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ORIGINAL RESEARCH **NEUROANESTHESIA**

Combined nefopam-fentanyl use in PCA for postoperative analgesia in spinal surgery patients: a randomized, controlled, single-blind trial

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ABSTRACT

Background & objective: The use of fentanyl to manage postoperative pain in spinal surgery patients is common, although there have been concerns about potential of drug abuse and dependence. We investigated the effects of the combined administration of nefopam and fentanyl through intravenous (IV) patient-controlled analgesia (PCA) on early postoperative pain and possible side effects in patients undergoing spinal surgeries.

Methodology: In this randomized, controlled study, 70 patients were allocated to receive either fentanyl 10 µg/mL (Group F) or fentanyl 10 µg/mL with nefopam 1.2 mg/mL (Group FN), with a total PCA volume of 100 mL per infusion bag. Patients received a background dose of 0.25 µg/kg/h and bolus dose of 0.5 mL SOS (fentanyl 5 µg). The lockout interval was set at 10 min and upper limit was set at 15 mL/4 h. The PCA parameters were set according to the body weight of each patient.

Results: The cumulative postoperative fentanyl consumptions after 48 h for Group F and Group NF were reported as 744.6 ± 94.2 µg and 631 ± 62.5 µg ($P < 0.05$) respectively. The average number of bolus doses requested by the patients in Group F and FN were 20.8 ± 11.0, and NF 11.4± 7.6). The A/D ratio of both groups for the bolus doses were 70%. Group NF consistently scored a lower VAS and VAS-D score during the 48-hour postoperative period. However, the VAS scores significantly differ statistically between groups at 1, 6, 9, and 12 hours. Within group differences, the VAS score differed significantly statistically during the 0-1, 1-2, and 2-3 hours for Group F, while 24-36 hours for Group NF.

Conclusion: The inclusion of nefopam in patient-controlled analgesia for spine surgery patients significantly reduced total use of fentanyl within the 48 hours postoperatively after the surgery. Patients receiving fentanyl with nefopam consistently had lower VAS scores at different time points.

Abbreviations: PCA - patient-controlled analgesia; VAS - Visual Analogue Scale

Keywords: postoperative pain, fentanyl, nefopam, patient-controlled analgesia

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1. INTRODUCTION

Postoperative period after spinal procedures is critical and demands adequate pain management, which would result in better functional outcomes, early discharge, and avoiding chronic pain development.[1] However, the prolonged use of opioids as postoperative analgesics causes concerns about potential abuse, while also showing adverse outcomes for the patient.[2] Based on one study,[3] lumbar decompression surgery is associated with a consumption of approximately 80 pills of pain-killer drugs. With approximately 61% of cases reporting unused opioid medication, and only 41% of patients reporting appropriate disposal of unused opioid pills, a big problem is a large over prescription of opioids in postoperative pain management scenario.[3]

To reduce opioid consumption, nefopam is commonly combined with opioids. It is the preferred choice for multimodal analgesia due to its documented advantages.[4,5] It is non-opioid and non-steroidal drug and has no sedative effects and is commonly used as an analgesic drug.[6] Various studies demonstrated that administrating a combination of nefopam and opioids (e.g., morphine) effectively reduced postoperative pain in patients, while reducing the opioid or morphine consumption.[6–9] However, there is limited evidence to demonstrate the effectiveness of the combination nefopam and a synthetic opioid, namely fentanyl, in spine surgery.

The main objective of this study was to determine the efficacy of fentanyl and nefopam administrations for intravenous (IV) patient-controlled analgesia (PCA) on postoperative pain scores in patients undergoing spine surgery. Another objective was to evaluate any adverse effects of this combination.

2. METHODOLOGY

2.1. Study design and study population

This prospective, randomized, controlled, single-blind study was approved by the Ethical Board of 108 Military Central Hospital, Hanoi, Vietnam, on January 2022. The participants included patients aged 16-70 y with an American Society of Anesthesiologists (ASA) physical status of I-III. Exclusion criteria were patients with a history of seizures, urinary retention, other urinary disorders, impaired hearing sense, psychological disorder, visual sensory defects, intubation, tracheostomy, mechanical ventilation, angle-closure glaucoma, heart failure, myocardial infarction, liver failure, kidney failure, alcohol and opioid use disorder, known intolerance or hypersensitivity to nefopam and fentanyl, a history of opioid- or fentanyl- or nefopam-related complications, or inability to understand the use of PCA.

