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Effects of nefopam with fentanyl in intravenous patient-controlled analgesia after arthroscopic orthopedic surgery: a prospective double-blind randomized trial

You Na OH[1], Kyu Nam KIM[2,*], Mi Ae JEONG[2], Dong Won KIM[2], Ji Yoon KIM[2], Hyun Seo KI[2]

[1]Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Department of Anesthesiology and Pain Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea

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Background/aim: We performed this prospective randomized double-blind study to compare the effects of nefopam versus ketorolac in intravenous fentanyl-based patient-controlled analgesia (PCA) after shoulder arthroscopic orthopedic surgery.

Materials and methods: Ninety-two patients were randomly divided into two groups to receive intravenous PCA. Patients were assigned to either the nefopam group (nefopam 120 mg and fentanyl 20 μg/kg) or the ketorolac group (ketorolac 2 mg/kg and fentanyl 20 μg/kg). Pain was assessed on a visual analogue scale (VAS) and a numeric rating scale (NRS). Additionally, patient satisfaction, adverse events, and vital signs were monitored.

Results: There were no significant differences in VAS score (P = 0.48) or NRS score (P = 0.15) between the two groups. Similarly, patient satisfaction did not differ between the two groups [8.5(0.8) vs. 8.2(1.0), P = 0.14]. There were no statistically significant differences in the incidence of nausea (P = 0.72), vomiting (P = 0.46), urinary retention (P = 0.82), sweating (P = 0.49), or dizziness (P = 0.45) between the two groups. Likewise, there were no differences in heart rate [78.2(7.7) vs. 75.2(6.5), P = 0.18] or SpO2 [98.4(1.8) vs. 98.5(1.9), P = 0.83].

Conclusion: Nefopam is an appropriate alternative for co-administration with fentanyl-based PCA in patients who have difficulty using nonsteroidal antiinflammatory drugs.

Key words: Analgesia, balanced; analgesia, patient-controlled; nefopam; randomized controlled trial

1. Introduction

Postoperative analgesia is necessary for patient rehabilitation and for reducing the incidence of postoperative complications such as hypertension, atelectasis, and prolonged hospital stay. Patient-controlled analgesia (PCA) is associated with decreased pain intensity and improved satisfaction compared with conventional opioid analgesia (1). Since analgesia with opioids has been associated with side effects such as nausea, vomiting, sedation, and respiratory depression (2), drug combinations have been used to improve the analgesic effects and reduce the incidence of complications (3,4). Nonsteroidal antiinflammatory drugs (NSAIDs) are nonopioids that are most commonly used to decrease various opioid-caused side effects, by enabling the opioid dose to be decreased (5,6). However, NSAIDs cause other side effects such as renal dysfunction, gastroduodenal mucosal injury, and platelet dysfunction (7–9).

Nefopam was first discovered in the 1970s as an antidepressant. It was shown to have central acting and nonnarcotic analgesic effects by inhibiting uptake of dopamine, norepinephrine, and serotonin (10,11). In contrast to opioids, nefopam is not associated with any risk of respiratory depression (12); moreover, nefopam causes less gastroduodenal mucosal injury and interferes less with platelet function than NSAIDs do (13,14). Although many studies have been conducted with nefopam (15–17), the combined use of nefopam and fentanyl in PCA is not well known.

In the present study, we hypothesized that combined use of nefopam and fentanyl would yield similar analgesic effects and reduced adverse effects compared with conventional combination use of NSAIDs and fentanyl. We therefore performed this prospective randomized controlled double-blind trial to evaluate the efficacy and safety of the combined use of nefopam and fentanyl when PCA is used to control pain.

