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• Original Article •

# Efficacy of Nefopam Analgesia for Trauma Patients in the Emergency Department

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**Purpose**: Nefopam is a centrally acting non-narcotic analgesic that has mostly been used for postoperative pain. We examined the efficacy of nefopam analgesia (alone and in combination with ketorolac) for trauma patients in the emergency department.

**Methods**: We performed a retrospective chart review to select trauma patients who received nefopam at the emergency department of Korea University Medical Center Guro Hospital between January 2012 and December 2012. Patients younger than 15 years were excluded. The primary outcome measure was change of pain score (numeric rating scale) from baseline (before medication) to 30 min after medication. The secondary outcome measure was requirement for additional analgesia (pethidine).

**Results**: Records of 1465 trauma patients who received analgesics in the emergency department from January 2012 to December 2012 were examined. Patients were classified into five groups according to initial analgesic: nefopam (n=112), ketorolac (n=867), pethidine (n=365), nefopam+ketorolac (92), and nefopam+pethidine (22). There were no significant differences in pain score reductions among the five groups. Twenty-two patients in the nefopam group, 141 in the ketorolac group, and 29 in the nefopam+ketorolac group required rescue analgesia with pethidine; these rates were not significantly different.

**Conclusion**: The efficacy of nefopam analgesia for trauma patients in the emergency department is comparable to that of more commonly used agents, including ketorolac and pethidine. [ J Trauma Inj 2017; 30: 1-5 ]

**Key Words**: Trauma, Pain, Nefopam

## I. Introduction

Many patients come to emergency department (ED) because of acute pain, resulting from trauma and are treated with analgesics. Multimodal analgesic management that enhances the efficacy of standard treatments is becoming increasingly common.(1) Pain is a subjective sensation, and it is difficult to objectively estimate differences in degree of pain among individuals. The numeric rating scale (NRS) is commonly used to objectify the severity of pain.(2) Effective pain treatment must be varied according to individual variations in pain perception, and the search for broadly applicable high-efficacy methods of pain control is ongoing. However, the treatment of choice remains elusive, and in current practice, analgesics are used in varying ways in accordance with the protocol of a hospital or a doctor's experience. In general, most commonly used drugs for pain control are non-steroidal anti-inflammatory drugs

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(NSAIDs) and opiates. Medications in both of these classes may have dangerous side effects, and some patients may require drugs with a different mechanism. Nefopam is non-narcotic analgesic that is known to act by inhibiting 5-hydroxytryptamine and noradrenaline uptake and to reduce the presynaptic release of glutamate associated with pain. Nefopam also interferes with postsynaptic N-methyl-D-aspartate (NMDA) receptors.(3,4) It was initially introduced as having post-operative morphine-sparing effects following various types of surgery.(5-7) However, the effect of nefopam for initial pain management in trauma patients has not yet been studied. Therefore, this study investigated the efficacy of nefopam and nefopam+ketorolac in trauma patients in the ED in terms of pain score and rescue analgesia (pethidine) requirement. In other words, the primary endpoint of this study is the comparison about change in pain score between each group.

## II. Materials and Methods

This study was carried out with the approval of the Korea University Guro Hospital Institutional Review Board (approval number: KUGH-13234). The study was a retrospective chart review. Trauma patients who received nefopam (Acupan, Biocodex, Paris, France), ketorolac, and pethidine at the ED of Korea University Medical Center Guro Hospital over a 1-year period (January to December 2012) were enrolled.

Pain scores were estimated by numerical rating scale (NRS) before medication and 30 min after medication. Cases in which the pain score was not recorded due to the patient's condition, and those in which patients received nefopam, ketorolac, and pethidine for pain control were excluded. Finally, records of 1295 patients were included in the analysis. Patients were divided into groups according to the analgesic given: nefopam, ketorolac, pethidine, nefopam+pethidine (n+p), and nefopam+ketorolac (n+k), and the changes in the pain score were investigated (1,295 patients). Patients were secondarily divided into nefopam, ketorolac, and n+k groups, and the number of patients in each of these three groups who were treated with additional pethidine was confirmed (1,100 patients). Patient characteristics including age, gender, and types of trauma were identified, and patients were also classified according to the region of trauma: head and neck, facial, chest, abdomen and trunk, and extremity, and according to the pain severity, with NRS 0-4 defined as mild pain, 5-6 as moderate pain, and 7-10 as severe.

All calculations were performed using SPSS version 14.0 (SPSS, Inc, an IBM Company, Armonk, NY, USA), and null hypotheses of no difference were rejected if $p$-values were $<0.05$. Data were expressed as mean±SD. Comparisons between groups were divided according to medication and one-way and two-way ANOVA tests were used.

None of the authors have conflicts of interst.

