

The Efficacy of Low Dose Nefopam Combined with Fentanyl Injection for Controlling Immediate Postoperative Pain After Laparoscopic Surgery.

A Double-blinded, Randomized Controlled Trial

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Abstract

Background: Despite the widespread use of laparoscopic surgery across various procedures, effective postoperative pain management remains a challenge. Nefopam may be effective as an adjuvant analgesic for acute postoperative pain control. **Objective:** This study highlights the analgesic effects and risk of adverse events when using a low dose nefopam for laparoscopic surgical procedures. **Methods:** This study is double-blinded, prospective randomized controlled trial. There were 50 subjects who were divided into 2 groups. The nefopam group (n=25) received slow intravenous (IV) injection of 10 mg nefopam and IV 25 mcg fentanyl immediately in post-anesthetic care unit (PACU), while the placebo group (n=25) received IV isotonic saline and IV 25 mcg fentanyl. The primary outcomes include the numerical rating scales (NRS) of postoperative pain intensity, fentanyl consumption, adverse effects and patient satisfaction in PACU. **Results:** There was no difference in demographic data between groups. The NRS scores of the nefopam group at 30, 45 and 60 minutes postoperative were significantly lower than of the placebo group ($p < 0.05$). The amount of fentanyl consumption in PACU is comparable between groups ($p = 0.311$). Patients in both groups experienced some adverse effects including nausea, vomiting, tachycardia, dry mouth, and dizziness, however the incidence was not different between groups. Additionally, the nefopam group tended to have better patient satisfaction. **Conclusion:** The additional low dose nefopam administered by slow IV injection could reduce acute pain intensity after laparoscopic abdominal surgery, while this approach did not increase the risk of adverse effects.

Key words: Laparoscopy, Nefopam, Acute Pain Management

Introduction

Opioids are common analgesic drugs used for pain management intraoperative and postoperative. However, there is a high incidence of nausea, vomiting, hypotension, abuse potential, and respiratory depression (Apfel et al., 2012). Non-steroidal anti-inflammatory drug (NSAID) is another commonly use agent that could provide effective pain relief, but it may also relate to some serious adverse effects such as coagulopathy, gastrointestinal bleeding, and cardiovascular and renal toxicity (Moon et al., 2016). Currently, a multimodal pain management with some adjuvant analgesic agents including nefopam, paracetamol, α -2 agonists, or ketamine could help to intensify the analgesic effect, while lessening the adverse reaction related to opioids use after the surgery (Martinez et al., 2017; Kapfer et al., 2005; Maund et al., 2011; Girard et al., 2016).

Many patients in the PACU report experiencing moderate to severe pain, often compounded by agitation from physiological disturbances during emergence from anesthesia and surgery. These interactions can exacerbate risks and complications in the short and long term (Luo et al., 2017). Laparoscopic surgery is a minimally invasive

procedure that is widely applied in many surgical fields to provide less postoperative pain. Despite the advantages of laparoscopic surgery, effective postoperative pain management remains a significant concern (Bisgaard, 2006). Nefopam is a non-opioid and non-steroidal, centrally acting analgesic that impedes the reuptake of serotonin, dopamine, norepinephrine, monoamine, and the N-methyl-D-aspartate (NMDA) receptors (Moon et al., 2016; Noveli et al., 2005). It could provide rapid pain relief, and its plasma half-life is about 4 hr (range 3 hr to 8 hr) (Kapfer et al., 2005; Heel et al., 1980; Lee et al., 2013). Nefopam is reported of having a 30–50% of morphine-sparing effect (Kapfer et al., 2005; Mimoz et al., 2001; Tramoni et al., 2003), and 20 mg of nefopam is equipotent to morphine 6–12 mg (Sunshine & Laska, 1975). Nefopam appears to be effective in reducing postoperative pain and opiate requirements in major elective surgery (Kapfer et al., 2005; Mimoz et al., 2001). The co-administration of nefopam and opioids may deserve more consideration as balanced postoperative analgesic regimen to improve postoperative analgesic efficacy and reduce potential adverse effects, yet it is seldom used in clinical practice (Zhao et al., 2018). Ensuring adequate postoperative analgesia with minimal adverse effect is crucial for facilitating patient recovery and enhancing overall outcomes.

