The Effect of Nefopam on Postoperative Fentanyl Consumption: A Randomized, Double-blind Study

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Background: Nefopam is a non-opioid, non-steroidal, centrally acting analgesic drug. The concomitant use of opioids and nefopam is believed to have many advantages over the administration of opioids alone for postoperative pain management. We conducted a randomized, double-blind study to determine the fentanyl-sparing effect of co-administration of nefopam with fentanyl for postoperative pain management via patient controlled analgesia (PCA).

Methods: Ninety female patients who underwent laparoscopic total hysterectomy under general anesthesia were randomized into 3 groups, Group A, fentanyl 1,000 μg; Group B, fentanyl 500 μg + nefopam 200 mg; and Group C, fentanyl 500 μg + nefopam 400 mg, in a total volume of 100 ml PCA to be administered over the first 48 h postoperatively without basal infusion. The primary outcome was total fentanyl consumption during 48 h; secondary outcomes included pain scores and incidence of side effects.

Results: Eighty-one patients were included in the analysis. The overall fentanyl-sparing effects of PCA with concomitant administration of nefopam during the first 48 h postoperatively were 54.5% in Group B and 48.9% group C. Fentanyl use was not significantly different between Groups B and C despite the difference in the nefopam dose. There were no differences among the three groups in terms of PCA-related side effects, although the overall sedation score of Group B was significantly lower than that of Group A.

Conclusions: The concomitant administration of nefopam with fentanyl for postoperative pain management may allow reduction of fentanyl dose, thereby reducing the risk of opioid-related adverse effects. (Korean J Pain 2016; 29: 110-8)

Key Words: Deep sedation; Double blind study; Hysterectomy; Nefopam, Opioids; Pain measurement; Patient-controlled analgesia; Postoperative pain.

INTRODUCTION

Patient-controlled analgesia (PCA) is a commonly used method of postoperative pain (POP) control by the administration of analgesic medications as per the patient's needs and the maintenance of appropriate therapeutic concentrations for each patient [1,2]. Fentanyl, which is a synthetic opioid analgesic with 50–100 times greater potency than morphine, is now widely used in PCA for the management of POP [3]. However, as with other opioids, the use of fentanyl has been associated with side effects including nausea and vomiting, pruritus, hypotension [4,5] and, more severely, excessive sedation and respiratory depression [6–8].

In order to minimize the risk of adverse effects associated with the use of opioid analgesics and to obtain more effective POP control, multi-drug therapy regimens administered via PCA can be considered. Multi-drug therapies rely on various medications with varying analgesic efficacies and different mechanisms of action, thereby requiring lower doses of each agent and reducing the risks of the medication-related side effects that are commonly associated with the use of single analgesic agents [9,10]. Non-steroidal anti-inflammatory drugs (NSAIDs) have been suggested as the most commonly used partner of opioids [11,12]. However, the use of NSAIDs in POP management can also cause a number of side effects, such as coagulation disorders, renal function decline, cardiovascular toxicity, and gastrointestinal bleeding.

Nefopam (NFP) is a non-opioid, non-steroidal, centrally acting analgesic that was developed in the 1960s [13–15]. It is known to exert an analgesic effect by inhibiting the reuptake of monoamine and the NMDA (N-methyl-D-aspartate) receptor [16,17], and has been shown to have an analgesic effect relative to opioids, such that 20 mg of NFP exhibits efficacy equal to that of 6–12 mg of morphine [18]. Although NFP might have a ceiling effect [19], compared to NSAIDs, NFP has a better safety profile without coagulopathy compared to NSAIDs [20], gastrointestinal mucosal damage [21], or severe hepato- or renal toxicity [20–22]. The occurrence of dose-dependent respiratory depression is also absent with NFP when compared with opioids [22]. It appears that collectively, combination therapy with opioids and NFP would be safer than that using opioids and NSAIDs. Furthermore, it has been reported that the co-administration of NFP with morphine during postoperative PCA has demonstrated a morphine-sparing effect [23–26].

Accordingly, we hypothesized that NFP administered with FTN would have the same analgesic efficacy as FTN administered as a single agent and would ultimately result in a decrease in total perioperative FTN consumption. Therefore, the goal of our study was to investigate the FTN-sparing effect of NFP + FTN co-administration via PCA for POP management.

