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ORIGINAL ARTICLE

Slow injection of nefopam reduces pain intensity associated with intravenous injection: a prospective randomized trial

Young Min Kim · Byung Gun Lim · Heezoo Kim · Myoung Hoon Kong · Mi Kyoung Lee · Il Ok Lee

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Abstract
Purpose We aimed to investigate the frequency and severity of pain associated with intravenous injection of nefopam and to determine whether a slow rate of administration can effectively reduce such pain.
Methods We used a solution containing 30 mg nefopam diluted to 20 ml in saline. In all, 102 adult patients undergoing minor surgery were randomly allocated to one of three administration groups: A (60 ml/h, $n = 34$); B (120 ml/h, $n = 34$); or C (180 ml/h, $n = 34$). All patients scored the maximal pain experienced during the 120-s infusion period, using the visual analogue scale (VAS) and the verbal pain score (VPS). Adverse events including phlebitis were recorded.
Results Eighty-three patients (29 in group A, 27 each in groups B and C) were included in the final analysis. The incidence of injection pain was lower in group A (86.2 %) than in groups B (96.3 %) and C (100 %), but this difference was not statistically significant. The proportion of patients with a tolerable level of pain (VAS 0–3 and VPS 0–1) was significantly higher in group A (79.3 %) versus groups B (7.4 %) and C (3.7 %). The mean VAS scores for groups A, B, and C were 2.2 ± 1.3, 5.1 ± 1.6, and 7.2 ± 1.7, respectively, and these differences were statistically significant.
Conclusions At the slower rate of infusion (60 ml/h) of the 1.5 mg/ml nefopam solution, injection pain intensity was attenuated to a significantly greater degree than at the faster rates.

Keywords Intravenous injections · Injection pain · Nefopam · Visual analogue pain scale

Introduction

Nefopam (Acupan®; Phambio Korea, Seoul, Korea) is a nonnarcotic analgesic that acts centrally by inhibiting 5-hydroxytryptamine and noradrenaline uptake [1, 2]. It is usually administered by intravenous (i.v.) infusion or intramuscular (i.m.) injection, mainly during the postoperative period. Nefopam has the advantages of not affecting platelet function and having no respiratory depressive effect [3, 4]. Reported adverse events are mostly minor (sweating, tachycardia, malaise, nausea, or vomiting) [5]. However, fatal adverse events, especially convulsions and cardiac arrest, can also occur even at normal therapeutic dosages [5]. Nefopam is usually recommended by the manufacturer to be injected slowly to prevent these adverse events. Many studies that investigated the analgesic effect of nefopam have shown, however, that nefopam is administered in a variety of methods that involve different injection rates, concentrations, and solution dilutions [6–13]. Recently, we noticed that nefopam frequently causes pain upon injection, but we also found that few studies have mentioned this. Therefore, we investigated the frequency and severity of pain associated with i.v. administration of nefopam to determine whether control of the rate of administration can effectively reduce the incidence and intensity of injection pain.

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Y. M. Kim · B. G. Lim (✉) · H. Kim · M. H. Kong · M. K. Lee · I. O. Lee
Department of Anesthesiology and Pain Medicine, Guro Hospital, Korea University, College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul, Korea
e-mail: bglim9205@korea.ac.kr

Methods

This study was performed with the approval of our institutional review board, and all patients provided their written informed consent to participate. It was also registered as a clinical trial via the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr, identifier: R000012257).

We initially enrolled 102 patients 20–65 years of age with a physical status of 1 (American Society of Anesthesiologists rating) who were scheduled to undergo minor elective surgery. Of these, 83 who had a 20-gauge cannula sited in the dorsal hand or wrist vein and who were not subject to the exclusion criteria described below were included in the final analysis. Patients with a history of cardiovascular, kidney, or liver disease, those with a current convulsive disorder or hypersensitivity to drugs, and those receiving analgesics were excluded. We excluded patients with a vein that did not drain well; those with redness, swelling, and tenderness along the veins; and those with a history of difficult peripheral venous cannulation.

