

**THE POST-OPERATIVE ANALGESIC EFFECTIVENESS  
OF A NEFOPAM AND FENTANYL MIXTURE  
IN PATIENTS UNDERGOING SPINAL FUSION SURGERY**

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**Abstract**

**Objectives:** To evaluate the intravenous patient-controlled analgesic (PCA) effects of a combination of fentanyl and nefopam in patients who underwent spinal fusion surgery. **Methods:** 60 patients, who underwent spinal fusion surgery at the Spine Surgery Department, Military Hospital 103, from April to November 2022, were divided randomly into two groups: The F group (30 patients received fentanyl via intravenous PCA) and the NF group (30 patients received fentanyl and nefopam mixture via intravenous PCA). Patients in both groups were evaluated and compared for the pain level through the VAS (Visual Analog Scale), the Actual/Demand ratio (A/D), and the amount of post-operative fentanyl consumption. **Results:** The average VAS score of the patients in both groups at rest was < 4 and ranged from 2.3 - 4.2 during movement. The mean VAS score during movement after the first 24-hour period of the NF group was significantly lower than that of the F group ( $p < 0.05$ ). The A/D ratio of the two groups at studied time points was > 75%; in which, the A/D ratio of the NF group was statistically significantly higher than that of the F group ( $p < 0.05$ ). The amount of post-operative fentanyl consumption via PCA in the NF group was  $646.17 \pm 99.23$ mcg, 14.79% lower than in the F group ( $758.33 \pm 138.42$ mcg), with  $p < 0.05$ . **Conclusion:** Intravenous PCA with the mixture of nefopam and fentanyl and with fentanyl alone are effective methods of analgesia after spine fusion surgery. The combination use of nefopam and fentanyl in PCA provided a better analgesia effect than using fentanyl alone.

**Keywords:** Patient-controlled analgesic; Nefopam; Fentanyl; Spinal fusion surgery.

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## INTRODUCTION

Spinal fusion surgery is a surgery connecting spinal bones to prevent movement between them. Preventing movement helps prevent pain. However, patients often complain about moderate and severe pains after spinal fusion surgery; thus, effective post-operative analgesia is necessary to increase the advance and enhance patient satisfaction. Opioid-based PCA is commonly performed for post-operative pain control with adverse effects, including constipation, vomiting, etc. In order to minimize them, the decrease in post-operative opioid consumption by using a combination of opioid and non-opioid analgesics such as nefopam is essential.

Nefopam was first discovered in the 1970s as an antidepressant. It was shown to have central-acting and nonnarcotic analgesic effects by inhibiting the uptake of dopamine, norepinephrine, and serotonin [1, 2]. In contrast to opioids, nefopam is not associated with any risk of respiratory depression [3]. Moreover, nefopam causes less gastroduodenal mucosal injury and interferes less with platelet function than NSAIDs [4, 5]. Nefopam, as an adjuvant analgesic for fentanyl-based PCA, has been shown to provide similar post-operative analgesia to ketorolac.

In this study, we aimed to: *Compare the analgesic effects of a combination of nefopam and fentanyl with fentanyl alone using intravenous PCA after spinal fusion surgery in the thoracic and lumbar regions.*

## MATERIALS AND METHODS

### 1. Subjects

60 patients were randomly divided into two groups: Fentanyl (F group) and a mixture of nefopam and fentanyl (NF group), undergoing spinal fusion surgery at the Spine Surgery Department, Military Hospital 103, from April to November 2022. The randomization into two groups was performed using a computer-generated table of random numbers with a 1:1 allocation ratio.

\* *Inclusion criteria:* Patients agreed to cooperate and participate in the study; patients aged 18 - 65, ASA I - III; general anesthesia will be administered, and expected to be extubated at the end of surgery in the operating room; patients could understand and/or press the PCA button; patients had no contraindications to the drugs used in the study; patients had no pre-operative chronic pain and/or frequent use of opioid analgesics.

\* *Exclusion criteria:* Patients with severe complications related to anesthesia and/or surgery during and after the operation.

## 2. Methods

\* *Research methods:* A cross-sectional study was conducted.