Various doses of nefopam ranging from 20–40 mg has been suggested to be infused intravenously over a period of 15–60 minutes (Lee et al., 2013; Mimoz et al., 2001; Du et al., 2003; Remérand et al., 2013; Hwang et al., 2015; Na et al., 2016; Evans et al., 2008). Some studies recommended 1–5 mg/hr infusion (Remérand et al., 2013; Evans et al., 2008; Kim et al., 2014; Son et al., 2017) or 1–2.4 mg/dose for intravenous patient-controlled analgesia (PCA) with or without opioid (Mimoz et al., 2001; Hwang et al., 2015; Kim et al., 2014; Son et al., 2017; Jin et al., 2016; Yoon et al., 2016). Nefopam has demonstrated efficacy in reducing postoperative pain scores and fentanyl requirements particularly in the immediate PACU period (Kim et al., 2017). Moreover, Nefopam may have a more favorable safety profile than opioids and NSAID in terms of coagulopathy, renal, gastrointestinal, and respiratory adverse effects (Dordoni et al., 1994; Baltes, 1977; Bhatt et al., 1981). However, the side-effects of nefopam including tachycardia, sweating (Kapfer et al., 2005; Mimoz et al., 2001; Evans et al., 2008) nausea, vomiting (Son et al., 2017; Park et al., 2018) and dry mouth (Moon et al. 2016; Lee et al., 2013; Jin et al., 2016) were still observed. Currently, dose responsiveness and side-effect profile of nefopam remain unclear. Hence, we hypothesize that off-label administration of a low dose of nefopam via slow intravenous (IV) injection, emphasizing its ease of administration without the need for infusion instruments, may be an alternative approach to control mild to moderate pain intensity after laparoscopic surgery with minimal adverse effects. However, there was limited evidence supporting the use of low dose nefopam and a lack of valid clinical trial data of a slow IV injection of nefopam. Therefore, the purpose of this study was to evaluate the efficacy of this approach regarding acute pain intensity, adverse effects, and patient satisfaction after laparoscopic surgery.

Methods and Materials

Study design

We conducted a prospective randomized, placebo-controlled, double-blinded study at the Naresuan University Hospital, Phitsanulok, Thailand. The patients were enrolled after obtaining approval from Naresuan University institutional review board (IRB No.0229/61), and writing informed consent was collected from all patients participating in the study. The data was collected between 1 October 2018 and 30 April 2019.

The subjects were patients admitted for elective laparoscopic abdominal surgery under general anesthesia, with the American Society of Anesthesiologists (ASA) physical status class I–II and aged ≥ 20 years old. Exclusion criteria were patient with neurological and psychological deficits, coronary artery disease (CAD), chronic kidney disease (CKD) > stage 3, liver cirrhosis, acute glaucoma, chronic pain > 3 months, obesity (body mass index $\geq 35 \text{ kg/m}^2$), allergic reaction to nefopam or fentanyl, and patients who cannot use numerical rating scale (NRS). Patient who had opioids addiction or recent use of opioids, tramadol, NSAIDs, antidepressants, and anticonvulsant agents for the last 2 months before surgery was also excluded.