All patients were premedicated with 2 mg midazolam and 0.2 mg glycopyrrolate (both i.m.) 1 h before induction. In the operating room, all patients were assessed by electrocardiography, noninvasive arterial blood pressure (BP) measurement, and pulse oximetry, and their initial BP and heart rate (HR) were recorded. The i.v. site was confirmed to be free of any problems such as redness, swelling, or tenderness. After an i.v line was opened and fluid flow was confirmed to be free, a 20-gauge cannula was flushed with 25 ml normal saline; then, the ongoing main fluid infusion was continuously given at a rate of 40 ml/h throughout the study period. For preparation of the solution, 30 mg nefopam was diluted with 0.9 % isotonic saline to a total volume of 20 ml, and the solution was then drawn into a 20-ml polyethylene syringe (KOVAX-SYRINGE®; Korean Vaccine, Seoul, Korea) and placed on a pump (INJECTOMAT® MC AGILIA; Fresenius Kabi, Bad Homburg, Germany). Patients were randomly allocated to one of three groups on the basis of infusion rate; the i.v. solution was administered at a rate of 60 ml/h in group A, 120 ml/h in group B, and 180 ml/h in group C. For randomization, we applied a random allocation rule using a restricted randomization approach [14].

A 20-ml syringe containing 30 mg nefopam was attached through a thin i.v. line (LECTRO-SPIRAL PE100®; Sungbok Medical, Seoul, Korea) to a three-way stopcock that was connected between the i.v. line and the i.v. catheter, and nefopam was then infused via a side-drip at the different rates. One anesthesiologist was responsible for the infusion speed, and a second anesthesiologist, who was blinded to the rate of nefopam infusion, evaluated the pain scores. Each patient was asked to rate the maximum level of any pain experienced during the infusion period of 120 s using a visual analogue scale (VAS; 0 = no pain, 10 = worst pain imaginable) [15] and a verbal pain score (VPS; 0 = none, 1 = mild, 2 = moderate, 3 = severe). From these VAS results, we planned to compare the proportion of patients who reported a tolerable level of pain indicative of weak pain or absence of pain (VAS 0–3 and VPS 0–1) [16–18] as well as the incidence and intensity of the injection pain among the groups as the primary end points. After the 120-s infusion, BP and HR were recorded, and then i.v. propofol 2 mg/kg mixed with 40 mg lidocaine was administered for anesthesia induction. If the patient complained of severe pain, more than VAS 7 or VPS 3 during the 120-s infusion, nefopam was immediately stopped and the BP and HR recorded; an induction dose of propofol mixed with 40 mg lidocaine was then administered. Anesthesia was maintained with 50 % nitrous oxide and desflurane in oxygen. The remainder of the nefopam was continuously injected at the same rate after anesthesia induction. Complications at the i.v. injection site (e.g., phlebitis, swelling, redness, or tenderness) were assessed continuously until discharge from the postanesthesia care unit (PACU). Adverse events were also recorded, including sweating, nausea, vomiting, dizziness, dry mouth, tachycardia, hypertension, and sedation. Tachycardia and hypertension were defined as a 20 % increase above baseline values. In addition, blood pressure variation (BPV) and heart rate variation (HRV) were calculated from differences before and after the infusion of drugs using the following formulas: for BPV (mean $BP_{120\ s}$ − mean $BP_{baseline}$) × 100/mean $BP_{baseline}$ (%), and for HRV (mean $HR_{120\ s}$ − mean $HR_{baseline}$) × 100/mean $HR_{baseline}$ (%), where $BP_{120\ s}$ and $HR_{120\ s}$ are BP and HR after the 120-s drug infusion and $BP_{baseline}$ and $HR_{baseline}$ are baseline BP and HR, respectively.