\* *Study protocol and groups:*

Initiate intravenous sedation using: Atropine 0.02 mg/kg, Propofol dose 1.5 - 2.5 mg/kg, Fentanyl dose 2 mcg/kg, Rocuronium (Esmerone) dose 1 mg/kg. Squeeze the ventilation bag with 100% O<sub>2</sub> in 2.5 minutes, proceed with endotracheal intubation, check the lung sound to ensure adequate ventilation on both sides, fixation of the endotracheal tube, move the patient to a prone position, then recheck the endotracheal tube. At the end of the surgery, move the patient to the supine position, stop the sevoflurane anesthetic, turn off the operating room air conditioner, and warm the patient with a warm-up device. Reversal neuromuscular blockade with neostigmine 50 mcg/kg in combination with atropine 10 mcg/kg (20mL slow intravenous injection) or Sugamadex 2 mg/kg if necessary. The extubation was performed when the patient met the criteria with regard to perception, hemodynamics, respiration, muscle strength, and body temperature.

In the NF group (30 patients): Patients were administered an analgesic mixture containing 2 mg/mL nefopam and 25 mcg/mL fentanyl in a natriclorua 0.9% solution.

In the F group (30 patients): Patients were administered an analgesic medication containing fentanyl 100 mcg/mL in a natriclorua 0.9% solution.

With IV-PCA parameter settings for both groups are as follows: no background rate, lock-out time: 8 min; bolus dose: 1mL, maximum amount of fentanyl for 4 hours: 15mL.

Before starting PCA, patients with a VAS score  $\geq 4$  were titrated with drug solution in a PCA syringe until a VAS score  $< 4$ . Pain titration procedure after extubation.

\* *Pain titration procedure after extubation:*

In the NF group: Intravenous injection of 1mL (25mcg fentanyl and 2 mg nefopam) every 5 minutes until VAS score  $< 4$ ; in the F group: 1mL intravenous injection of 1mL (equivalent to 25mcg fentanyl) every 5 minutes until a VAS score  $< 4$  was achieved. The drug was injected into the patient by a separated vein or a trident with a stable flow. Initiating the PCA machine and transferring the patient to the spine surgery department. PCA was used for 72 hours after surgery.

If the patient felt pain and VAS  $\geq 4$ , checked the power supply, parameters on the PCA machine, IV line, and the remaining amount of medication. Titration with the analgesic solution in

the PCA machine (this amount was counted towards the patient's overall consumption) before restarting the PCA. If the pain does not subside after 4 successful button presses, proceed with analgesia rescue with 30mg ketorolac intravenous slowly. This dose may be repeated after 10 minutes if the VAS score is still > 4.

*\* Definition of variables:*

Data on age (years), weight (kg), height (cm), gender (male/female), ASA score, type of surgery, surgical time (minutes), intraoperative fentanyl consumption (mcg), other drugs used during surgery: Propofol (mg), rocuronium (mg), sevofluran (mL), titration dose, time, VAS score before titration, at rest and movement, and A/D ratio were recorded for each patient.

*\* Assessment of drug effect:*

VAS with titration dose, time, and VAS score before titration. VAS score (on a scale of 0 - 10) at rest and movement (patient actively leaning) at the 1<sup>st</sup>-hour, 2<sup>nd</sup>-hour, 6<sup>th</sup>-hour, 12<sup>th</sup>-hour, 24<sup>th</sup>-hour, 36<sup>th</sup>-hour, 48<sup>th</sup>-hour, 60<sup>th</sup>-hour, and 72<sup>nd</sup>-hour timepoints. The usage of analgesics (nefopam by mg, fentanyl by mcg) 72 hours after starting PCA was documented. The A/D ratio was between the number of successful button presses (Actual) and the total number of required button

presses (Demand). The A/D ratio was displayed frequently on the PCA and recorded 24, 48, and 72 hours after starting PCA. The number of administrations of intravenous rescue analgesic (ketorolac 30mg).

*\* Statistical analysis:*

The collected data were entered and processed according to medical statistical methods using SPSS 22.0 software. Variables with approximately standard distribution: Data are presented in the form of  $\bar{X} \pm SD$ , using the T-student test to compare the two mean values of two groups. Variables without normal distribution: Data were presented as a series of quartiles, using the corresponding non-parametric tests. Discrete variable: Data presented as percentage (%);  $\chi^2$  test was used to compare ratios; if more than 25% of cells had a theoretical frequency < 5, using Fisher's exact test.