Perioperative anesthesia protocol

All patients were admitted to the hospital one day before the surgery. The researchers explained the study protocols to the patients, including evaluation of the NRS, the common adverse effects of nefopam such as nausea, vomiting, sweating, shivering, pruritus, dry mouth and dizziness. The patients underwent laparoscopic abdominal surgery under general anesthesia and standard physiological monitoring in the operating room, including non-invasive arterial blood pressure, electrocardiography, peripheral oxygen saturation and end tidal carbon dioxide measurement. The induction of general anesthesia included administration of 1–2.5 mg/kg of propofol IV after sufficient pre-oxygenation, and then followed by 1–1.5 mg/kg of succinylcholine IV to facilitate endotracheal intubation. The anesthesia was maintained using 1.0 minimal alveolar concentration of sevoflurane, with a medical air and oxygen mixture providing a fraction inspired oxygen concentration of 0.50, cisatracurium IV injection as needed, and 1–3 mcg/kg of fentanyl IV throughout the surgery when it is necessary for intraoperative pain management. After the operation, 2.5 mg of neostigmine and 1.2 mg of atropine were given intravenously to antagonize any remaining muscle relaxation. The patients were extubated after regaining consciousness and the tidal volume was > 4–6 mL/kg with sustained spontaneous respiration rate > 12 /min.

At the post-anesthetic care unit (PACU), the patients were randomly divided into 2 groups by utilizing a computer-generated code. The nefopam (N) group received slow IV injection (approximately 10 seconds) of 10 mg nefopam (Acupan®, Laboratory Biocodex, France) which was mixed with normal saline to a total volume of 10 mL. The placebo (P) group was given 10 mL of IV isotonic saline (NSS) when arrived at PACU. All patients were also given with 25 mcg of fentanyl IV immediately at PACU. All patients received 25 mcg/dose of fentanyl IV as a rescue analgesia when NRS scores > 4. No additional analgesic drug was permitted during the study.

Outcome measures

The primary outcome was the postoperative pain intensity assessed by NRS scores, fentanyl consumption, and adverse effects. The NRS scores were determined as the patient rating of their pain from 0 to 10 representing ‘no pain’ to ‘worst pain imaginable’ (Jin et al., 2016). When sedation scores < 2, the evaluation of the NRS scores and adverse effects were done at 15, 30, 45, and 60 minutes after admission to the PACU. Total fentanyl consumption for rescue analgesia was recorded during admission at the PACU. The patients were assessed if they had experienced any of the following: nausea, vomiting, shivering, tachycardia, bradycardia, hypotension, pruritus, dry mouth, sweating, dizziness, urinary retention, respiratory depression, and sedation score (sedation scores were classified as 0 = no sedation, 1 = intermittent drowsiness, 2 = patient is drowsy but could be aroused verbally, and 3 = impossible to arouse the patient verbally) (Lee et al., 2013). Acceptable difference of cardiac rate and blood pressure was at 20% from preoperative baseline values. The secondary outcome was patient satisfaction scores (patient satisfaction score was classified as 0 = very dissatisfied, 1 = neither satisfied nor

dissatisfied and 2 = very satisfied) before transport to the hospital ward. Assessments of all outcomes were performed by nurses who were blinded to the study intervention.

Statistical analysis

Based on previous data, the sample size of 25 subjects in each group had a β -risk of 80% power and α -level of 0.05. The study aimed to detect a 30% decrease in the NRS score from a mean NRS score of 5.5 in the control group, with a standard deviation of 2, considering a 5% estimated dropout rate (Na et al., 2016).

Data were presented as mean \pm standard deviation. Data distribution was evaluated using the Shapiro-Wilk test. The demographic data including gender, ASA, and type of operation were compared between groups. The NRS scores of pain intensity and total fentanyl consumption at PACU were compared by using the Student's t-test or Mann-Whitney U test. The adverse effects and patient satisfaction were also compared by using the chi-square test or Fisher's exact test. A P value < 0.05 is considered as a statistically significant. SPSS software (version 17.0; SPSS Inc, Chicago, IL) was applied for all analysis.

Results

The study recruited 55 patients, and 2 declined to participate in the study and 3 met the exclusion criteria. The remaining 50 patients (P group $n = 25$, N group $n = 25$) were completed the study analysis (Fig. 1).