Sample size calculation was based on a pilot study. On the basis of a pilot study performed with five cases in each group, the mean VAS score for injection pain during administration of the study drug was 3.0 ± 1.0 in group A, 4.0 ± 2.6 in group B, and 5.2 ± 3.3 in group C. Using the G*power version 3.0 program, the effect size for the three groups based on the results of the pilot test was 0.36, and the total sample size was 78 with 26 in each group when it was calculated using a one-way analysis of variance (ANOVA), and two-sided test with a level of significance of 0.05 and a power of 0.8. Assuming a potential patient dropout rate of 30 %, the total sample size was increased to 102 including 34 patients per group.

All results were expressed as the mean ± standard deviation or as numbers of patients. SPSS (version 12.0; SPSS, USA) was used for the statistical analyses. Patient characteristics were compared using a one-way analysis of variance (ANOVA) or a Chi square test. For comparison of VAS scores among the groups, a Kruskal–Wallis test was

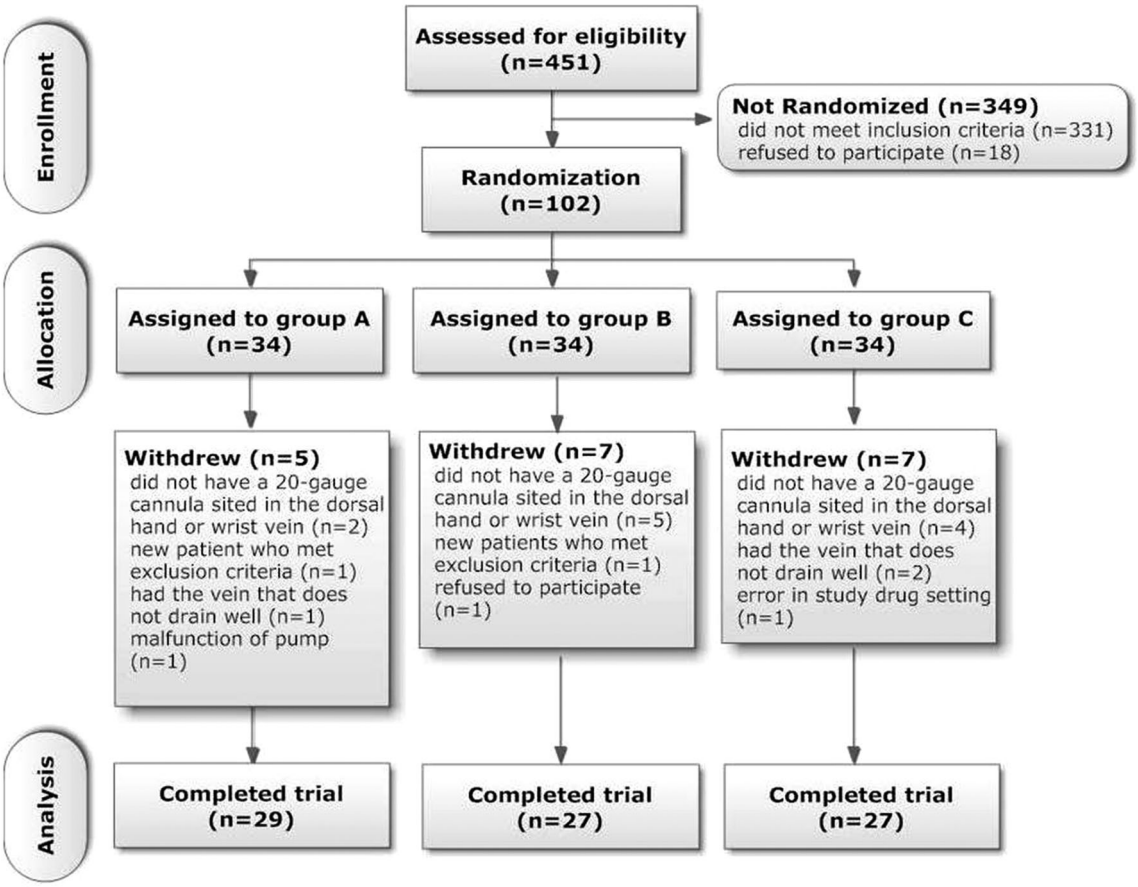

Fig. 1 Flow chart of patient recruitment, randomization, and withdrawal. One hundred two patients who had met all inclusion criteria were randomly assigned to one of three groups: group A (60 ml/h, $n = 34$), group B (120 ml/h, $n = 34$), group C (180 ml/h, $n = 34$). In all, 83 patients (29 in group A, 27 in group B, 27 in group C, respectively) completed this study