**3. Ethics**

The study was approved by the Ethics Committee at Military Hospital 103 (ref number 52/KH-HDDD) in October 4th, 2022. Patients' data were kept confidential throughout the study to protect the anonymity of their patients. To participate in the trial, every patient provided written and fully informed consent.

RESULTS

The average age, height, and weight in the F group were 50.97 years old, 162.83cm, and 59.57kg, respectively; the NF group was 46.4 years old, 161.3cm, and 58.33kg. The proportion of men in both groups was 56.7%; the ratio of women to men was 1/1.31. In group F, the proportion of men was 63.3% (19/30); females accounted for 36.7% (11/30). In the NF group, the proportion of male and female patients was about 50%. There were no statistically significant differences in mean age, gender distribution, height, and weight between the two groups with  $p > 0.05$ . Besides, the mean surgical time was  $142.50 \pm 39.12$  minutes in the F group and  $147.33 \pm 40.3$  minutes in the NF group.

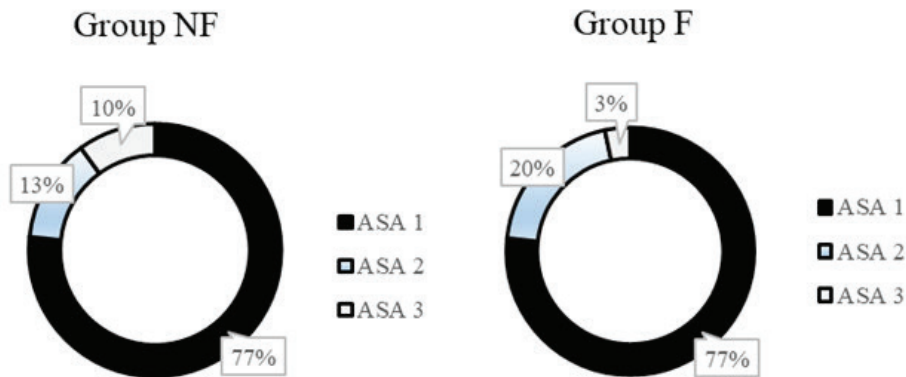


Figure 1. ASA classification.

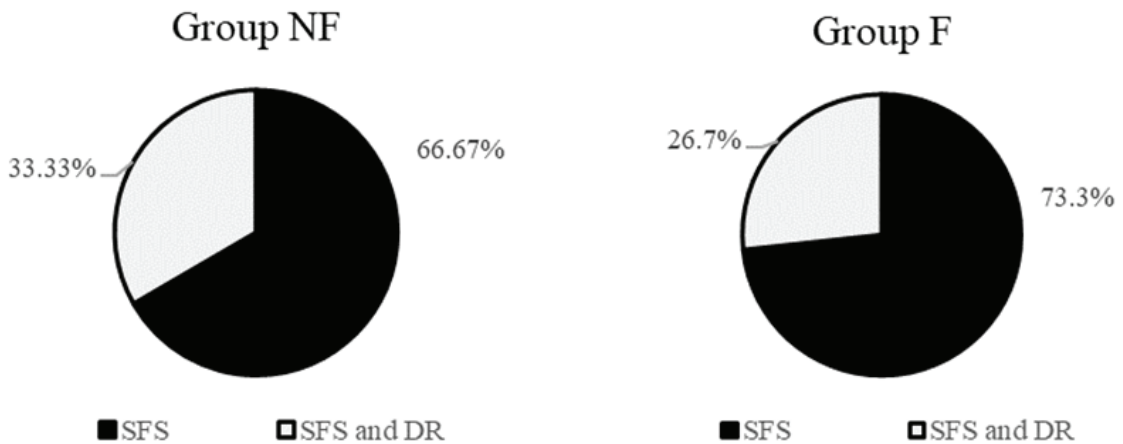


Figure 2. Patient distribution by type of surgery.