METHODS AND METHODS

We conducted a single-center, prospective randomized, double-blind study from November 2011 for one year. This study was initiated after obtaining approval of the Institutional Review Board (KUGH11074), and documented informed consent was collected from all patients after an explanation of the study's aim and methods. Retrospective registration to *ClinicalTrials* was done (R000019202).

1. Study population

The study enrolled female patients 18–70 years of age with the American Society of Anesthesiologists (ASA) physical status class I–II who were scheduled for laparoscopic total hysterectomy under general anesthesia. The exclusion criteria were as follows: 1) BMI ≥ 35; 2) history of drug abuse or suspected drug abuse; 3) history of illegal drug use or drug dependence; 4) those with a medical history of a recent major procedure or surgery; 5) those who have or had conditions with a possible risk of affecting the interpretation of the study results, safety, and subject participation including cancer, neurologic, psychologic, cardiac, hepatic, hematologic, muscular, dermatologic, genital problems, or were in an immunocompromised state; 6) those with major pain that is caused by something other than their operation; 7) known intolerance of or hypersensitivity to NFP; and 8) others who the investigator judged to be inappropriate candidates for participation in the clinical study. All patients received a general explanation of the study process, including instruction in the use of the verbal pain score (VPS), with 0 = pain-free, 1 = minor pain, 2 = moderate pain, and 3 = severe pain, and the 10-point numerical rating scale for pain (NRS), with 0 = pain-free and 10 = the most severe pain ever. The patients were also carefully instructed in the use of the Acumate®1100 PCA device (Wooyoung Medical Co. Ltd.,

Jincheon, Korea) that was used in the study.

2. Randomization

Since the goal of the study was to evaluate the FTN-sparing effect of concomitant NFP administration for the management of POP, the total consumption of FTN for 48 h postoperatively was chosen as our primary endpoint. The patients were randomly assigned into three PCA groups (1 : 1 : 1) in accordance with a pregenerated random number table (available at http://www.randomization.com/). Group A received FTN alone (1,000 μg); Group B received FTN 500 μg in combination with 200 mg NFP; and Group C received 500 μg of fentanyl in combination with 400 mg NFP. In the post anesthesia care unit (PACU), the medications were mixed with saline according to the table in order to make a total solution of 100 ml by a PACU nurse who was working independently from the study. This solution was to be administered via PCA during the first 48 h postoperatively. Based on the findings of previous studies [24,27,28], the PCA was provided without continuous administration of a basal infusion, and with limits of 1 ml of bolus, 5 min lockout time, 10 ml maximum per hour, and a total daily maximum of 60 ml. All the PCA devices were applied to patients with hidden labels so neither patients nor medical staff who had direct contact with the patients knew the content of the PCA. The outcome was analyzed by a biostatistician who was not a participant in the study and was not informed of the study except for the study design.

3. Anesthesia and PCA

All patients received presurgical pretreatment with intramuscular glycopyrrolate 0.2 mg and midazolam 2 mg. In the operating room, all patients underwent routine physiological monitoring including pulse oximetry, electrocardiography, and noninvasive arterial blood pressure measurements. After sufficient preoxygenation, general anesthesia was induced with IV administration of thiopental sodium, 5 mg/kg, followed by rocuronium, 0.9 mg/kg, which was administered after confirmation of loss of consciousness. Endotracheal intubation was carried out after stabilization of vital signs and sufficient muscle relaxation, and a 50 : 50 combination of nitrogen oxide and oxygen with 5–7 vol% desflurane was used for the maintenance of anesthesia. For preemptive pain control and maintenance of hemodynamic stability during the initial

phase of the operation, 50 μg of fentanyl was administered intravenously immediately before skin incision. No other medications besides those stated above were administered unless hemodynamic instability occurred, at which point IV ephedrine 4 mg or labetalol 5 mg (single dose) were administered as needed. Upon completion of the operation, at the time of skin closure, pain control via PCA was initiated with a single bolus dose of 2 ml out of the 100 ml PCA solution (Group A, 20 μg FTN; Group B, 10 μg FTN and 4 mg NFP; Group C, 10 μg FTN and 8 mg NFP). The patients were extubated after regaining consciousness and reaching tidal volumes > 4–6 ml/kg with sustained spontaneous respiration rate > 12/min. To antagonize any remaining muscle relaxation, 10 mg bromide with 0.4 mg glycopyrrolate was administered intravenously. The temperature of the operating room was maintained at $23 \pm 1^{\circ}C$.