used followed by a Mann–Whitney U test with Bonferroni's correction. Fisher's exact test with Bonferroni's correction was used to compare VPS scores among the groups, and a chi-squared test or Fisher's exact test with Bonferroni's correction was used for comparison of the incidence of tolerable pain (VAS 0–3 and VPS 0–1) among the groups. The incidence of complications or adverse events was compared with Fisher's exact test. For the BPV and HRV comparisons, a one-way ANOVA or Kruskal–Wallis test was applied. A value of $P < 0.05$ was considered statistically significant.

Results

Of the 102 patients originally enrolled in the study, 19 patients were excluded for violations of the study protocol. The results from the remaining 83 patients were evaluated, with 29 patients finally included in group A, and 27 patients each in groups B and C (Fig. 1).

Table 1 Characteristics of the patients

Variable	Group A ($n = 29$)	Group B ($n = 27$)	Group C ($n = 27$)
Age (years)	44.9 ± 11.5	45.6 ± 11.9	40.2 ± 11.4
Sex (M/F)	15/14	12/15	13/14
Weight (kg)	65.8 ± 9.9	65.7 ± 10.5	66.9 ± 14.8
Height (cm)	164.1 ± 8.7	163.2 ± 7.7	165.6 ± 9.4
Body mass index (kg/m^2)	24.4 ± 2.8	24.4 ± 2.9	24.2 ± 4.0
Location of venous cannula (dorsum/wrist)	17/12	18/9	16/11

Data are mean ± standard deviation or numbers of patients. There were no significant differences among the groups

No significant differences were found among the groups in terms of patient characteristics including age, sex, weight, height, body mass index, and location of the venous cannula (Table 1).

Table 2 Verbal pain score (VPS) during the infusion period of the study drug

VPS	Group A ($n = 29$)	Group B ($n = 27$)	Group C ($n = 27$)	Sum	P value
0 (none)	4 (13.8 %)	1 (3.7 %)	0 (0 %)	5 (6.0 %)	0.122
1 (mild)	19 (65.5 %)	1 (3.7 %)*	1 (3.7 %)*	21 (25.3 %)	<0.0001
2 (moderate)	6 (20.7 %)	21 (77.8 %)*	6 (22.2 %)†	33 (39.8 %)	<0.0001
3 (severe)	0 (0 %)	4 (14.8 %)	20 (74.1 %)*†	24 (28.9 %)	<0.0001

Data are numbers of patients (%)

*$P < 0.05$ vs. group A; †$P < 0.05$ vs. group B

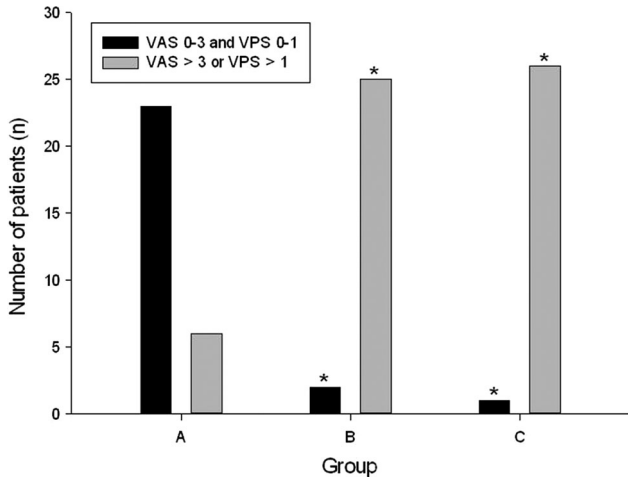

Fig. 2 Incidence of tolerable pain [visual analog scale (VAS) 0–3, verbal pain score (VPS) 0–1] and intolerable pain (VAS > 3 or VPS > 1) during the infusion period of the study drug. *$P < 0.05$ vs. group A