**Table 1.** Surgical time and drugs used in anesthesia and surgery.

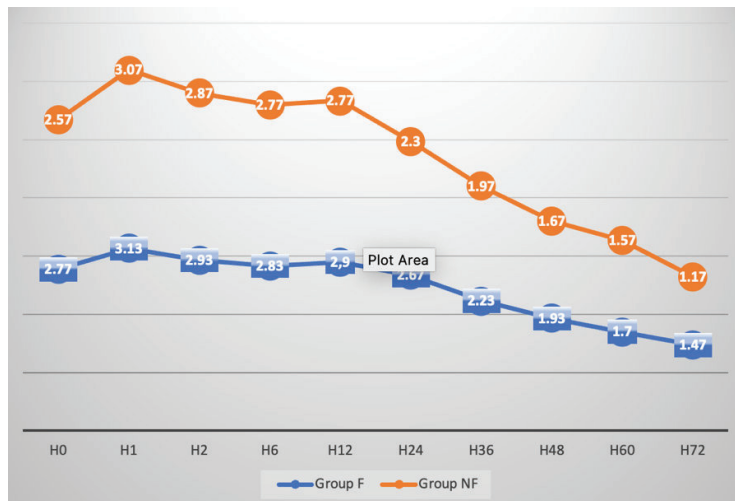
Parameters	Group F (n = 30)	Group NF (n = 30)	p
	$\bar{X} \pm SD$ (Min - max)	$\bar{X} \pm SD$ (Min - max)	
Fentanyl (mcg)	360 ± 72.4 250 - 500	361.67 ± 87.77 300 - 500	> 0.05
Propofol (mg)	123.33 ± 28.08 80 - 180	134 ± 32.44 90 - 200	> 0.05
Rocuronium (mg)	104 ± 29.55 50 - 170	109.33 ± 28.03 50 - 190	> 0.05
Sevofluran (mL)	23.05 ± 6.32 16 - 34	25.57 ± 3.88 18 - 35	> 0.05
Surgical time (min)	142.50 ± 39.12 70 - 240	147.33 ± 40.3 75 - 240	> 0.05

The average amount of analgesics (fentanyl) consumed during surgery was 360 ± 72.4mcg in the F group and 361.67 ± 87.77mcg in the NF group.

**Table 2.** Time and dose of titration and VAS score before titration.

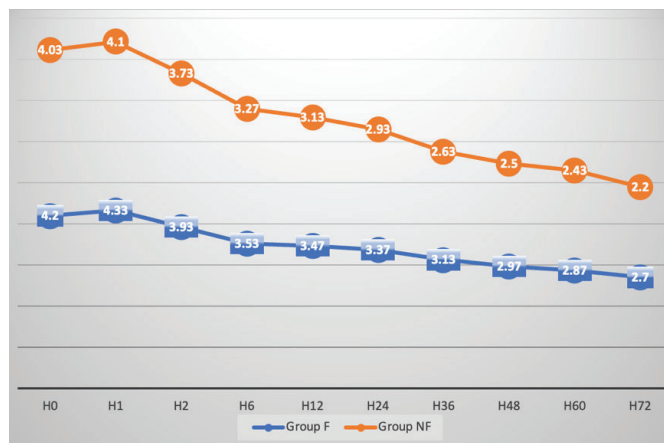
Parameters	Group F (n = 30)	Group NF (n = 30)	p
	$\bar{X} \pm SD$ (Min - max)	$\bar{X} \pm SD$ (Min - max)	
Titration time (min)	9.00 ± 6.22 0 - 20	11.33 ± 6.81 0 - 25	> 0.05
Titration dose (mcg)	43.33 ± 29.31 0 - 100	51.67 ± 28.57 0 - 100	> 0.05
VAS at rest before titration	5.37 ± 0.85 4 - 8	5.03 ± 1 4 - 7	> 0.05
VAS on movement before titration	6.53 ± 0.97 5 - 8	6.90 ± 0.99 5 - 9	> 0.05





**Chart 1.** VAS score at rest.

The mean VAS score at rest after titration of the two groups was  $2.77 \pm 0.82$  in the F group and  $2.57 \pm 0.97$  in the NF group. During the use of PCA, the mean VAS score in the rest of both groups was  $< 3$  (corresponding to a low pain level). There was no statistically significant difference in this value between the two groups ( $p > 0.05$ ). During the use of PCA, the average VAS score at rest in both groups tended to decrease gradually. The average VAS score on movement after titration of the two groups was  $4.2 \pm 1.13$  in the F group and  $4.03 \pm 1.1$  in the NF group.