4. Assessments

The primary endpoint was the cumulative dose of FTN administered via PCA during the first 48 h postoperatively. Secondary outcomes included VPS and NRS pain scores and the number of button-presses recorded by the PCA devices after patients were extubated and as recorded at 1 and 2 h postoperatively in the PACU and at 6 h, 12 h, 24 h, and 48 h on the ward. Incidence of side effects and patient satisfaction scores were also evaluated as secondary outcomes.

In the PACU, the number of single doses via PCA, the number of button presses, the requirements for rescue analgesia (ketorolac), and the occurrences of side effects were recorded by medical personnel who did not have information about the study. The analgesic agent was administered through PCA in accordance with degree of pain as evaluated every 5 min. When the VPS was > 2 (moderate pain), a single dose of 1 ml was administered by PCA every 5-min until the VPS reached a score of 0 (pain-free) or 1 (minor pain). If the VPS was > 2 even after the administration of medication through the PCA device, an additional dose of 30 mg of IV ketorolac was administered.

The occurrence of side effects was assessed by checking for nausea and vomiting, sedation, dry mouth, pain during IV administration through the PCA, shivering, sweating, and other unwanted symptoms. Tachycardia was defined as heart rate > 100 beats/min for more than 5 min, and bradycardia was defined as a heart rate < 50

beats/min for more than 5 min, while respiratory depression was defined as a respiration rate of < 12/min or oxygen saturation of < 95%. The degree of sedation was scored as follows: 0 = clearly conscious; 1 = temporarily drowsy; 2 = drowsy but responsive to verbal communication; and 3 = drowsy without response to verbal communication, with the presence of sedation defined by a score of > 1. The administration of the medication was discontinued if the respiratory rate was < 12/min, the oxygen saturation was < 95%, or the sedation score was > 2. Metoclopramide 10 mg was administered intravenously in cases of nausea and vomiting.

After 2 h in the PACU, patients were transferred to the ward. Medical personnel who did not have any information about the study assessed the patients in the ward at 6 h, 12 h, 24 h, and 48 h after extubation and assessed the amount of medication administered through the PCA device, the NRS pain score (0–10), the number of button presses recorded by the PCA device, the requirement for and dose of rescue analgesia, the vital signs (blood pressure, heart rate, respiratory rate, and body temperature), and the patient satisfaction score, as determined by a 5-point Likert scale at 48 h after extubation (1 = very satisfied, 2 = satisfied, 3 = so-so, 4 = not satisfied, 5 = very dissatisfied).

5. Sample size

The calculation of sample size was based on the findings of our preliminary study, in which the cumulative PCA dose of FTN at 48 h was 235.1 ± 151.4 μg (mean ± standard deviation [SD]) in an FTN-only group and 115.3 ± 91.9 μg in an FTN with NFP group (500 μg FTN and 200 mg NFP). In the present study, we performed two comparisons to evaluate the FTN-sparing effect of NFP, Group A vs. Group B and Group A vs. Group C. Therefore, we used a type 1 error of 0.025 as the Bonferroni adjustment. Based on a type 1 error of 0.025, a type 2 error of 0.2, and a one-sided t-test, we determined that at least 26 patients per group were required for the analysis. Allowing for 10% attrition, 87 randomized patients (29 patients per group) were needed for the study.

6. Statistical analysis

The measured values were presented as mean ± SD (95% Confidence Interval, CI) or as a proportion (%). For the comparison of each group, Fisher's exact test or Chi-squared test was used for categorical variables and the ANOVA was used for continuous variables. A P value of < 0.05 was considered statistically significant. In subgroup analysis, we used Bonferroni correction to minimize the chance of type 1 errors and an adjusted P value of < 0.017 was considered statistically significant. The SPSS Statistics program version 21.0 for Windows was used for the statistical analysis.