The PCA device was administrated and the use of Visual Analogue Scale (VAS) scores were explained to the participants of the study. Participants were instructed to press the demand button of the PCA device when they feel intolerable pain. Prior to this, both written and verbal informed consents were obtained from all participants or their relatives after a full explanation of the purpose of this study.

2.2. Randomization process

Subjects were randomly assigned by computer-generated random numbers either to Group F and Group FN. Group F consisted of 35 patients to receive fentanyl 10 µg/mL through IV PCA, and Group FN (n = 35) received a combination of fentanyl 10 µg/mL and nefopam 1.2 mg/mL.

One member of this study was assigned to gather and record data from the participants and the PCA device, and collate the data generated for the first 24 h after surgeries. Another member of this study was responsible for assigning the correct drugs to each PCA device according to the results of the randomization setting. These two members did not participate in the statistical analysis.

The nurses in the recovery room recorded data on postoperative nausea and vomiting using the verbal numerical rating scale; these nurses were not part of the study team.

2.3. Anesthetic process

Clinical examination included history taking, ASA evaluation, Apfel scores, BMI, and vital signs measurements), as well as laboratory test evaluations were conducted a day prior to the spinal operations. Patients were explained about the process of anesthesia, the PCA set-ups, and possible unwanted outcomes.

All patients were administrated fentanyl as an analgesic, for the process of induction and maintenance of anesthesia, followed by propofol 2 mg/kg or etomidate 0.3 mg/kg (in case patients were hypersensitive to propofol), rocuronium bromide 0.6 mg/kg, and fentanyl 2 µg/kg. Endotracheal intubation with an appropriate-sized ETT was accomplished. For maintenance of anesthesia we used isoflurane (2-3%), fentanyl 50 µg/kg every 30 min. Fentanyl and propofol were stopped when the wound closure was started. Patients were transferred to the recovery room and monitored. Subsequently, the process of randomly selected patients was conducted.

The background dose of fentanyl 0.25 µg/kg/h was started when the ETT was removed and the VAS score was ≥ 4. Pain management evaluation was assessed