**Chart 2.** VAS score at movement.

At the 24<sup>th</sup>-hour, 36<sup>th</sup>-hour, 48<sup>th</sup>-hour, 60<sup>th</sup>-hour, and 72<sup>nd</sup>-hour timepoints, the average VAS scores on movement in the NF group were statistically significantly

lower than in the F group ( $p < 0.05$ ). During the use of PCA, the average VAS score on movement in both groups tended to decrease.

**Table 3.** Post-operative fentanyl (mcg) and nefopam (mcg) consumption.

Parameters	Group F (n = 30)	Group NF (n = 30)	p
	$\bar{X} \pm SD$ (Min - max)	$\bar{X} \pm SD$ (Min - max)	
Fentanyl consumption via PCA	646.17 ± 99.23 (525 - 900)	758.33 ± 138.42 (525 - 1125)	< 0.05
Fentanyl consumption via titration and PCA	724.37 ± 106.19 (600 - 1025)	839.83 ± 145.01 (675 - 1275)	< 0.05
Nefopam	61.27 ± 13.17 (38 - 84)		

The average amount of fentanyl consumption after surgery (including titration) and the average amount of fentanyl consumed via PCA in the NF group was lower than that of the F group.

**Table 4.** A/D ratio at 24, 48, and 72 hours.

Parameters	Group F (n = 30)	Group NF (n = 30)	p
	$\bar{X} \pm SD$ (Min - max)	$\bar{X} \pm SD$ (Min - max)	
A/D(H24) (%)	76.18 ± 3.19 71 - 94	73.12 ± 4.14 71.5 - 90	< 0.05
A/D(H48) (%)	77.32 ± 2.43 72.5 - 100	74.38 ± 4.57 72.2 - 90	< 0.05
A/D(H72) (%)	78.63 ± 3.61 75 - 100	75.76 ± 3.67 73.4 - 94	< 0.05

The average A/D ratio was significantly higher in the NF group than in the F group at the 24<sup>th</sup>-hour, 48<sup>th</sup>-hour, and 72<sup>nd</sup>-hour timepoints ( $p < 0.05$ ).



**Table 5.** The number of patients required “rescue bolus”.

	<b>Group NF</b> <b>n = 30</b>	<b>Group F</b> <b>n = 30</b>	<b>P</b>
Number of patients required “rescue bolus” n (%)	1 (3.3)	3 (10)	> 0.05
One-time bolus n (%)	1 (3.3)	2 (6.7)	
Two times bolus n (%)	0 (0)	1 (3.3)	

The difference in the number of patients and the number of "rescue bolus" between the two groups was not statistically significant ( $p > 0.05$ ).

### **DISCUSSION**

The mean age in our study was 50.97 years old in the F group and 46.4 years old in the NF group. This result was also consistent with the study by Vu Hoang Phuong et al. (2021) when studying the analgesic effect of spinal erector anesthesia after lumbar spine surgery with an average surgical age of  $50.7 \pm 13.3$  years old [6]. The average weight of patients in this study was 59.57kg in the F group and 58.33kg in the NF group, which was also consistent with studies on spine surgery patients such as Vu Hoang Phuong ( $56.6 \pm 6.7$ kg and  $58.1 \pm 8.2$ kg, respectively).

The proportion of men in both groups was 56.7%, women were 43.3%, and the ratio of men to women was 1.31/1. The influence of gender on pain and analgesic needs remained

controversial. A study conducted by Chia et al. in Chinese patients ( $n = 2298$ ) confirmed gender as a major predictor of morphine consumption via IV PCA with the result that men consumed more morphine from 23% - 43% than women [7]. Therefore, our results minimized the confounding effects of gender in the testing techniques because many studies have confirmed that the analgesic effect of fentanyl was different between men and women.

Most of the patients in our study were healthy with ASA I - II, in which the proportion of patients with ASA I - II accounted for 97% in the F group and 90% in the NF group. The distribution of ASA characteristics in our study is similar to that of the authors Schenk M. R. et al. (2006) [8], with the majority of patients in good

health, ASA I - II. We did not select patients with severe pre-operative illness for the study because the severe condition of the combined disease could lead to the risk of complications due to the side effects of analgesics.