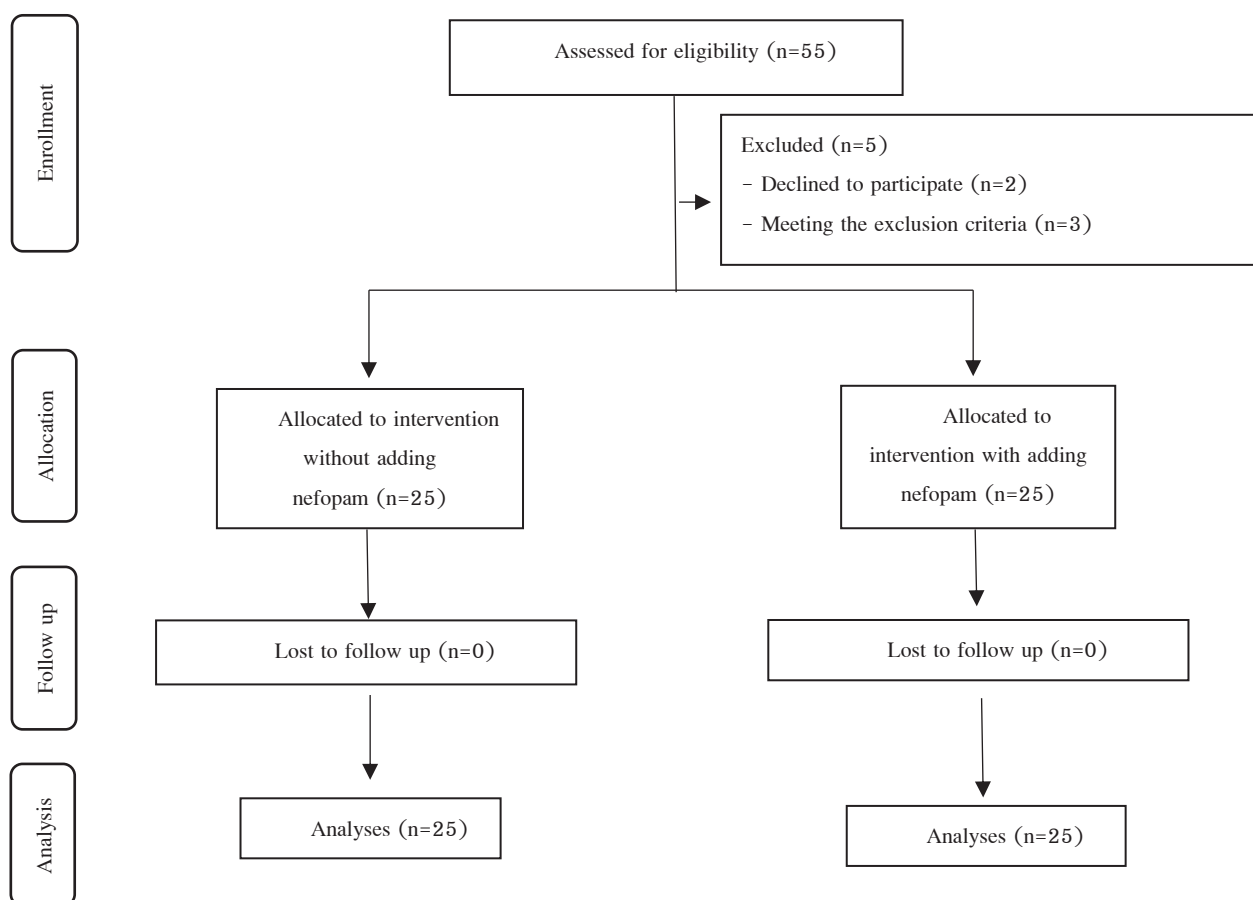


Figure 1 The Flow Diagram

There was no difference between the P group and the N group in terms of age, weight, height, body mass index (BMI), ASA, duration of anesthesia and operation, type of laparoscopic surgery regarding general surgery (cholecystectomy, laparoscopic appendectomy) or gynecological condition (cystectomy, laparoscopic salpingectomy), total fentanyl consumption during operation, and NRS scores at immediate PACU admission (Table 1).