## III. Results

Among trauma patients who visited the ED during

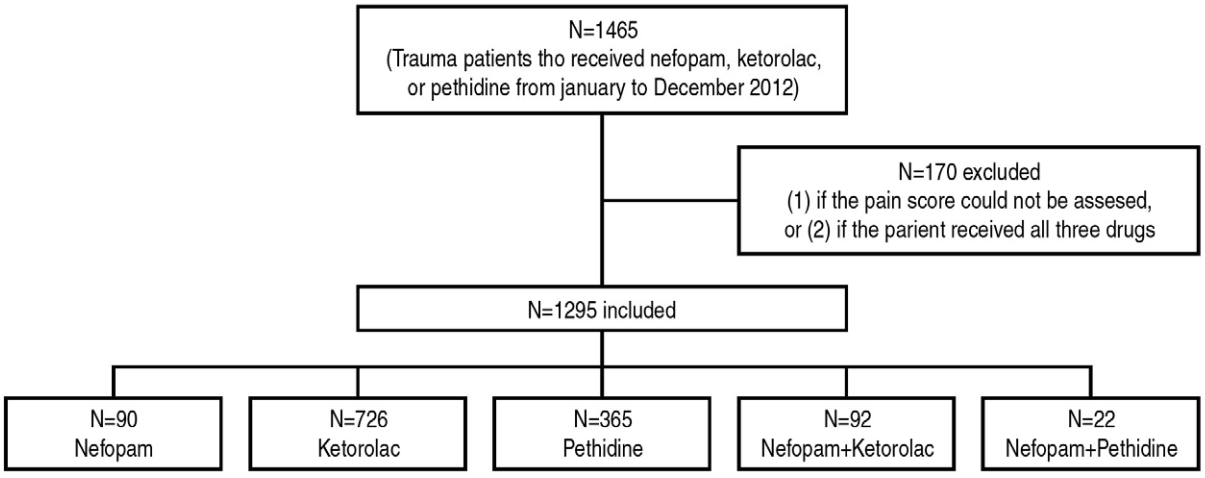


**Fig. 1.** A flowchart for number of patients included in analysis.

the study period, a total of 1465 patients were treated with nefopam, ketorolac, pethidine, or combinations thereof. Cases in which the pain score could not be assessed due to the condition of patient, and those who received all three drugs were excluded. Thus, the analysis included 1295 patients, 1,100 of whom required rescue analgesia with pethidine.

Ninety patients received nefopam, 726 received ketorolac, 365 received pethidine, 92 received n+k, and 22 received n+p (Fig. 1). There were no statistically significant differences in age, sex, and trauma site, initial pain score, and pain severity among the groups. Patient characteristics and initial and post-treatment pain scores are listed in Table 1. Average reductions in pain score were 3.2±2.2 in the nefopam group, 3.4±2.2 in the ketorolac group, 3.4±2.2 in the pethidine group, 3.2±2.1 in the n+k group, and 3.7±2.2 in the n+p group (Table 1). The differences in pain score reduction among groups were not significant.

**Table 1.** Patient characteristics and comparison of pain scores

| | Nefopam | Ketorolac | Pethidine | N+K | N+P | *p* |
|---|---|---|---|---|---|---|
| N | 90 | 726 | 365 | 92 | 22 | |
| Age (yr.) | 48.2±19.0 | 48.5±19.2 | 47.1±18.9 | 48.6±19.3 | 53.0±17.4 | 0.609 |
| Male (n) | 48 | 431 | 202 | 50 | 10 | 0.207 |
| Initial pain score | 6.0±2.1 | 6.0±2.0 | 5.9±2.0 | 5.7±2.0 | 7.0±2.4 | 0.191 |
| Change of pain score | | | | | | |
| | -3.2±2.2 | -3.4±2.2 | -3.4±2.2 | -3.2±2.1 | -3.7±2.2 | 0.685 |
| Site of trauma (n) | | | | | | 0.379 |
| Head and neck | 12 | 89 | 51 | 8 | 1 | |
| Extremity | 51 | 386 | 194 | 57 | 15 | |
| Face | 9 | 68 | 26 | 9 | 1 | |
| Chest | 5 | 52 | 17 | 3 | 0 | |
| Abdomen and trunk | 13 | 131 | 77 | 15 | 5 | |
| Intensity of pain (NRS) (n) | | | | | | 0.691 |
| Mild (0-4) | 20 | 172 | 90 | 23 | 4 | |
| Moderate (5-6) | 46 | 387 | 196 | 49 | 8 | |
| Severe (7-10) | 24 | 167 | 79 | 20 | 10 | |