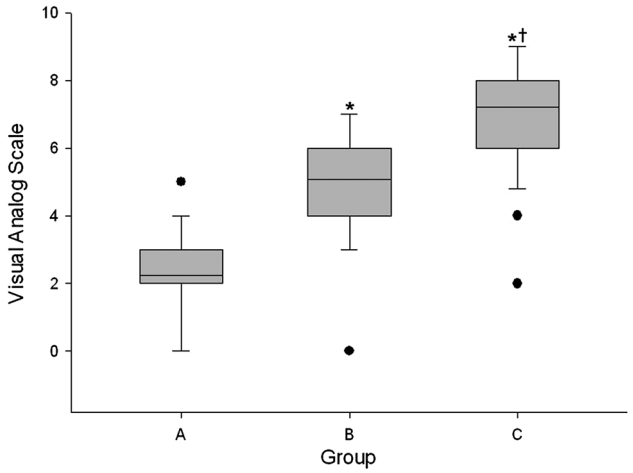

Fig. 3 Visual analog scale (VAS) scores on injection pain of study drug (0 = no pain, 10 = worst pain imaginable). *$P < 0.05$ vs. group A; †$P < 0.05$ vs. group B

The overall incidence of pain (VAS 1–10 or VPS 1–3) was 94.0 % in all three treatment groups: 86.2 % in group A, 96.3 % in group B, and 100 % in group C. The incidence of injection pain was lower in group A (86.2 %) than in groups B (96.3 %) and C (100 %), but this difference was not statistically significant ($P = 0.122$) (Table 2). Significantly more patients reported severe pain (VPS 3) in group C (74.1 %) than in groups A (0 %) and B (14.8 %) ($P < 0.05$), but there was no significant difference between groups A and B (Table 2). The proportion of patients who reported a tolerable level of pain (VAS 0–3 and VPS 0–1) was significantly higher in group A (79.3 %) than in groups B (7.4 %) and C (3.7 %) ($P < 0.05$), but there was no significant difference between groups B and C ($P = 1.00$) (Fig. 2). Four of the 29 patients in group A experienced no pain, and 19 had mild pain, but all patients except for 1 in group C experienced moderate to severe pain (Fig. 2).

The overall pain intensity was significantly different among the three groups (VAS 2.2 ± 1.3 in group A, 5.1 ± 1.6 in group B, and 7.2 ± 1.7 in group C; $P < 0.05$). The VAS score was also significantly lower in group A than in groups B and C ($P < 0.05$), and significantly lower in group B than in group C ($P < 0.05$) (Fig. 3).

Complications at the i.v. injection site, including redness or swelling, occurred in five patients in group C immediately after injection, but there were no significant differences between groups A and C or between groups B and C, and no erythema, swelling, or tenderness at the site was observed in the PACU among patients in all three groups. In addition, the incidence of other adverse events, including hypertension, tachycardia, nausea, vomiting, dry mouth, headache, sedation, and restlessness, did not differ among the groups. Restlessness was noted in one patient in group A after arrival in the PACU, but this symptom disappeared spontaneously within 30 min without any treatment. There were no statistical differences in BPV and HRV among the groups (Table 3).