RESULTS

A total of 90 patients were enrolled. Among these, 9

Table 1. Baseline Demographics of Study Groups

	Group A (n = 27)	Group B (n = 28)	Group C (n = 26)	P value
Age (years)	49.4 ± 7.1 [46.7–52.2]	47.0 ± 5.5 [44.9–49.2]	49.4 ± 7.1 [46.5–52.2]	0.312
Weight (kg)	60.9 ± 7.5 [57.9–65.5]	61.7 ± 9.9 [57.8–65.5]	57.4 ± 6.1 [55.0–59.9]	0.126
Height (cm)	155.7 ± 4.7 [153.8–157.5]	158.7 ± 5.7 [156.5–160.8]	156.1 ± 6.7 [153.4–158.8]	0.114
Hypertension	1 (3.7%)	0 (0.0%)	1 (3.8%)	0.581
Diabetes Mellitus	8 (29.6%)	0 (0.0%)	2 (7.7%)	0.003*
ASA Physical Class				0.598
ASA I	16 (59.3%)	20 (71.4%)	18 (69.2%)	
ASA II	11 (40.7%)	8 (28.6%)	8 (30.8%)	

Results are expressed as mean ± standard deviation [95% confidence intervals] or number (%). Group A: Fentanyl 1,000 μg, Group B: Fentanyl 500 μg + Nefopam 200 mg, and Group C: Fentanyl 500 μg + Nefopam 400 mg. ASA: the American Society of Anesthesiologists. *In subgroup analysis, P = 0.002 in Group A vs. B, P = 0.044 in Group A vs. C, and P = 0.227 in Group B vs. C.

patients dropped out, 3 due to severe nausea, 1 because the planned surgery was not performed, 4 who did not push the bolus button on the PCA device on their own, and 1 who had to be excluded because of an error on the control device. Finally, 81 patients (Group A, n = 27; Group B, n = 28; and Group C, n = 26) were included in the analysis. Since there was no result data from drop-out patients because none of them finished the study, it was not possible to run the analysis by intention to treat, so we chose per protocol analysis. There were no significant differences in patient characteristics except for the presence of diabetes mellitus as a comorbidity (**Table 1**).

The primary endpoint of cumulative consumption of FTN at 48 h postoperatively is shown in **Table 2** and **Fig. 1**. Total FTN consumption at 48 h was 236.1 ± 128.1 mg in Group A, 107.5 ± 74.0 mg in Group B, and 120.7 ± 91.1 mg in Group C ($P < 0.001$ for Group A vs. Group B and $P < 0.001$ for Group A vs. Group C). When compared with Group A, FTN-sparing effects of 54.5% for Group B and 48.9% for Group C were noted. The amount of FTN administered via PCA was less for Group B than for Group A at all time points and for Group C vs. Group A at all time points except 6 h ($P = 0.101$) and 12 h ($P = 0.121$). There was no statistically significant difference between
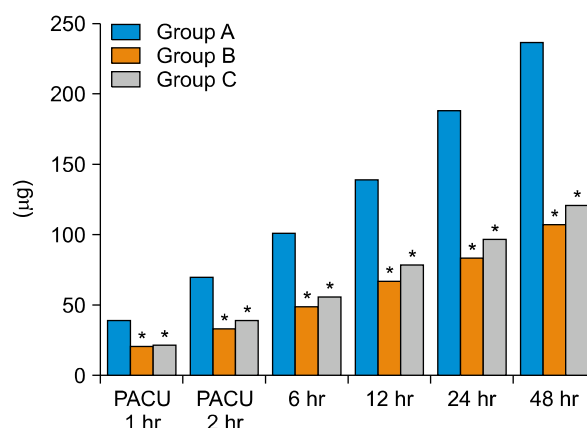

Fig. 1. The cumulative dose of postoperative fentanyl (FTN) administered via PCA over 48 hours. FTN consumption during the 48 h follow-up period is significantly lower in Groups B and C than in Group A. PACU 1 h: the 1st hour after extubation at the Post anesthesia care unit (PACU), PACU 2 h: the 2nd hour after extubation at the PACU, 6 h: the 6th hour after extubation on the ward, 12 h: the 12th hour after extubation on the ward; 24 h: the 24th hour after extubation on the ward; 48 h: the 48th hour after extubation on the ward. Group A: FTN 1,000 μg, Group B: FTN 500 μg + Nefopam (NFP) 200 mg, and Group C: FTN 500 μg + NFP 400 mg. *< 0.01 compare to Group A.