* Correspondence: vesicle100@naver.com

2. Materials and methods

2.1. Participant selection and randomization

This study was approved by the Institutional Review Board of our hospital and is registered at http://cris.nih.go.kr (Clinical Research Information Service, registration number: KCT0001285). After obtaining written informed consent, patients between 20 and 75 years of age who were scheduled for elective orthopedic shoulder arthroscopic surgery under general anesthesia were included in this study. Patients were excluded if they met any of the following criteria: (1) American Society of Anesthesiologists (ASA) physical status more than III; (2) serious respiratory, cardiovascular, renal, liver, or neuropsychiatric disorder; (3) impaired cognitive function; and (4) chronic use of analgesics and sedatives before the study.

Eligible patients were randomly assigned into two groups. The PCA regimen sequence was allocated by opening sealed envelopes after induction of general anesthesia. Each envelope contained the name of a group that had been randomly assigned using a random number generator in Excel by one of the authors (KNK). Allocation concealment was maintained until all data were collected and analyzed.

2.2. Study protocol and groups

Two groups were used in this study. In the N group, nefopam 120 mg, fentanyl 20 μg/kg, and ondansetron 16 mg were mixed with normal saline for the PCA maintenance dose and nefopam 20 mg, fentanyl 2 μg/kg, and ondansetron 4 mg were administered as the initial bolus dose. In the K group, ketorolac 2 mg/kg, fentanyl 20 μg/kg, and ondansetron 16 mg were mixed with normal saline for the PCA maintenance dose and ketorolac 0.5 mg/kg, fentanyl 2 μg/kg, and ondansetron 4 mg were administered as the initial bolus dose. The total PCA volume was 100 mL with a maintenance dose of 1 mL/h and a bolus demand dose of 1 mL. The lockout interval was 15 min and the maximal hourly infusion volume was 5 mL. The PCA device used was an Accumate 1100 PCA pump (WooYoung Medical, Seoul, Korea).

General anesthesia was conducted using the same predefined protocol. Specifically, anesthesia was induced using 1% lidocaine 0.5 mg/kg, propofol 1.5 mg/kg, rocuronium 0.6 mg/kg, and remifentanil 0.05–0.15 μg/kg/min. Anesthesia was maintained using desflurane and 50% oxygen.

Anesthesiologists who were blinded to group assignment performed the anesthesia and recorded all data. Another anesthesiologist checked the randomly assigned envelope that contained the group number, prepared the PCA drugs, and delivered PCA according to each patient's group during surgery. Consequently, patients, heath care provider, and assessor were blinded to group assignment. Ten minutes before the end of surgery, an initial bolus dose of PCA was administered to each patient. After surgery, the patients were moved to recovery rooms. PCA was started after their cognitive function had recovered. The patients were informed of the use of the PCA pump and were asked to press the bolus button when the visual analogue scale (VAS) score was more than 4. When the VAS score remained greater than 4 or upon patient request, additional analgesics (intravenous injection of tramadol 25 mg) were administered. All additional analgesic administration was recorded afterwards. If nausea and vomiting worsened, ondansetron 4 mg was administered for treatment. When the VAS was lower than 1 and the patient had no discomfort, PCA was removed.

2.3. Assessment of drug effect

The primary endpoints were pain assessment using a VAS and a numeric rating scale (NRS). We used the 0–10 VAS ruler. Data were extracted 10 and 30 min, and 1, 4, 8, 12, 24, and 48 h after the surgery. Along with the degree of pain, patient satisfaction was investigated on the NRS. Safety-related parameters including heart rate, SpO_2, Ramsey sedation score, and body temperature in addition to adverse events such as nausea, vomiting, urinary retention, pruritus, shivering, sweating, and dizziness were also recorded. After the initiation of PCA, the total PCA infusion volume used during the first 24 h, the number of bolus button presses by each patient, and the duration of the PCA application were recorded. The number of additional analgesics and antiemetics administered during the first 48 h was also recorded.

2.4. Justification of sample size and statistical analysis

A previous study that compared the effects of PCA after surgery reported a mean VAS score (standard deviation) of 4.2 (2.5) when fentanyl and ketorolac were used in combination (18). Setting the result of this study as a standard, we decided that the difference would be significant only if the VAS score gap was more than 1.5. The number of patients required with an α error of 5% and a β error of 10% was calculated to be 45. Assuming a dropout rate of 10%, the study was designed to have 100 patients in total, with 50 patients in each group.

