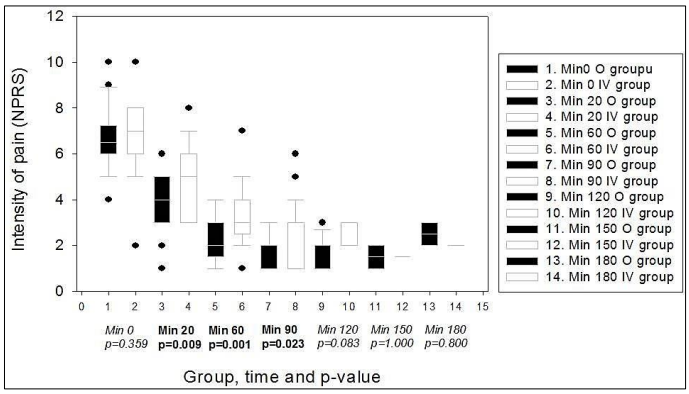
The general population was aged 29 [18 - 70] years with a masculine predominance (sex ratio: 6.3). In 93% of cases, the patients did not have co-morbidities (ASA I physical status) and 7% of the patients were classified ASA II. The "O Group" and "IV Group" were comparable to each other, for the following variables: age, gender, ASA classification, type of fracture and accident, vital parameters and the intensity of the initial pain (before administration of nefopam at Min 0) (*Cf* Table I). The delay in the arrival of patients in the emergency room in relation to the accident was 85 [5 - 367] min for the general population.

Table I: Population study

		O Group	**IV Group**	**p**[a]
Median age	(years)	30	26.5	*0,265*
Gender [n]	Men / Women	25 / 5	26 / 3	*0,490*
ASA[b] **classification**	I [n(%)]	29 (97%)	26 (90%)	*0,296*
	II [n(%)]	1 (3%)	3 (10%)	
Type of accident [n(%)]	Public road accident	7 (23%)	6 (21%)	*0,648*
	Circulation accident	13 (43%)	9 (31%)	
	Work accident	3 (10%)	2 (7%)	
	Civil liability accident	0 (0%)	1 (3%)	
	Sport accident	2 (7%)	3 (10%)	
	Home accident	5 (17%)	6 (21%)	
	School accident	0 (0%)	2 (7%)	
Type of fracture [n(%)]	Closed fracture	19 (63%)	17 (59%)	*0,648*
	Open fracture	11 (37%)	22 (76%)	
	Upper member(s)	17 (57%)	16 (55%)	
	Lower member(s)	13 (43%)	12 (41%)	
	Upper and lower members	01 (3%)	01 (3%)	
Signs at admission (median)	Pain intensity (NPRS[c])	6	7	*0,199*
	Systolic arterial blood pressure	125	130	*0,663*
	Diastolic arterial blood pressure	80	80	*0,677*
	Mean arterial blood pressure	93	97	*0,796*
	Heart rate	84	85	*0,433*
	Respiratory rate	20	21	*0,249*

[a]: The two groups were comparable (p>0.05), [b]:American Society of Anesthesiologists, [c]: Numerical Pain Rating Scale

The pain assessment was performed for all patients from the arrival at ER (Min 0) to the 90th (Min 90) minute in ER. The intensity of pain was different but not significant between the two groups at the admission (Min 0), 6.5 [4-10] for the "O Group" *versus* 7 [5-10] for the "IV group" (Figure 1). The decrease in pain was significant from the 20th min (Min 20) to the 90th minutes (p <0.05) (Figure 1). From the 120th minute, not all the patients remained in ER; the pain intensity (from 120th to 180th minute) between the 2 groups was not significant (p>0.05).



"O group": black boxes, "IV group": white boxes.
*Bold **p-value**: significant, Italic* p-value*: not significant*
Min: minute

Figure 1: Evolution of intensity of pain in the 2 groups

Only one type of analgesia was performed (combination of acetaminophen and nefopam) in 98%. The correlation between the use of acetaminophen and nefopam was not significant (p= 0.872). The use of morphine was not needed in any group. A cast for restraining the fracture was performed in 47% ("O Group") and 21% ("IV Group"). Surgical intervention was needed in 47% of patients in the "O Group" and 79% in the "IV Group".