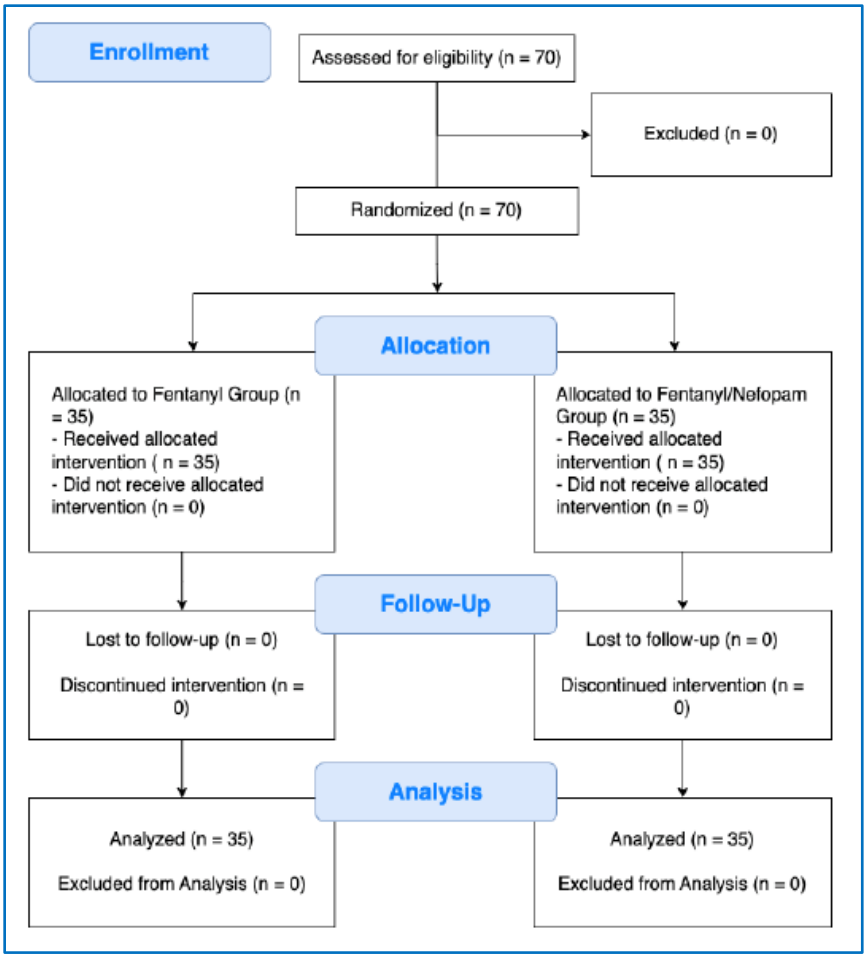

Figure 1: Study flow diagram

every 10 min until the VAS score was less than 4. Patients were excluded from the study in the case of using 5 background doses or more and the VAS score was still ≥ 4. Patients with the VAS score less than 4 were considered to use bolus dose, which was an infusion bag of 50 mL for Group F with fentanyl 5 mL and saline 45 mL; and for Group FN with fentanyl 5 mL, nefopam 6 mL, and 39 mL of saline. The lockout interval was set at 10 min and the upper limit was set at 15 mL/4 h.

Figure 1 offers a step-wise progression of the anesthetic management process.

2.4. Analysis

Data were processed using SPSS 20.0 and presented as mean ± SD, or median (interquartile range) and percentages (%). Patient characteristics and parameters related to anesthesia were analyzed with unpaired t-test, χ^2 and P < 0.05 was considered as significant. The postoperative pain intensity was measured by VAS within group and between groups at each time, and were analyzed using 'one-way repeated measures ANOVA'/Mann-Whitney U test, or Kruskal-Wallis test respectively.

Incidence of side effects was analyzed using Chi-square test. P < 0.05 was regarded as significant.

3. RESULTS

3.1. Demographic Data / PCA drug consumption

Seventy patients were assigned to two groups and the study flow has been demonstrated in Figure 1. Both groups were monitored and completed the 48-h follow-up with adequate pain scores. The demographic characteristics of the patients were comparable between the groups (Table 1) (P > 0.05).

Total preoperative fentanyl consumption was equivalent in both groups (Group F: 307.14 ± 76.83 μg vs. Group FN: 334.28 ± 62.74; P = 0.11). However, there was significant difference in the fentanyl total postoperative consumption at postoperative 48 h (856.07 ± 126.39 vs. 758.86 ± 110.54 µg, P = 0.001) in Group F and Group FN respectively (Table 2).

The demand of having analgesic consumptions at postoperative 48 h, in other words the number of time

Table 1: Comparative demographic parameters in two groups

Demographic parameters		Group F	Group FN	P-values
Age (y)	Mean ± SD (Min–Max)	49.4 ± 8.17 31–60	48.7 ± 11.05 16–67	0.778
Height (cm)	Mean ± SD (Min–Max)	156.3 ± 5.8 145–165	159.7 ± 6.5 42–77	0.055
Weight (kg)	Mean ± SD (Min–Max)	53.86 ± 5.94 44–67	57.14 ± 8.88 42–77	0.073
BMI (kg/m^2)	Mean ± SD (Min–Max)	22.12 ± 2.21 17.63–27.77	22.38 ± 2.9 15.23–28.84	0.681
Gender	(F/M)	25/10	21/14	0.321

Table 2: Descriptive Statistics of PCA drugs consumptions

PCA drugs consumption		Group F	Group FN	P-values
Total fentanyl used (µg)	Mean ± SD (Min–Max)	307.14 ± 76.83 200–500	334.28 ± 62.74 250–500	0.11
Total fentanyl used (µg) in 48 h	Mean ± SD (Min–Max)	856.07 ± 126.39 654–1100	758.86 ± 110.54 562–1056	**0.001**
Total nefopam used (mg) in 48 h	Mean ± SD (Min–Max)	0	104.5 ± 10.2 89–128	-
Total number of PCA pump uses	Median ± IRQ (Min–Max)	18 ± 10 4–40	10 ± 5 0–24	**0.0007**
Total number of bolus doses	Median ± IRQ (Min–Max)	12 ± 8 4–30	8 ± 4 2–10	**0.0003**
Background dose	Mean ± SD	111.43 ± 42.16	127.14 ± 49.02	0.259

Note: values are presented as mean ± standard deviation, or minimum and maximum.