Table 2. Fentanyl and Nefopam Consumption after Extubation

	Group A (n = 27)		Group B (n = 28)		Group C (n = 26)	
	Fentanyl	Nefopam	Fentanyl	Nefopam	Fentanyl	Nefopam
PACU 1 h	39.6 ± 20.8 [31.4−47.9]	-	21.3 ± 10.5[†] [17.2−25.3]	8.5 ± 4.2 [6.9−10.1]	21.7 ± 11.2[†] [17.2−26.3]	17.1 ± 9.0[§] [13.8−21.0]
PACU 2 h	30.4 ± 17.4 [23.5−37.3]	-	12.1 ± 8.3[†] [8.9−15.4]	4.9 ± 3.3 [3.6−6.1]	17.5 ± 7.6[†] [14.4−20.6]	14.0 ± 6.1[§] [11.5−16.5]
6 h	31.1 ± 29.1 [19.6−42.6]	-	16.3 ± 20.1* [8.4−24.1]	6.5 ± 8.0 [3.4−9.6]	17.1 ± 20.3 [8.9−25.3]	13.7 ± 16.2[†] [7.1−20.3]
12 h	38.0 ± 28.2 [26.8−49.1]	-	17.1 ± 23.1* [8.2−26.1]	6.8 ± 9.2 [3.3−10.4]	22.5 ± 29.4 [10.6−34.4]	18.0 ± 23.5[†] [8.5−27.5]
24 h	48.1 ± 53.9 [26.8−69.5]	-	16.6 ± 26.5* [6.3−27.0]	6.6 ± 10.6 [2.5−10.8]	18.1 ± 22.7 [8.9−27.2]	14.5 ± 18.1 [7.1−21.8]
48 h	48.9 ± 38.6 [33.6−64.1]	-	24.1 ± 28.7* [13.0−35.2]	9.6 ± 11.5 [5.2−14.1]	23.8±28.2* [12.4−35.2]	19.1 ± 22.6 [10.0−28.2]
Total	236.1 ± 128.1 [185.4−286.8]	-	107.5 ± 74.0[†] [78.8−136.2]	43.0 ± 29.6 [31.5−54.8]	120.7 ± 91.1[†] [83.9−157.6]	96.6 ± 72.9[†] [67.1−126.1]

Results are expressed as mean ± SD [95% CI]. Group A: Fentanyl 1,000 μg, Group B: Fentanyl 500 μg + Nefopam 200 mg, and Group C: Fentanyl 500 μg + Nefopam 400 mg. *$P < 0.05$ vs. Group A, [†]$P < 0.001$ vs. Group A, [‡]$P < 0.05$ vs. Group B; and [§]$P < 0.001$ vs. Group B in subgroup analysis.

groups B and C in the amount of FTN received via PCA.

The VPS score in the PACU and the NRS scores at 6 h, 12 h, 24 h, and 48 h after extubation showed no significant differences across the 3 groups (**Table 3**). The number of doses of ketorolac 30 mg required as rescue analgesia was 1.1 ± 1.4 for Group A, 0.9 ± 1.1 for Group B, and 0.6 ± 0.8 for Group C without statistical significance ($P = 0.294$). The total number of button pushes for bolus delivery as recorded by the PCA devices was 30.3 ± 21.8 for Group A, 27.6 ± 24.4 for Group B, and 32.7 ± 25.6 for Group C ($P = 0.733$).

With regard to the occurrence of PCA-related side effects, there were no significant differences across the 3 groups (**Table 4**). Although the prevalence of sedation was not different across the 3 groups, Group A had a higher sedation score than Group B, on average (0.94 ± 0.72 and 0.48 ± 0.50, respectively) during 2 h in the PACU; thus, Group B showed significantly less sedation than Group A ($P = 0.025$). However, no statistically significant differences in the degree of sedation were observed between Group A and Group C (0.60 ± 0.68, $P = 0.148$). Two patients in Group A and 1 patient in Group C had respiratory depression; among them, one patient in Group A had presented with respiratory depression and sedation together during the first hour in the PACU and recovered with ventilation assist. Hypotension was recorded during the first