Categorical data were expressed as numbers of patients (or percentages as appropriate) and compared via Pearson's chi-square test with Fisher's exact test. Continuous data were expressed as mean (standard deviation). Continuous data were tested for normality; gaps between groups of parametric data were compared through the unpaired t-test, whereas groups of nonparametric data were compared using the Mann–Whitney U test. One-way repeated measures ANOVA was used for comparisons within groups according to time. Statistical significance was defined as a P value less than 0.05. All statistical analysis was performed with SPSS (version 21.0 SPSS Ins., Chicago, IL, USA).

3. Results

After evaluating the standards for 113 participants, 13 patients were excluded because nine did not meet the inclusion criteria and four declined to participate. As a result, 100 patients were randomly assigned to two groups. A total of 4 patients in the N group and 4 patients in the K group were discharged from the hospital before 48 h had elapsed after surgery; these patients were excluded from the statistical analysis. Consequently, the data from 92 patients were included in the analysis (Figure 1). The patient demographic data are summarized in Table 1. There were no statistically significant differences in any of the patient characteristics between the two groups.

3.1. Drug efficacy

The VAS scores at 10 and 30 min, and 1, 4, 8, 12, 24, and 48 h after surgery were not significantly different between the two groups (P = 0.48) (Figure 2a). There were also no significant differences in NRS scores between the groups (P = 0.15) (Figure 2b). The duration of PCA application in the N and K group was 57.2 (20.2) h and 50.6 (19.7) h, respectively; these values were not significantly different (P = 0.12). There were no statistically significant differences regarding total PCA infusion volume or number of bolus button presses by the patients between the two groups (Table 2). Similarly, patient satisfaction did not differ between the two groups [8.5 (0.8) vs. 8.2 (1.0), P = 0.14].

3.2. Drug safety

Data regarding adverse effects are summarized in Table 3. There were no statistically significant differences in the incidence of nausea (P = 0.72), vomiting (P = 0.46), urinary retention (P = 0.82), pruritus (P = 1.00), shivering (P = 1.00), sweating (P = 0.49), or dizziness (P = 0.45) between