PCA pump were statistically significant different between 2 groups (Group F: 18 ± 20 vs Group FN: 9 ± 13, P = 0.0007. Similar statistical difference happened in the actual bolus doses were given to both groups (Table 2). The background dose usage between 2 groups were not statistically difference (P = 0.259) although the average of usage in Group FN were slightly higher than in Group F.

3.2. Pain scores and satisfaction levels

The level of pain was measured using VAS at 0, 1, 2, 3, 6, 9, 12, 24, and 48 hours for both groups after the operations. Overall, the pain scores of both groups were gradually reduced within the postoperative 48 h. However, the VAS scores of Group FN consistently were less than the scores of Group F (Figure 2). However, from the statistical view point, VAS scores of postoperative points at 1, 6 and 12 h were different between Group F and FN (Table 3).

The case of median values, at the 12 h and 48 h, there were different between Group F (2.5 and 2, respectively) and Group FN (2 and 1, respectively). The rest of other timepoints, the VAS scores were the same for both groups if using median to evaluate differences. Note that before operations, the VAS scores for both groups were not statistically different (P = 0.16).

Satisfaction levels were measured after the 48 h of operations. Both groups had no differences in statistical satisfaction levels since P = .13, which was less than 0.05 cut-point. However, there was 5.7% of patients in Group FN, who felt very satisfied in using the anesthetic drug to lessen the pain.

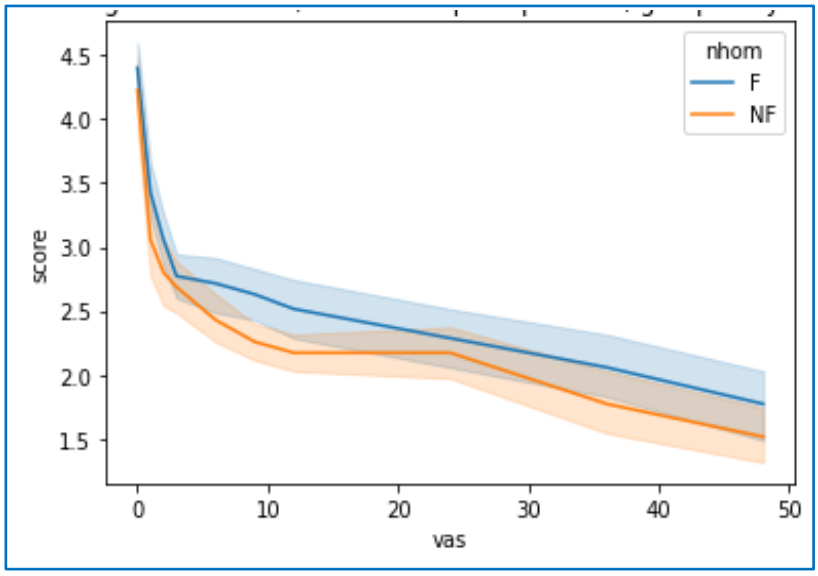

Figure 2: Postoperative VAS scores of during 0 to 48 h

Looking at the pain scores within groups and changes in the pain levels between different hours, Group F showed the pain level consistently improved from the first to the third hours with P s were less than 0.05 while Group FN only showed the improved in the first and the second hour and later on between 24 h and 36 h.