Table 3. Verbal Pain Score (VPS) and Numeric Rating Scale (NRS) Results

	Group A (n = 27)	Group B (n = 28)	Group C (n = 26)	*P* value
PACU 1 h (VPS)	1.7 ± 0.8 [1.4−2.1]	1.6 ± 0.6 [1.4−2.1]	1.7 ± 0.8 [1.4−2.0]	0.798
PACU 2 h (VPS)	1.2 ± 0.5 [1.0−1.4]	1.2 ± 0.6 [1.0−1.4]	1.2 ± 0.6 [1.0−1.5]	0.954
6 h (NRS)	3.4 ± 1.8 [2.7−4.1]	3.2 ± 1.8 [2.5−3.9]	3.2 ± 2.0 [2.4−4.0]	0.891
12 h (NRS)	2.8 ± 1.2 [2.3−3.4]	3.3 ± 2.0 [2.4−4.1]	3.0 ± 1.6 [2.3−3.7]	0.710
24 h (NRS)	2.9 ± 2.4 [1.9−3.8]	2.9 ± 1.8 [2.2−3.6]	3.1 ± 1.7 [2.4−3.8]	0.862
48 h (NRS)	1.7 ± 1.7 [1.0−2.4]	2.0 ± 1.4 [1.4−2.5]	2.0 ± 1.2 [1.5−2.5]	0.750

Results are expressed as mean ± SD. No significant differences were found among three groups at each time point. PACU: postanesthesia care unit, VPS: Verbal Pain Score (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain), NRS: Numeric Rating Scale (0 = no pain and 10 = worst pain imaginable). Group A: Fentanyl 1,000 μg, Group B: Fentanyl 500 μg + Nefopam 200 mg, and Group C: Fentanyl 500 μg + Nefopam 400 mg.

Table 4. Adverse Effects

	Group A (n = 27)	Group B (n = 28)	Group C (n = 26)
Nausea and vomiting, n (%)	17 (59.3%)	18 (64.3%)	18 (69.2%)
Sedation, n (%)	21 (77.7%)	16 (57.1%)	16 (61.5%)
Sweating, n (%)	0 (0%)	1 (3.6%)	3 (11.5%)
Dry mouth, n (%)	20 (74.1%)	26 (92.9%)	22 (92.3%)
Respiratory depression, n (%)	2 (7.4%)	0 (0%)	1 (3.8%)
Shivering, n (%)	4 (14.8%)	2 (7.1%)	0 (0%)
Tachycardia, n (%)	0 (0%)	0 (0%)	0 (0%)
Bradycardia, n (%)	1 (3.7%)	2 (7.1%)	0 (0%)
Hypotension, n (%)	2 (7.4%)	1 (3.6%)	1 (3.8%)

Results are expressed as number (%). There is no significant difference among 3 groups. Group A: Fentanyl 1,000 μg, Group B: Fentanyl 500 μg + Nefopam 200 mg, and Group C: Fentanyl 500 μg + Nefopam 400 mg.

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Table 5. Five-point Patient Satisfaction Scale at 48 Hours

Satisfaction scale		A (n = 27)	B (n = 28)	C (n = 26)	Total (n = 81)
1	Very satisfied	9 (33.3%)	9 (32.1%)	10 (38.5%)	28 (34.6%)
2	Satisfied	12 (44.4%)	11 (39.3%)	11 (42.3%)	34 (42.0%)
3	So-so	3 (11.1%)	6 (21.4%)	4 (15.4%)	13 (16.0%)
4	No satisfied	1 (3.7%)	2 (7.1%)	1 (3.8%)	4 (4.9%)
5	Very dissatisfied	2 (7.4%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
Average		2.07 ± 1.14	2.04 ± 0.92	1.85 ± 0.83	

Results are expressed as number (%) or mean ± SD. There were no significant differences in patient satisfaction across the 3 groups ($P = 0.691$ by Fisher's exact test or $P = 0.663$ by one-way ANOVA). Group A: Fentanyl 1,000 μg, Group B: Fentanyl 500 μg + Nefopam 200 mg, and Group C: Fentanyl 500 μg + Nefopam 400 mg.

hour in the PACU; all of these patients recovered immediately upon the administration of an IV normal saline infusion. Finally, during the first hour in the PACU, shivering was reported in 4 patients from Group A and 2 patients from Group B; shivering was not observed on the ward in any patient from any of the 3 groups.

Patient satisfaction scores are shown in **Table 5**. There were no significant differences among the 3 groups ($P = 0.663$) and overall, the patients were satisfied with their POP control via PCA across all 3 Groups.