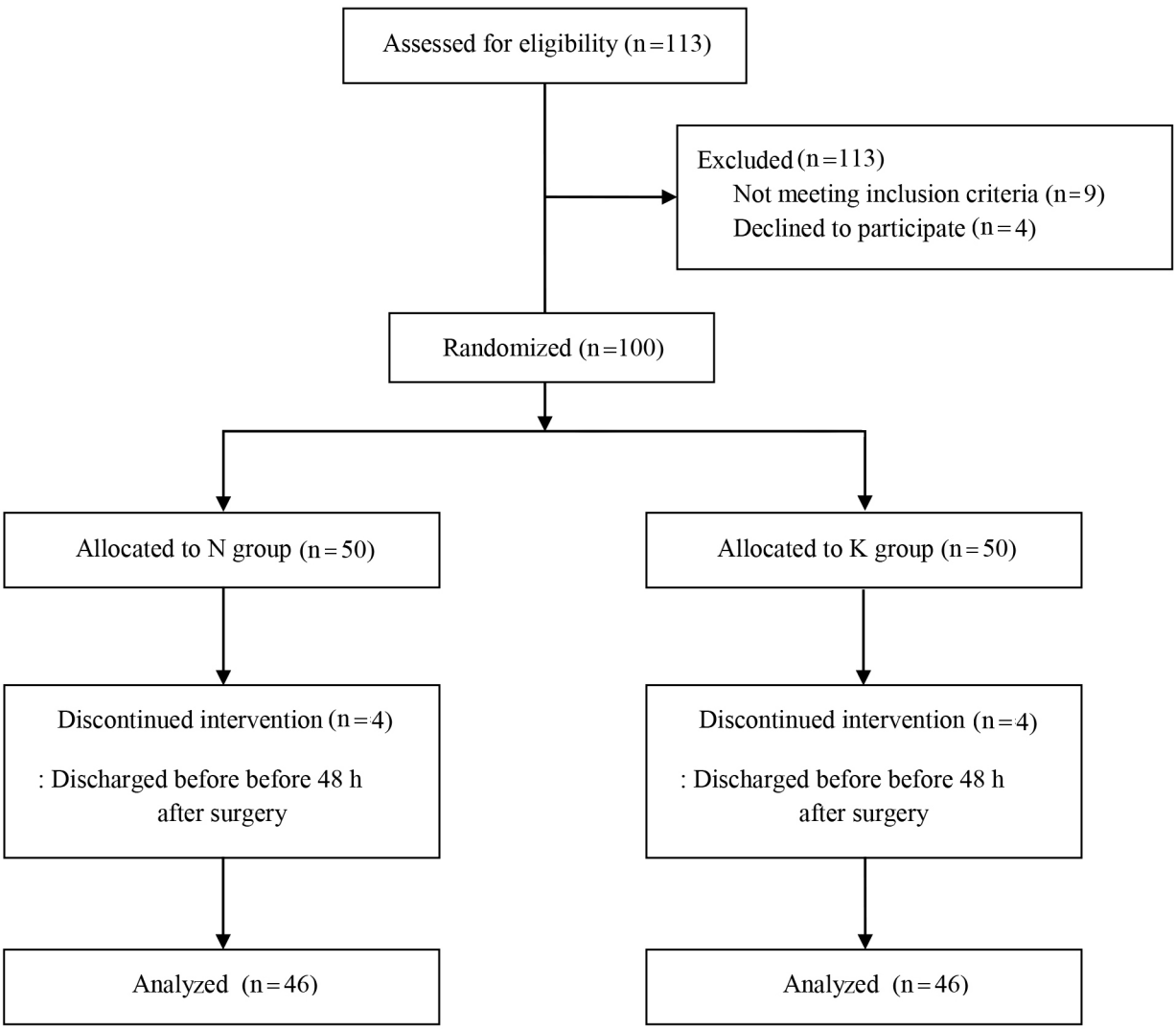

Figure 1. Flow diagram of patient recruitment and study exclusion criteria.

Table 1. Patient demographic data.

Variable	N group (n = 46)	K group (n = 46)	P value
Age (years)	53.3 (12.8)	51.9 (11.5)	0.59
Male sex	25 (54)	21 (46)	0.53
Height (cm)	162.6 (11.7)	162.8 (7.9)	0.93
Weight (kg)	65.3 (9.7)	66.7 (9.7)	0.48
ASA physical status			
I/II	23 (50)/23 (50)	25 (54)/21 (46)	0.84
Duration of anesthesia (min)	135.9 (39.0)	128.5 (29.3)	0.31
Duration of operation (min)	87.5 (36.8)	80.8 (26.4)	0.32

Values represent number of patients (%) or mean (standard deviation).

the two groups. Additional analgesics were injected into 19 (41) patients in the N group and 18 (39) patients in the K group; additional antiemetics were injected into 7 (15) patients in the N group and 6 (13) patients in the K group. There were also no differences in heart rate [78.2 (7.7) vs. 75.2 (6.5), P = 0.18], SpO_2 [98.4 (1.8) vs. 98.5 (1.9), P = 0.83], body temperature [36.2 (0.7) vs. 36.3 (0.2), P = 0.19], or level of sedation as measured by the Ramsey score during the first 48 h postoperative [1.9 (0.08) vs. 1.9 (0.09), P = 0.87].