Discussion

Nefopam has been used extensively in many countries of the world for the treatment and prevention of postoperative pain as well as acute and chronic malignant and nonmalignant pain in the nonsurgical setting, often despite the lack of valid clinical trial data [19]. In the surgical setting,

Table 3 Incidences of i.v. injection-site complications and other side effects from during/after the infusion of the study drug until discharge from postanesthesia care unit

Side effects	Group A ($n = 29$)	Group B ($n = 27$)	Group C ($n = 27$)	P value	Sum
Hypertension[a]	3 (10.3 %)	6 (22.2 %)	6 (22.2 %)	0.402	15 (18.1 %)
Tachycardia[a]	0 (0 %)	2 (7.4 %)	1 (3.7 %)	0.310	3 (3.6 %)
Hypertension[b]	0 (0 %)	1 (3.7 %)	1 (3.7 %)	0.540	2 (2.4 %)
Tachycardia[b]	5 (17.2 %)	2 (7.4 %)	5 (18.5 %)	0.534	12 (14.5 %)
Nausea/vomiting	4 (13.8 %)	2 (7.4 %)	1 (3.7 %)	0.492	7 (8.4 %)
Transient phlebitis (redness, swelling)	0 (0 %)	0 (0 %)	5 (18.5 %)	0.006[c]	5 (6.0 %)
Dry mouth	3 (10.3 %)	0 (0 %)	0 (0 %)	0.103	3 (3.6 %)
Headache	1 (3.4 %)	1 (3.7 %)	0 (0 %)	1.000	2 (2.4 %)
Sedation	0 (0 %)	1 (3.7 %)	0 (0 %)	0.651	1 (1.2 %)
Restlessness	1 (3.4 %)	0 (0 %)	0 (0 %)	1.000	1 (1.2 %)
BPV (%)	7.4 (8.9)	12.4 (11.1)	12.8 (7.8)	0.086	
HRV (%)	1.4 (8.1)	−0.78 (11.0)	1.4 (10.4)	0.258	

Data are numbers of patients (%) or mean (standard deviation)

BPV blood pressure variation [(mean $BP_{120\ s}$ − mean $BP_{baseline}$) × 100/mean $BP_{baseline}$ (%)], *HRV* heart rate variation [(mean $HR_{120\ s}$ − mean $HR_{baseline}$) × 100/mean $HR_{baseline}$. (%)], $BP_{120\ s}$ or $HR_{120\ s}$, BP or HR after the drug infusion period of 120 s; $BP_{baseline}$ or $HR_{baseline}$, baseline BP or HR)

[a] Side effects after the infusion period of 120 s

[b] Side effects in postanesthesia care unit

[c] As the result of the Bonferroni correction, there were no significant differences among the three groups

nefopam 20 mg was equipotent to morphine 6–12 mg [20] or to meperidine 50 mg [21]. The analgesic potency seems to be similar to nonsteroidal antiinflammatory drugs. According to a meta-analysis report [22], nefopam has a morphine-sparing effect in the postoperative period when used in adults undergoing surgery and it decreases pain intensity at 24 h.

Nefopam is a serotonin and catecholamine reuptake inhibitor [22] and a noncompetitive *N*-methyl-D-aspartate receptor antagonist [23]. Nefopam also directly interacts with α2-adrenoceptors [22]. Nonetheless, it does not have sedative and hemodynamic effects as do α2 agonists, nor does it cause respiratory depression as do opioids [4]. In contrast to nonsteroidal antiinflammatory drugs, nefopam has no effect on platelet function [3]. Also, nefopam reduces the shivering threshold without having any discernible effect on vasoconstriction or sweating thresholds [24]. Therefore, nefopam may be useful for postoperative analgesia of patients, especially elderly patients, who are vulnerable to opioid-induced complications including sedation and respiratory depression, and shivering, or patients who have a bleeding tendency.

To the best of our knowledge, this is the first randomized, double-blind study to investigate the incidence and severity of injection pain associated with i.v. nefopam based on injection rate in patients undergoing minor elective surgery under general anesthesia. We showed that i.v. administration of nefopam was frequently associated with significant pain, and that slow injection of nefopam can significantly reduce the intensity of such pain.