DISCUSSION

In this study, the overall FTN-sparing effect during 48 h of PCA with coadministered NFP was 54.5% in Group B and 48.9% in Group C compared to Group A. Total consumption of FTN was not significantly different between Groups B and C although the amount of NFP was doubled in Group C. Although there were no differences in the occurrence of PCA-related side effects in the 3 groups, Group B had a lower sedation score with significantly less sedation than Group A.

NFP is a centrally-acting non-opioid benzoxazocine derivative analgesic [13–15]. Although the analgesic potency of NFP is less than that of morphine or oxycodone [18], NFP has not been associated with respiratory depression and it has a low prevalence of side effects such as coagulopathies, nephrotoxicity, and cardiovascular toxicity, as well as a low risk of abuse [20–22]. Hence, the concomitant administration of opioids and NFP is considered to have many advantages over the administration of opioids alone [13,15,29]. In previous studies, use of NFP in

the management of POP has resulted in morphine-sparing effects ranging from approximately 20–50% [24,26]. This is equivalent to the morphine-sparing effect of NSAIDs and better than that of acetaminophen [30–32]. However, to the best of our knowledge, the FTN-sparing effect of the concomitant administration via PCA of NFP and FTN had not been previously reported. Thus, this is the first study to confirm an FTN-sparing effect of NFP. In our study, during the first hour in the PACU, FTN-sparing effects of 46.2% (Group B) and 45.2% (Group C) were observed, and during the second hour, FTN-sparing effects of 60.2% and 42.4% were determined for Group B and Group C, respectively. During the 48 h after extubation, 54.5% and 48.9% reductions in the amount of administered FTN were recorded for Group B and Group C, respectively; the difference in the FTN-sparing effect between the two groups was not significant and there were no differences in pain scores (VPS and NRS) across groups, and no differences in terms of overall patient satisfaction scores. Accordingly, NFP can be considered a useful adjunct to strong opioids such as FTN and morphine in the management of POP.

Besides sedation, which occurred to a significantly higher ($P = 0.02$) degree in Group A (FTN only), there were no differences among the groups in terms of the occurrence of treatment-related side effects, and the incidence of sedation did not differ among the 3 groups. There was no increase in opioid-related side effects such as nausea and vomiting, sedation, dry mouth, and respiratory depression associated with NFP co-administration with FTN, and this is in line with the results from previous studies of the concomitant administration of NFP and morphine

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[23,24]. Although tachycardia is known as one of the major side effects of NFP, reported in 12–20% of patients [17,33] and requiring caution when NFP is administered to patients with a high risk of cardiovascular complications, there was no reported incidence of tachycardia in any patient in the present study. This may be because pain was managed via a small total dose of NFP that was administered slowly [33–35] and in small doses via PCA. The incidence of sweating, which is another known side effect of NFP [36], did not show any significant differences across the 3 groups in the present study. NFP has also been shown to be effective for postoperative shivering [34]. However, in our study, a prevalence of postoperative shivering was not different across the 3 groups, which may have been due to the relatively short operation times, the continuous monitoring of body temperature in all the patients during the operation, and the active prevention of hypothermia by using an air warmer when a patient's body temperature fell below 36°C.

There exist several limitations in the present study. The study results did not provide a dose-response relationship for the efficacy of NFP. The consumption of FTN was not significantly different between Group B and Group C, although the amount of NFP was twice as high in Group C than in Group B. This may be due to the ceiling effect of NFP that was demonstrated in previous studies in which additional doses of up to 90 mg of oral NFP did not result in greater pain relief [19,37]. However, the dose-response relationship needs to be confirmed with the administration of the various other doses. In addition, this study included only female patients who were expected to experience acute moderate pain following laparoscopic total hysterectomy, and further studies will be needed in order to demonstrate the FTN-sparing effects of NFP during treatment of POP from different types of surgery that may cause different degrees of pain. Finally, studies including a greater number and variety of study patients should be conducted in order to provide more accurate assessments of the safety and efficacy of the use of NFP.

In conclusion, the concomitant administration of NFP and FTN through a PCA device for the management of POP resulted in an FTN-sparing effect related to the administration of NFP. This reduced the required dose of FTN without related side effects or differences in the levels of patient satisfaction. Therefore, NFP can be considered a useful adjunct to strong opioids, such as FTN, in the management of POP.

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