Table 1 Demographic Data (n=50)

Parameters	P group (n=25)	N group (n=25)	P value
Gender			1.000‡
Male	3 (12.00)	3 (12.00)	
Female	22 (88.00)	22 (88.00)	
Age (yrs)	50.24±18.03	48.84±14.44	0.763§
Weight (kg)	60.16±10.31	61.30±10.93	0.707§
Height (cm)	158.40±6.24	157.96±7.89	0.828§
Body mass index (kg/m ²)	24.02±4.29	24.57±4.06	0.646§
ASA physical status classification			0.333†
ASA I	5 (20.00)	8 (32.00)	
ASA II	20 (80.00)	17 (68.00)	
Operation time (min)	56.80±24.15	65.60±22.28	0.187§
Anesthetic time (min)	87.00±24.20	98.00±22.41	0.102§
Type of operation			0.157‡
Laparoscopic abdominal surgery	18 (72.00)	22 (88.00)	
Laparoscopic gynecological surgery	7 (28.00)	3 (12.00)	
Total fentanyl consumption in operation (mcg)	95.80±27.83	98.00±28.80	0.785§
Immediate NRS scores of pain intensity at PACU	4.56±3.61	4.32±3.40	0.810

Data are shown as mean ± standard deviation or number (%)

Abbreviations: ASA, American Society of Anesthesiologist; NRS, numerical rating scale; PACU, post-anesthetic care unit; P, placebo; N, nefopam,

† Chi-square test

‡ Fisher's exact test

§ Student's t-test

|| Mann-Whitney U test

The NRS scores assessed at 15, 30, 45 and 60 minutes postoperative were 3.88 ± 3.19 , 5.12 ± 2.15 , 3.08 ± 1.44 and 2.52 ± 0.96 , respectively for the P group; and 4.16 ± 2.43 , 2.80 ± 2.02 , 2.04 ± 1.37 and 1.84 ± 1.34 , respectively for the N group. The difference of NRS scores between groups reached statistical significance at 30, 45 and 60 minutes after the surgery (Fig. 2).