4. Discussion

We conducted this prospective, randomized, controlled, double-blind trial to evaluate the efficacy and safety of combinatorial nefopam and fentanyl in PCA. Our study demonstrated that combined use of nefopam and fentanyl in PCA provided similar analgesic effects to those provided by ketorolac and fentanyl; moreover, nefopam and fentanyl did not lead to increased adverse effects, including nausea, vomiting, urinary retention, pruritus, shivering, sweating, or dizziness.

Appropriate pain control after surgery helps decrease stress reactions caused by pain, which can lead to organ failure and morbidity (19). Therefore, appropriate pain control is an important aspect of recovery time, patient satisfaction, and length of hospital stay. Although opioids play a main role in perioperative pain control, side effects such as sedation, nausea, vomiting, urinary retention, respiratory depression, and delirium may occur with opioid use. Balanced multimodal analgesia, through co-administration of different classes of analgesics or through the use of different administration sites, has been suggested to reduce the amount of opioids used (3,4,20). In addition, PCA has been used since the early 1980s and is used throughout medical institutions for pain control after surgery. PCA is also being used as a method for increasing analgesic effects and decreasing side effects by mixing opioid-based PCA with additional nonopioids.

According to a study by Kim et al. (21), nefopam showed an analgesic effect similar to that of fentanyl after heart surgery. In addition, PCA consisting of half fentanyl/half nefopam showed an analgesic effect similar to that of nefopam or fentanyl alone. In our study, there were no differences in the VAS or NRS scores between the groups. The total PCA infusion volumes and the numbers of bolus button presses by the patients were also not different. These results demonstrate that nefopam could be an appropriate alternative combination drug for patients who have difficulty using NSAIDs or fentanyl-based PCA.

Nefopam is generally viewed as a safe drug, since its reported side effects (dizziness, nausea, vomiting, sweating, and urinary retention) are not serious. However, it can also have serious side effects, including tachycardia, confusion, and convulsion (22). In the present study, the occurrences of dizziness, nausea, and vomiting were similar between the two groups. The occurrences of dizziness, nausea, and vomiting caused by nefopam when used as a combination drug in PCA were not more frequent than those observed when ketorolac was used as a combination drug in PCA. However, Hwang et al. (23) compared oxycodone with nefopam versus oxycodone with ketorolac in PCA and reached a different conclusion. Specifically, the group in which nefopam was used showed less nausea than the group in which ketorolac was used. These findings should be given careful consideration in subsequent studies. Moreover, drugs used in combination with opioids (the basis of PCA) may interact. This possibility should also be explored in future studies.