In our study, fentanyl was the only analgesic used during surgery, with an average consumption of  $360 \pm 72.4$ mcg in the F group and  $361.67 \pm 87.77$ mcg in the NF group. This result was also consistent with the results of other authors in Vietnam, such as Nguyen Toan Thang et al. ( $336 \pm 66.9$  and  $360 \pm 59.3$ mcg) [9]. Analgesics consumption during surgery was a factor that could influence pain severity, analgesics consumption, and side effects in the immediate post-operative period. Shapiro confirmed a direct relationship between intraoperative fentanyl usage and post-operative respiratory depression with intravenous PCA.

The average total fentanyl consumption in 3 days post-operatively (including the amount of fentanyl used for titration) was  $839.83 \pm 145.01$ mcg in the F group and  $724.37 \pm 106.19$ mcg in the NF group. The fentanyl consumption in the NF group was significantly lower than that in the F group, which was 13.75% ( $p = 0.01$ ). The PCA consumption of fentanyl

alone (excluding fentanyl dose for titration) was  $758.33 \pm 138.42$ mcg in the F group and  $646.17 \pm 99.23$ mcg in the NF group. The results showed that the amount of fentanyl consumed in the NF group was also 14.79% lower than that in the F group ( $p = 0.01$ ). This reflected the fentanyl-sparing effect of nefopam used in PCA for post-operative analgesia. The fentanyl-sparing effect of nefopam in our study was lower than the results of some other studies. Tran Thanh Tuan et al. (2020) studied PCA analgesia with fentanyl and nefopam during 24 hours after burn debridement and grafting surgery with fentanyl consumption in the F group was  $562.50 \pm 17.06$ mcg higher than that in the NF group ( $295.42 \pm 17.52$ mcg) [10].

The average VAS score of the patients before titration in our study was 5.03 - 5.37 at rest and 6.53 - 6.90 during movement (Table 1). The results showed that most patients had moderate pain scores and felt more pain on movement, which could be explained by the amount of fentanyl used in surgery, which was not excessive (360 - 361.67mcg). In addition, the surgical time was also relatively long (142.5 - 147.33 minutes). This result was consistent with the result of Nguyen Toan Thang in abdominal

surgery, with the average VAS score at rest and on movement after extubation being  $5.27 \pm 1.02$  and  $6.77 \pm 1.04$ , respectively [9]. We found no difference in mean pain scores between the two groups immediately before titration. Thus, pain levels in the two groups were relatively similar before titration and PCA was started.

The average VAS score during movement varied from 2.3 - 4.2. Thus, most patients achieve good analgesia, especially when lying. This was also consistent with the results of the review that included many studies of intravenous PCA using opioids with better analgesia and higher levels of patient satisfaction compared with other traditional use of opioids.

The ideal value that could be achieved was 1 (100%); however, when  $A/D > 75\%$  was considered acceptable. The results show that the A/D ratio at the 24<sup>th</sup>-hour, 48<sup>th</sup>-hour, and 72<sup>nd</sup>-hour timepoints in both groups was  $> 75\%$ . This reflected the pain relief effect, and the parameter setting was relatively reasonable. Considering the difference between the two groups, we found that the average A/D ratio at the above time points in the NF group was statistically significantly higher than in the F group. Specifically at the 24<sup>th</sup>-hour

timepoint, the A/D ratio in the F group and the NF group were  $73.12 \pm 4.14$  and  $76.18 \pm 3.19$ , respectively ( $p = 0.02$ ); at the 48th-hour timepoint, they were  $74.38 \pm 4.57$  and  $77.32 \pm 2.43$  ( $p = 0.03$ ); and at the 72th-hour timepoint, they were  $75.76 \pm 3.67$  and  $78.63 \pm 3.61$ , respectively (*Table 4*,  $p = 0.03$ ). It was also relatively consistent with the result that the average pain score on movement after the first 24 hours in the NF group was statistically significantly lower than that in the F group. Thus, it was clear that the analgesic effect of nefopam and fentanyl was better than that of fentanyl alone in PCA for post-operative pain relief.

There were 4 cases requiring rescue analgesia, of which 3 cases were in the F group (10%) and 1 case was in the NF group (3.3%). In the F group, there was 1 patient who required rescue analgesia boluses two times, and there was no case that needed to bolus "rescue analgesia" more than twice.

## CONCLUSION

Intravenous PCA with the mixture of nefopam and fentanyl and with fentanyl alone are effective methods of analgesia after spine fusion surgery. The combination use of nefopam and fentanyl in PCA provided a better analgesia effect than using fentanyl alone.

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