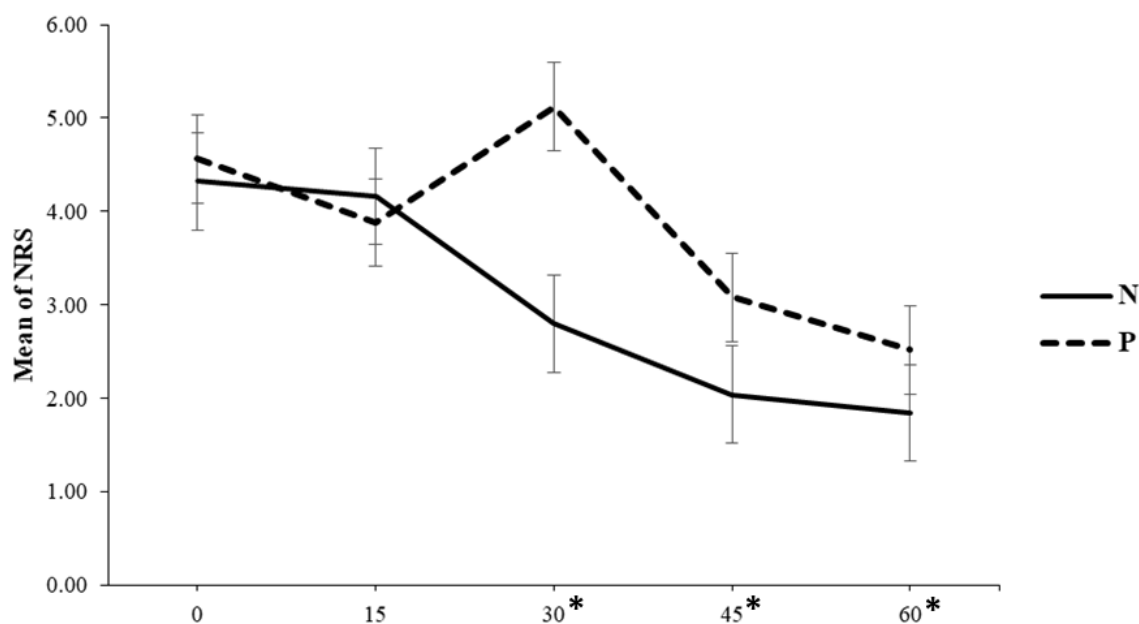


Figure 2 The NRS scores of pain intensity at different times (minutes) at PACU

Abbreviations: NRS = numerical rating scale; PACU = post-anesthetic care unit; P = the placebo group;

N = the nefopam group

* = statistical significance ($P < 0.05$) by Mann-Whitney U test

The N group had significantly lower NRS scores than the P group at 30, 45 and 60 minutes after the surgery. $P < 0.05$ is considered statistically significant by Mann-Whitney U test.

Total fentanyl consumption for rescue analgesia at PACU was 48.00 ± 17.56 mcg in the P group and was 43.00 ± 16.96 mcg in the N group ($p = 0.311$) (Table 2).

Table 2 Fentanyl consumption as a rescue analgesia at PACU

Parameter	P group (n=25)	N group (n=25)	P value
Total fentanyl consumption (mcg)	48.00 ± 17.56	43.00 ± 16.96	0.311†

Data were shown as mean \pm standard deviation

Abbreviations: PACU, post-anesthetic care unit; P, placebo; N, nefopam

† Student's t-test

Eleven patients in the P group experienced some adverse effects at PACU showed nausea, vomiting, tachycardia, headache, dry mouth, dizziness and local pain at site of injection, while 16 patients in the N group had adverse effects showed nausea, vomiting, tachycardia, dry mouth and dizziness as detailed in (Table 3).

Table 3 Adverse effects at PACU

Parameters	P group (n=25)	N group (n=25)	P value
Nausea and Vomiting			0.894†‡
Nausea	3 (12.00)	2 (8.00)	
Vomiting	1 (4.00)	1 (4.00)	
Shivering	0 (0.00)	1 (4.00)	0.312‡
Tachycardia	1 (4.00)	1 (4.00)	1.000‡
Bradycardia	0 (0.00)	0 (0.00)	NA
Headache	1 (4.00)	0 (0.00)	0.312‡
Sedation score ≥ 2	0 (0.00)	0 (0.00)	NA
Respiratory depression	0 (0.00)	0 (0.00)	NA
Hypotension	0 (0.00)	0 (0.00)	NA
Pruritus	0 (0.00)	0 (0.00)	NA
Dry mouth	5 (20.00)	10 (40.00)	0.217†
Sweating	0 (0.00)	0 (0.00)	NA
Dizziness	1 (4.00)	1 (4.00)	1.000‡
Urinary retention	0 (0.00)	0 (0.00)	NA
Local pain at site of injection	2 (8.00)	0 (0.00)	0.149‡

Data are shown as number (%)

Abbreviations: PACU, post-anesthetic care unit; P, placebo; N, nefopam; NA = Not applicable

† Chi-square test

‡ Fisher's exact test

According to patient satisfaction responses, there was no significant difference was found between the 2 groups, even if the N group tended to have better patient satisfaction (Fig. 3).