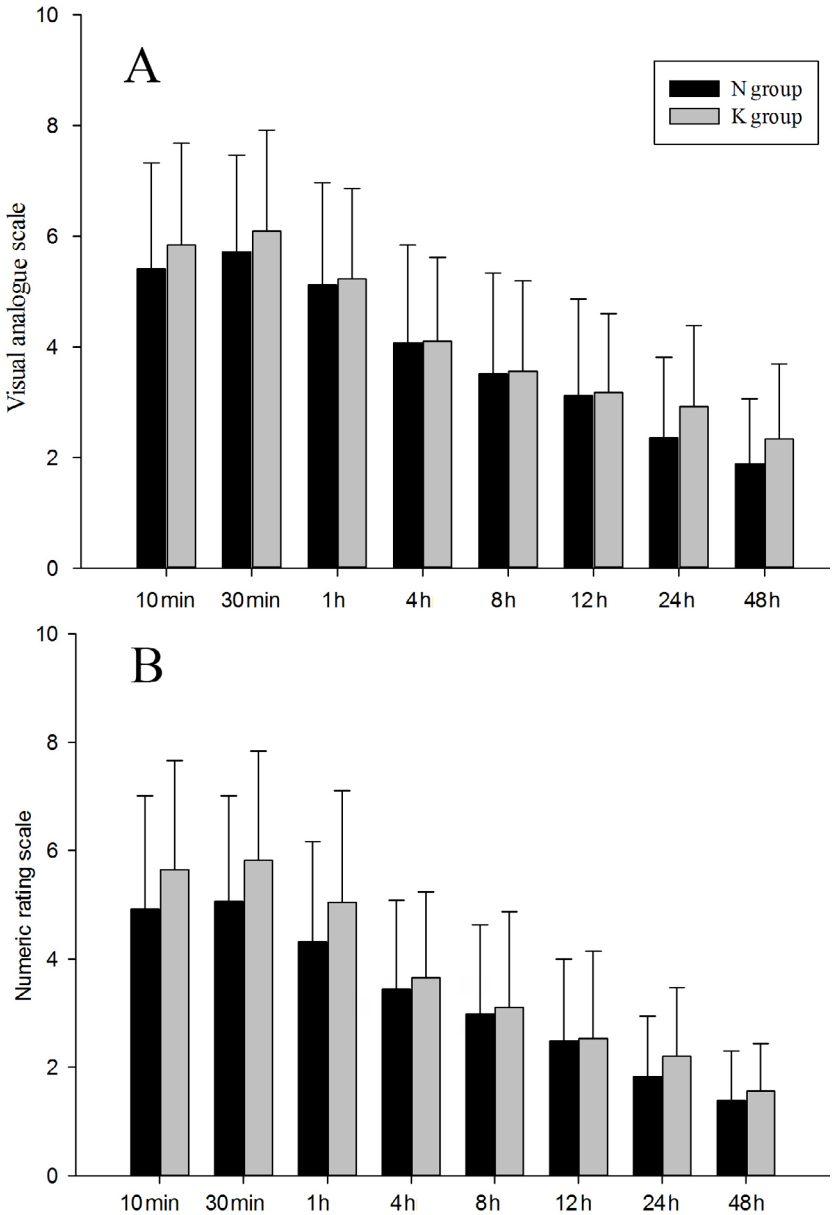

Figure 2. Visual analogue scale scores for pain (a) and numerical rating scale scores for pain (b) 10 min, 30 min, 1 h, 4 h, 8 h, 12 h, 24 h, and 48 h after surgery. Data are presented as mean and standard deviation.

Regarding the cardiovascular effects of nefopam, tachycardia was widely known as one of the common adverse effects of nefopam. Although Mimoz et al. reported that tachycardia was more common in patients with nefopam, significant differences were not observed (24). In addition, all patients in our study showed a heart rate of less than 100 beats per minute. Since the two groups did not show statistically significant differences in heart rate during the study, nefopam was not associated with any serious cardiovascular adverse events. This result is similar to that reported by Kim et al. (21), where no significant differences in tachycardia incidence were observed between the group that received nefopam and the group that did not. Continuous infusion of a small dose of nefopam by PCA is thought to reduce the incidence of adverse events.

Case reports of elderly individuals have suggested that nefopam may be associated with neurologic adverse effects such as delirium, confusion, and convulsion (25,26). The incidence of neurologic adverse effects of nefopam was

Table 2. Total PCA infusion volume (mL) and number of bolus button presses during the first 24 h postoperative.

	N group (n = 46)	K group (n = 46)	P value
Total PCA infusion volume (mL)			
10 min	0.84 (0.47)	1.00 (0.69)	0.22
30 min	1.74 (0.71)	2.00 (0.85)	0.12
1 h	3.28 (0.99)	3.58 (1.16)	0.18
4 h	8.50 (2.74)	9.13 (3.05)	0.30
8 h	13.66 (3.64)	14.57 (4.82)	0.31
12 h	18.69 (4.51)	19.76 (6.10)	0.34
24 h	32.84 (7.17)	34.44 (8.02)	0.32
Number of bolus button presses			
10 min	1.50 (1.97)	2.26 (2.51)	0.11
30 min	3.59 (5.04)	5.17 (5.84)	0.17
1 h	6.17 (8.38)	8.04 (7.44)	0.26
4 h	5.43 (6.07)	7.59 (7.32)	0.13
8 h	1.71 (3.15)	2.88 (5.47)	0.21
12 h	1.59 (3.09)	1.87 (3.19)	0.67
24 h	3.65 (9.48)	3.24 (4.69)	0.79

Values represent mean (standard deviation). PCA, patient-controlled analgesia.