3.3. Adverse effects

Physiological symptoms, including sweating, dry mouth, palpitation, nausea, vomiting, and the use of anti-emetics were recorded during 48 h post-operatively. Among these adverse effects, only frequency of dry mouth

Table 3: Postoperative VAS scores at 0 to 48 h

Postop timepoint	Group F	Group FN	P-values
H_0	4.40 ± 0.60	4.23 ± 0.77	0.689
H_1	3.43 ± 0.65	3.06 ± 0.87	**0.015**
H_2	3.06 ± 0.59	2.80 ± 0.76	0.069
H_3	2.77 ± 0.55	2.69 ± 0.58	0.501
H_6	2.71 ± 0.67	2.43 ± 0.56	**0.040**
H_9	2.63 ± 0.65	2.26 ± 0.44	0.005
H_{12}	2.51 ± 0.70	2.17 ± 0.45	**0.015**
H_{24}	2.29 ± 0.71	2.17 ± 0.62	0.393
H_{36}	2.06 ± 0.76	1.77 ± 0.73	0.151
H_{48}	1.77 ± 0.74	1.51 ± 0.66	0.280

Data presented as mean ± SD; P < 0.05 considered as significant (bold)

Table 4: VAS scores between groups at different time points

Postoperative period	Group F (P-values)	Group FN (P-values)
H_0 vs H_1	**0.000**	**0.000**
H_1 vs H_2	**0.022**	0.199
H_2 vs H_3	**0.042**	0.655
H_3 vs H_6	0.729	0.005
H_6 vs H_9	0.573	0.186
H_9 vs H_{12}	0.473	0.449
H_{12} vs H_{24}	0.182	0.909
H_{24} vs H_{36}	0.181	**0.020**
H_{36} vs H_{48}	0.102	0.117

P < 0.05 considered as significant (bold)

was significantly more in Group FN (Mann Whitney U statistic = 489; P = 0.02).

4. DISCUSSION

A total of 70 participants were involved in this study. The spinal operations were performed for correction of kyphosis and scoliosis, and spondylolisthesis. There were 2 groups, namely Group F that only used fentanyl and Group FN that used a combination of fentanyl and nefopam in order to investigate the possibility of reducing the use of fentanyl in spine surgeries.

Overall, the percentage of males (34.3%) was much less than the females (65.7%). However, if looking at gender difference in Group F, the percentage of females (71.4%) was much more in comparison to their counterpart (28.6%) while in Group FN, the distribution was less skewed with 40% males and 60% of females. The differences were statistically not significant (P > 0.05). Other demographic parameters, such as age, height, weight, BMI also showed no statistical differences in two groups. This result minimizes the confounding effects caused by demographic characters, such as gender, age, height, weight, and BMI in using different anesthetic drugs.

This study examined the analgesic efficacy and side effects of fentanyl and a combination of fentanyl and nefopam via IV-PCA for postoperative analgesia among spinal patients. The results of this study showed that there were significant differences in postoperative analgesic consumption of fentanyl between Group F and FN. Total consumption of fentanyl within 48 h in Group FN was 856.07 µg, which was 97 µg less than in Group F (758.86 µg). The results agree with the results of earlier studies, which showed that to reduce opioid consumption, nefopam can be combined with opioids. It is the preferred choice for multimodal analgesia due to its known advantages.[4,5] It is non-opioid and non-steroidal drug and has no sedative effects and is commonly used as an analgesic drug.[6] However, there were no significant difference in pain intensity between Group F and FN, which proves that the doses of the drugs in two groups were almost equipotent. The use of nefopam is a common practice in treating mild and moderate postoperative pain. The current study showed that nefopam co-administered with fentanyl can be used for postoperative pain management in spinal surgeries, thus reducing the fentanyl consumptions. The pain scores between two groups were statistically significant at 1, 6, and 12 h, being higher in fentanyl group, which can be explained with the better analgesia being provided by the combination of analgesics.

5. CONCLUSION

A combination of fentanyl and nefopam gives better results for postoperative analgesia after spinal surgery, thus reducing the total dose of fentanyl and its associated side effects.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgement

We gratefully thank Faculty of Medicine, 108 Military Central Hospital, Hanoi, Vietnam for their help and guidance in the conduct of this study.

8. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

9. Authors' contribution

Xuan Duong Le: Conceptualization, Supervision, Writing – review & editing

Thanh Hoa Do: Formal analysis, Writing – review & editing

Minh Ly Nguyen: Writing – review & editing

Duy Thang Nguyen: Formal analysis, Data curation

Hai Ghi Nguyen: Writing – original draft

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