In the two groups, the adverse effects appeared fewer in "O group", with a significant difference between the two groups at the 20th minute [(Min 20), p = 0.003] and at the 60th minute [(Min 60), p=0.011]. In the general study population, patients presented tachycardia (81%), dry mouth (25%) and dizziness (13%). Nausea and vomiting, drowsiness, urinary retention, sweats, confusion have not been reported. For drowsiness and tachycardia, the incidence was fewer in "O group" but with no significant difference with "IV group". Nevertheless, there was a significant difference (p=0.005) with dry mouth adverse effect between the "O group" (13%) and "IV group" (87%).

After being taken care into the ER (median ER length= 148 [120 - 287] min for the general population), patients were admitted (i) to the Trauma Department for 37% patients of "O Group" and 7% in "IV Group", (ii) to the Emergency Resuscitation Department for "O Group" (43%) and "IV Group" (80%), (iii) in other services besides those mentioned before for "O Group" (7%) and "IV Group" (0%) patients. If patients were not transferred, they were discharged from hospital (13% for both "O Group" and "IV Group").

DISCUSSION

Nefopam is an interesting molecule due to its pharmacodynamic properties, even if, like all drugs, its side effects seem to limit its use [5, 13, 14]. In Madagascar, it only appeared since July 2007. Nefopam has been used in Europe for intravenous and oral administration since 1976 [1, 12] Before 1990, most of the studies evaluated the analgesic effect of a single oral or intramuscular administration. The results of these studies suggested that the analgesic effect of nefopam 20 mg equaled with meperidine 50 mg or morphine 6±12 mg [3]. Due to insufficient works on the oral use of nefopam, oral nefopam is not yet widely prescribed despite the ease of this administration [3].

Although the study population is quite small, better analgesic efficiency has been observed for oral nefopam, from the 20th minute after administration, until the 90th minute. This decrease in pain, by 1.5 to 2 points using oral nefopam (figure 1) was observed, with lesser incidence of adverse effects for the "O Group" compared to "IV Group".

According to some studies, oral nefopam seems to be comparable to intravenous nefopam, in healthy subjects [5, 15, 16]. Moreover, once daily oral dose of nefopam hydrochloride could be used for management of acute post-surgical pain which might augment patient-compliance [6]. In addition, desmethyl-nefopam (enantiomer of nefopam) is known to contribute to analgesia, when administered orally [5, 15]. Desmethyl-nefopam enantiomers' plasma concentrations following oral administration, peaked earlier and higher than after IV administration (p<0.05) and can contribute to the analgesic effect of racemic nefopam [17]. Regardless of the route of administration, the half-life of desmethyl-nefopam is longer than that of nefopam [5].

Oral nefopam efficiency was desmontrated [18]. Rémérand F *et al*. [10] find that nefopam decreased postoperative pain by 8 points in hip surgery in the first 24 postoperative hours, when included in multimodal analgesia. Heissat T *et al*. [19] found a reduction in pain of 4.6 ± 2.1 one hour after administration of sublingual nefopam compared to intravenous nefopam in abdominal pain. Also, morphine consumption decreased by 6.1 to 10.4 mg after orthopedic surgery when nefopam is added in multimodal analgesia [11]. In a study of Fethi J *et al*. [14], using of oral and intravenous nefopam does not make significant difference in postoperative pain and morphine consumption even if morphine consumption may be higher when nefopam given orally (25,2 ± 12,1 mg *versus* 23,9 ± 10,09, *p* = 0,18). Moreover, combining low oral analgesic doses of nefopam and other drugs such as aspirin, can provide an additive antinociceptive effect in acute pain model and it is convenient to convert from intravenous nefopam (60 – 120 mg/day) during hospitalization into oral medication (3 to 6 times with a total of 90 – 180 mg/day) after discharge [9, 18]. The current practice of oral nefopam allows an analgesic effectiveness from 30 minutes to an hour on average [8, 13].