Table 3. Incidence of adverse events and requirement of additional treatment during the first 48 h postoperative.

		N group (n = 46)	K group (n = 46)	P-value
Adverse events				
Nausea	PACU	2 (4)	3 (7)	0.50
	1–4 h	7 (15)	7 (15)	1.00
	4 –12 h	12 (26)	11 (24)	0.50
	12–24 h	2 (4)	1 (2)	0.50
	24–48 h	2 (4)	1 (2)	0.50
Vomiting	PACU	0	0	1.00
	1–4 h	3 (7)	3 (7)	1.00
	4 – 12 h	3 (7)	0	0.24
	12–24 h	0	0	1.00
	24–48 h	0	0	1.00
Urine retention	PACU	1 (2)	0	1.00
	1–4 h	3 (7)	1 (2)	0.62
	4–12 h	9 (20)	3 (7)	0.12
	12–24 h	6 (13)	2 (4)	0.27
	24–48 h	4 (9)	1 (2)	0.36
Dizziness	PACU	6 (13)	1 (2)	0.11
	1–4 h	6 (13)	6 (13)	1.00
	4–12 h	5 (11)	7 (15)	0.76
	12–24 h	3 (7)	3 (7)	1.00
	24–48 h	3 (7)	0	0.24
Sweating		2 (4)	0	0.49
Shivering		0	0	1.00
Pruritus		0	0	1.00
Additional treatment				
Analgesics		19 (41)	18 (39)	1.00
Antiemetics		7 (15)	6 (13)	1.00
Urinary catheter insertion		6 (13)	1 (2)	0.11

Values are numbers of events (%).

not observed in the present study because we excluded patients with impaired cognitive function. In addition, the included patients were relatively young to have had neurologic symptoms (Table 1). Since these neurologic adverse effects may occur within the therapeutic dose as well as in patients who overdosed (26), careful observation of neurologic adverse effects is needed.

The optimal dose and administration route for analgesics used after surgery for pain control differ widely according to the intended use, the surgery type, the occurrence of adverse effects, and the interactions between the co-administered drugs. Since many recent studies used various combinations and doses, it is difficult to infer the equivalent doses of different drugs. In addition, it is also difficult to confirm whether doses of nefopam and ketorolac mixed with fentanyl were equal in our study. Moreover, considering that an infra-additive effect was reported when morphine and nefopam were administered together (27), current information on drug interactions with nefopam is insufficient. Our study demonstrated that nefopam with fentanyl-based PCA yielded analgesic effects similar to those achieved with ketorolac with fentanyl-based PCA; moreover, the incidence of adverse effects was not increased. The aim of our study was not to demonstrate drug equivalence or interactions of nefopam. Therefore, future well-controlled randomized studies are needed to assess the potential drug equivalence and drug interactions of nefopam.

Our study has some limitations. First, this study included only patients who were scheduled for elective orthopedic shoulder arthroscopic surgery under general anesthesia. Therefore, the general physical condition of these patients was better than that of patients with chronic diseases. Thus, it cannot be inferred from our data whether nefopam and fentanyl should be used for PCA in patients with chronic diseases. Second, the degree of pain could have been decreased because patient movement was limited due to fixation of the operated part.

We conclude that the combination use of nefopam and fentanyl in PCA provided analgesic effects similar to those provided by ketorolac and fentanyl. Moreover, nefopam and fentanyl were not associated with an increased incidence of any adverse effect, including nausea, vomiting, urinary retention, pruritus, shivering, sweating, and dizziness. Consequently, our data indicate that nefopam is an appropriate alternative drug to be co-administered with fentanyl-based PCA in patients for whom NSAIDs are unsuitable assistant drugs for fentanyl-based PCA.

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