Nefopam is usually administered over 15 min by i.v. route, which is the method of administration recommended by the manufacturer. However, previous studies that investigated the analgesic effect of nefopam have reported nefopam administration using many different methods that involve different infusion rates, concentrations, and dilutions [6–13]; one study even reported the rapid infusion of 20 mg nefopam in a volume of 10 ml over 5 min [13]. Although nefopam can be useful for postoperative pain control, the recommended slow injection time of 15 min may be one reason why practitioners are reticent to use nefopam when many other analgesics are readily available.

We tried to find a solution to maximize the injection speed of nefopam while minimizing its adverse events. However, we noticed unexpectedly that nefopam can cause significant pain upon injection, but only few studies have focused on this phenomenon [7, 8]. Furthermore, there is a lack of information in these studies regarding the location or state of the vein in which the i.v. cannula is located, and the intensity of injection pain. We determined that injection pain and other possible adverse events of nefopam should be considered before factors influencing convenience of use, such as rapidity of injection, to ensure the safety and comfort of patients. That is, we attempted to identify a reasonable rate of injection of nefopam that has both a tolerable level of pain requiring no other analgesic intervention and fewer adverse events. We therefore

administered a 1.5 mg/ml nefopam solution at three different rates (60, 120, and 180 ml/h). There were few adverse events, and no statistically significant difference in their incidence among the three groups. However, pain intensity assessed by VAS was significantly different among the three groups; it was highest in patients who were administered the 1.5 mg/ml nefopam solution at a rate of 180 ml/h and lowest when administered at the rate of 60 ml/h. Notably, significantly more patients complained of severe pain in the 180 ml/h infusion rate group. Although the incidence of pain was not statistically different among groups, the intensity of pain was significantly attenuated to a tolerable level of no or mild pain in the 60 ml/h infusion group. At this rate, 13.8 % of patients did not experience any pain, 65.5 % of patients experienced mild pain (VAS 1–3, VPS 1), and 20.7 % complained of moderate pain (VAS 4–6, VPS 2); no patient complained of severe pain (VAS 7–10, VPS 3).

In our study, the total amount of nefopam administered was 30 mg for all patients, but it was infused at a different rate for each of the three groups. This dosage was selected based on a previous study that investigated the median effective analgesic dose (28 mg) of nefopam for moderately painful surgery [8]. In addition, by using a dorsal hand or wrist vein that drains well without redness, swelling, or tenderness, we could reduce the bias caused by different vein states. The incidence of nefopam-induced pain (VAS 1–10 or VPS 1–3) was 94 % in our study. That is, most patients receiving nefopam complained of pain, and this incidence is much higher than that reported in previous studies (0–7 %) [7, 8]. In particular, Delage et al. [7] reported an incidence of local injection pain of 0 %, but this extremely low incidence could partly be caused by a slow infusion rate during 20 min. Most of all, it is likely that our higher incidence of 94 % resulted from the use of a relatively small vein on the dorsum of the hand or wrist, which could maximize the injection pain caused by nefopam. According to our unpublished data, the incidence of nefopam-associated injection pain is as low as 12.8 % when it is administered in a vein located in the forearm.

It has been advocated that the injection pain of most anesthetic agents, such as propofol and rocuronium, is evoked by direct activation of C-nociceptors by the unphysiological osmolality or pH of the solution or by the release of endogenous mediators including histamine, kinin, and other inflammation mediators [25, 26]. Acidic or alkaline solutions at a pH <4 or >11 with high osmolality are known to cause injection pain [26]. In contrast, according to our data, which were collected by osmometer (PSI 2430 Multi-OSMETTE™; Precision Systems, MA, USA) and pH meter (Orion 720A$^+$; Thermo Scientific, MA, USA), nefopam is almost isotonic (osmolality of Acupan®, 266 mosm/kg; Acupan® plus normal saline, 277 mosm/kg; iso-osmolality range, 248–288 mosm/kg) and has a pH value > 5 (pH of Acupan®, 5.376; Acupan® plus normal saline, 1.5 mg/ml, 5.367, 0.08 mg/ml, 5.495). Therefore, the aforementioned theories may not be sufficient to explain the mechanism of nefopam injection pain, and further studies are needed to elucidate the mechanism. In addition, a continual effort is needed to develop new strategies to alleviate injection pain, such as the preventive methods that have been proposed to reduce anesthetic drug-induced injection pain associated with control of the concentration or temperature of nefopam and pretreatment with other drugs [25, 27, 28]. Regarding the influence of injection speed on the injection pain associated with other anesthetic drugs, some studies of propofol have reported conflicting results [28–30]. In contrast, slow injection of nefopam was found to be a reasonable technique for reducing pain in our study.