Sometimes, the mismanagement of pain related to trauma (fractures or injuries), as well as the significant and inadequate consumption of analgesics in perioperative or in fracture pain management, lower the threshold of nociception; to manage the post fracture pain becomes then difficult [20, 21]. Current recommendations, therefore, recommend multimodal analgesia (the use of at least dual therapy) in traumatology emergency in addition to a stabilization of the fractured bone and a minimal bed rest [4, 8].

The administration of nefopam can lead to some adverse effects but fewer when orally administrated [18]. It was also found in the present study that adverse effects (tachycardia, dry mouth and drowsiness) were less frequent in "O group" than "IV group". But this fact is not constant; indeed, drowsiness was more recorded when nefopam is administrated orally than intravenously [5]. In our study, the dry mouth was significantly fewer in "O group"; which was different from a study of Pasutharnchat K *et al*. [22] where dry mouth was more frequent than placebo (40% *versus* 25%) but with no significant difference. Moreover, in some studies, the apparition of oral nefopam adverse effects does not significantly differ with intravenous nefopam or placebo [14, 22].

The interest of the present study was the comparison of oral and intravenous nefopam in fracture pain management in emergency room. Indeed, there are few studies about oral nefopam, so our results could add relevance about this administration mode. However, this study is limited by the small sample which does not represent the whole Malagasy hospital population. The use of acetaminophen for 98% of patients may underestimate the efficiency of nefopam. Also, the other managements (cast, surgery, etc…) of FP could be a bias of

our results even if there was no difference about these procedures between the 2 groups.

CONCLUSION

Oral nefopam bring a better analgesia with few adverse effects in fracture pain management in emergency room. The difference was significant comparing intravenous route from 20th to 120th minute. Due to the ease of administration of oral nefopam, this latter can be introduced in the multimodal analgesia of fracture pain.

Conflicts of interest

All the authors declare that they have no conflict of interest.