N+K: nefopam+ketorolac, N+P: nefopam+pethidine, NRS: numeric rating scale

**Table 2.** Patient characteristics and comparison of additional analgesic requirements (pethidine)

| | Nefopam | Ketorolac | N+K | *p* |
|---|---|---|---|---|
| N | 112 | 867 | 121 | |
| Age (yr) | 47.1±18.7 | 48.4±19.1 | 47.4±18.8 | 0.719 |
| Male (n) | 58 | 507 | 61 | |
| Initial pain score | 6.2±2.2 | 6.0±2.0 | 5.8±2.1 | 0.31 |
| Add pethidine (n, %) | 22 (19.7) | 141 (16.3) | 29 (24.0) | 0.105 |
| Site of trauma (n) | | | | 0.786 |
| Head and neck | 13 | 103 | 14 | |
| Extremity | 66 | 464 | 70 | |
| Face | 10 | 83 | 12 | |
| Chest | 5 | 62 | 4 | |
| Abdomen and trunk | 18 | 155 | 21 | |
| Pain intensity (NRS) (n) | | | | 0.471 |
| Mild (0-4) | 24 | 208 | 29 | |
| Moderate (5-6) | 54 | 485 | 64 | |
| Severe (7-10) | 34 | 194 | 28 | |

N+K: nefopam+ketorolac, NRS: numeric rating scale

Twenty-two out of 112 patients (19.7%) who were initially treated with nefopam required additional pethidine, along with 141 of 867 patients (16.3%) who initially received ketorolac, and 29 of 121 patients (24.0%) who initially received n+k. Initial pain scores among these three groups were not significantly different, nor were the rates of additional analgesic (pethidine) administration (Table 2).

## IV. Discussion

According to our results, in trauma patients in the ED, the efficacy of reduction of pain score of nefopam alone or in combination with ketorolac or pethidine was comparable to that of ketorolac alone, pethidine alone, or the combination of ketorolac and pethidine and was not associated with a greater need for rescue analgesia.

To date, the analgesic efficacy of nefopam has been evaluated in post-operative patients,(5,6,8,9) and, more recently, in patients with renal colic.(10) Nefopam is a central analgesic with non-opiate action, and its efficacy relies on medullar and/or supramedullary mechanisms. It is known to take about 10 to 20 minutes for the analgesic effect to begin, and the duration of action is approximately 6 h. Nefopam can reduce patient requirements for morphine after surgery(5-7) and few adverse effects have been reported in association with its use. Until now, there has not been extensive evaluation of the efficacy of nefopam in trauma patients in the ED for initial pain control. In ED, there are a lot of patients complaining of pain with a variety of trauma mechanism. In this study, the effects of additional use and the exclusive use of nefopam on the acute traumatic pain of patients brought to ED were examined in terms of change in pain score and whether additional medication was administered, and according to the results, nefopam did not show significant difference compared to ketorolac in the NSAID series or pethidine with opiate action. The time to the onset action of ketorolac, which is an NSAID that is commonly prescribed for trauma patients in the ED, is about 30 minutes and the maximum effect lasts for approximately 2 to 3 hours. The most common adverse effects of NSAIDs are GI problems, such as dyspepsia, and NSAIDs have occasionally been associated with renal dysfunction after surgery.(11) The most common side effect is the allergic reaction, and there was a report that as many as 20% of patients showed the allergic reaction. Pethidine is known to have 8-12 hours of half-life, and act as an agonist at the $\mu$-opioid receptor as morpine. Typical side effects include nausea, vomiting, sedation, dizziness, diaphoresis, urinary retention, and constipation, and it may cause respiratory depression depending on dosage, so attention is required.(12-14) In the case of NSAID and pethidine, they are relatively commonly used analgesics,(15,16) but side effects or allergy may limit their applicability.(17) The analgesic mechanism of nefopam is unique, and, to date, fewer adverse effects, such as sedation (25%), sweating (23.9%), tachycardia (12%), and nausea (10.9%), have been reported.(18) Nefopam may be a reasonable alternative for analgesia in trauma patients in acute care settings such as the ED.

A limitation of this study is that only reductions in NRS scores were used to grade the efficacy. Since pain severity is highly subjective and variable from patient to patient, using pain scores alone may not be sufficient. However, given that pain itself is subjective phenomenon and that the goal of analgesia is to eliminate this subjective phenomenon, reductions in pain score should largely be acceptable as valid indicators of efficacy. Results concerning requirements for additional analgesia may also have been affected by subjective factors, in the case of strong or continuing complaining of pain depending on the individual propensity, medication may have been administered additionally, this also may serve as a limitation. However given that the severity of pain in each group was not much different, this does not seem to have had a large effect on the results. Another limitation of the study is that since it is a retrospective study, criteria for prescription of analgesia were not uniform. However, this was not thought not to have an undue influence because the site of injury did not vary significantly among groups.

## V. Conclusion

The efficacy of nefopam alone or in combination

with ketorolac compares favorably with ketorolac and pethidine in trauma patients in the ED. Future studies evaluating the synergetic effect of ketorolac and nefopam in hyperalgesic situations in EDs must take into account additional factors, including the placebo effect, which appears to be more relevant in this setting.

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