Various adverse events can occur at rates of 120 and 180 ml/h as these are faster than the rate recommended by the manufacturer. Complications at the i.v. injection site were observed in five patients in the 180 ml/h infusion group immediately after injection but not in the PACU. Other adverse events observed in this study were relatively mild, and there were no differences in the incidence of these effects among the three treatment groups. Therefore, with respect to adverse events, the injection rates of the 60 and 120 ml/h infusion group were more acceptable than that of the 180 ml/h infusion group.

A limitation of this study is that the time schedule does not correspond with the clinical situation. Nefopam is usually administered during or after anesthesia for postoperative analgesia, but it was done before anesthesia induction in this study. The study protocol should be justified for the correct evaluation of the severity of pain, but this time schedule is far from clinical situations. Initially, the study was to be carried out at the postoperative period, but a study based in a ward was somewhat impractical because it is not a place in which we work. Also, the study schedule in a recovery room was difficult to design properly because the grades of sedation and pain varied between individuals. Finally, we chose the induction time as a study schedule. Although nefopam can be administered before anesthesia induction for pain control, further studies are needed to evaluate the severity of the injection pain when nefopam was administered in a postoperative period.

Another limitation to consider is the fact that midazolam used as a premedication may affect the degree of nefopam injection pain of patients in this study. It had been reported that i.m. 4 mg midazolam reduced capsaicin-induced hyperalgesia and allodynia [31], and a γ-aminobutyric acid receptor agonist including midazolam might evoke analgesia and sedation in the adult [32]. Zacny et al. [33] examined the effects of i.v. midazolam (0.75, 1.5, and

3 mg per 70 kg) on pain induced by a cold pressor test in healthy volunteers, and they concluded that midazolam at subanesthetic doses had no effects on either the sensory or affective components of the pain experience. Also, Zacny et al. [34] reported that i.v. midazolam (0.5, 1, and 2 mg per 70 kg) did not influence i.v. fentanyl-induced analgesia (0.1 mg per 70 kg) in healthy volunteers. Taken together, we think that a subanesthetic dose (2 mg) of i.m. midazolam administered at 1 h before induction had little effect on the assessment of nefopam-induced pain in this study. In addition, if some analgesic effects by midazolam had existed in this study, they would not have been different among the three groups.

Another limitation associated with the study design is the absence of control groups with only normal saline infusion at 60, 120, or 180 ml/h. Thus, we also examined the injection pain of only 0.9 % isotonic saline infusion at 60 ml/h ($n = 26$), 120 ml/h ($n = 27$), or 180 ml/h ($n = 28$) with a study protocol consistent with our nefopam injection study. We found VAS and VPS scores of 0 in all patients of the three groups: no patient in the three groups experienced any pain and the VAS and VPS scores did not differ among the three groups. Therefore, we suggest that different infusion rates of 0.9 % isotonic saline do not affect the incidence and intensity of nefopam injection pain in our main study when it is administered at 60, 120, or 180 ml/h.

In conclusion, at a rate of 60 ml/h, the intensity of pain associated with the infusion of a 1.5 mg/ml nefopam solution was attenuated to a significantly greater degree than at rates of 120 and 180 ml/h. The incidence of a tolerable level of pain (no or mild pain) was also reduced to a significantly greater degree than at the faster rates and without significant adverse events.

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