Authors' contribution

All authors confirm her/his contribution to the present study

REFERENCES

1. Kim KH, Abdi S. Rediscovery of nefopam for the treatment of neuropathic pain. Korean J Pain. 2014; 27(2):103-111. doi:10.3344/kjp.2014.27.2.103.
2. Nair AS. Nefopam: another pragmatic analgesic in managing chronic neuropathic pain. Indian J Palliat Care. 2019; 25(3):482-483. doi:10.4103/IJPC.IJPC_215_18.
3. Evans MS, Lysakowski C, Tramèr MR. Nefopam for the prevention of postoperative pain: quantitative systematic review. Br J Anaesth. 2008; 101(5):610-617. doi:10.1093/bja/aen267.
4. Mitchell SAT, Majuta LA, Mantyh PW. New insights in understanding and treating bone fracture pain. Curr Osteoporos Rep. 2018; 16(4):325-332. doi:10.1007/s11914-018-0446-8.
5. Aymard G, Warot D, Démolis P, Giudicelli JF, Lechat P, Le Guern ME, Alquier C, Diquet B. Comparative pharmacokinetics and pharmacodynamics of intravenous and oral nefopam in healthy volunteers. Pharmacol Toxicol. 2003; 92(6):279-86. doi: 10.1034/j.1600-0773.2003.920605.x.
6. Sharma N, Arora S, Madan J. Nefopam hydrochloride loaded microspheres for post-operative pain management: synthesis, physicochemical characterization and in-vivo evaluation. Artif Cells Nanomed Biotechnol. 2018; 46(1):138-146. doi:10.1080/21691401.2017.1301459.
7. Keating L, Smith S. Acute Pain in the Emergency Department: The Challenges. Rev Pain. 2011; 5(3):13-17. doi:10.1177/204946371100500304.
8. Vivien B, Adnet F, Bounes V, Cheron G, Combes X, David JS, *et al*. Sédation et analgésie en structure d'urgence. Réactualisation 2010 de la Conférence d'experts de la Sfar de 1999. Ann Fr Anesth Reanim. 2012; 31(4):391-404. doi:10.1016/j.annfar.2012.02.006.
9. Kim KH, Seo HJ, Abdi S, Huh B. All about pain pharmacology: what pain physicians should know. Korean J Pain. 2020; 33(2):108-120. doi:10.3344/kjp.2020.33.2.108.
10. Remerand F, Le Tendre C, Rosset P, Peru R, Favard L. Néfopam après prothèse totale de hanche: quelle place dans l'analgésie multimodale. Rev Traum Orth 2013; 99(2):138-143.
11. Du Manoir B, Aubrun F, Langlois M, Le Guern ME, Alquier C, Chauvin M, Fletcher D. Randomized prospective study of the analgesic effect of nefopam after orthopaedic surgery. Br J Anaesth. 2003; 91(6):836-841. doi:10.1093/bja/aeg264.
12. Choi JI. Use of Nefopam in Perioperative Pain Management; Keeping Nefopam in between. Korean J Pain. 2016; 29(2):71-72. doi:10.3344/kjp.2016.29.2.71.
13. Merle JC, Vandrou D, Odin I, Dupuis JL, Bougault A, Mehaddi Y, *et al*. Effets analgésiques de l'administration intraveineuse continue de néfopam après chirurgie urologique. Ann Fr Anesth Reanim. 2005; 24(1):13-18. doi:10.1016/j.annfar.2004.11.008.
14. Fethi J, Bilel M, Walid A, Ali J, Lotfi G. Comparaison de deux protocoles analgésiques en postopératoire de césarienne: voie orale versus voie intraveineuse. Anesthésie et Réanimation 2015; 1(Suppl1):A153-4. doi.org/10.1016/j.anrea.2015.07.236.
15. Ahmad M, Yaqoob M, Murtaza G. Study of pharmacokinetics and comparative bioavailability of nefopam 30 mg tablets in twelve fasting healthy Pakistani male young subjects: single-dose, randomized, two-period, two-treatment and two-way cross-over design. Med Princ Pract. 2012; 21(3):271-276. doi:10.1159/000333560.
16. Sanga M, Banach J, Ledvina A, Modi NB, Mittur A. Pharmacokinetics, metabolism, and excretion of nefopam, a dual reuptake inhibitor in healthy male volunteers. Xenobiotica. 2016; 46(11):1001-1016. doi:10.3109/00498254.2015.1136989.
17. Chawla J, Le Guern ME, Alquier C, Kalhorn TF, Levy RH. Effect of route of administration on the pharmacokinetic behavior of enantiomers of nefopam and desmethylnefopam. Ther Drug Monit. 2003; 25(2):203-210. doi:10.1097/00007691-200304000-00010.
18. Girard P, Chauvin M, Verleye M. Nefopam analgesia and its role in multimodal analgesia: A review of preclinical and clinical studies. Clin Exp Pharmacol Physiol. 2016; 43(1):3-12. doi:10.1111/1440-1681.12506.
19. Heissat T. Traitement par néfopam des douleurs abdominales de l'adulte en médecine ambulatoire d'urgence par les praticiens de SOS Médecin. 54: Enquête de pratiques sur l'utilisation des voies injectable et sublinguale [Thèse] Médecine humaine: Université Poincaré, Nancy 1; (France)2009.
20. Riel AM, Rakotoarison RCN, Rakotoarivony ST, Rakotomavo FA, Randriamiarana JM, Starzk F. Analgésie post-opératoire en orthopédie. Rev Anesth Réa Med Urg. 2011; 3(2): 11-3.
21. Mimoz O, Incagnoli P, Josse C, *et al*. Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection. Anaesthesia. 2001; 56(6):520-525. doi:10.1046/j.1365-2044.2001.01980.x.
22. Pasutharnchat K, Wichachai W, Buachai R. Analgesic efficacy of nefopam for cancer pain: a randomized controlled study. F1000Res. 2020;9:378. Published 2020 May 19. doi:10.12688/f1000research.23455.1;