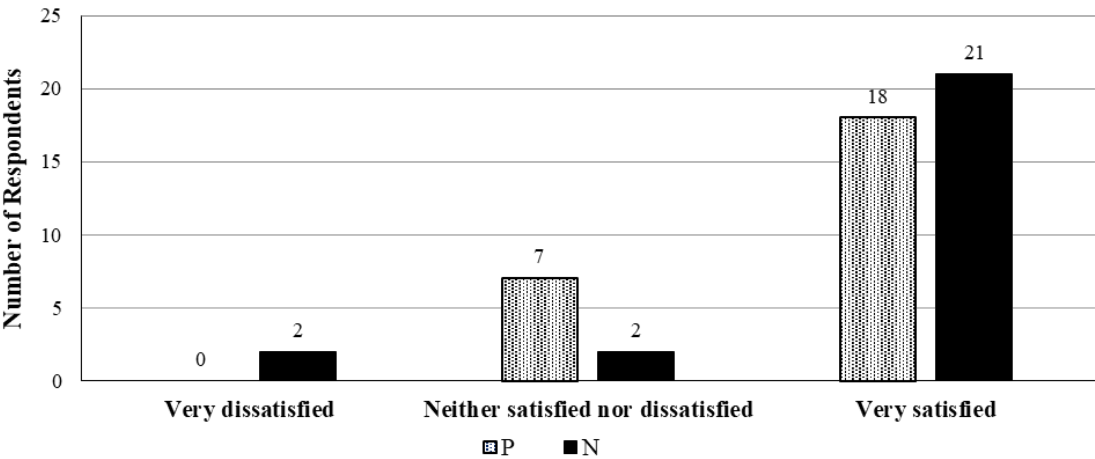


Figure 3 Patient satisfaction at PACU

Abbreviations: PACU = post-anesthetic care unit; P = the placebo group; N = the nefopam group

Discussion

Nefopam is a centrally acting non-opioid analgesic and its IV administration could rapidly inhibit the nociceptive reflex (Guirimand et al., 1999). The present study demonstrated that a low dose nefopam which was slow IV injection can significantly reduce NRS scores at 30, 45, and 60 minutes after the surgery when compared to the placebo group. Although, total fentanyl consumption as a rescue analgesia in the N group was less than those used in the P group, the difference was not statistically significant. However, this approach did not significantly increase risk of adverse effects.

A systemic review including 9 trials which composed of 847 patients and 347 received nefopam (20–160 mg) orally or IV, as single or multiple doses shown that nefopam group had lower pain intensity at 24 h as well as cumulative 24 h morphine use (Evans et al., 2008). Lee et al (Lee et al., 2013) conducted a randomized controlled trial (RCT) to compare postoperative analgesic effect of placebo, 20 and 40 mg of nefopam in laparoscopic cholecystectomy. They found significantly lower pain scores at 10 minutes, 2 hr, and 6 hr postoperative in patients who received 20 or 40mg of nefopam. Nevertheless, the 20 mg nefopam group had significantly lower incidence of nausea than both the 40 mg nefopam and placebo group. Kim et al. (Kim et al., 2017) randomly divided 60 patients undergoing laparoscopic cholecystectomy into 3 groups that received placebo, nefopam (0.3mg/kg) and ketamine (0.3mg/kg). They revealed that the pain scores (VAS) and fentanyl consumption for 1 h after surgery of nefopam and ketamine groups were significantly lower than those of the control group. However, these three groups had no differences in VAS and number of rescue analgesia from 1 to 8 h after surgery. In comparison to our study, where a lower dose of intravenous nefopam (10 mg) was administered, we also observed a reduction in pain numerical rating scale (NRS) scores postoperatively. However, there was no statistically significant difference in fentanyl consumption during the initial postoperative period. This suggests that while low-dose nefopam effectively lowered pain NRS scores when administered concomitantly with fentanyl, it may not be sufficient to significantly reduce fentanyl consumption compared to the standard dose. Recently, Zhao et al. (Zhao et al., 2018) performed meta-analysis of RCTs reporting efficacy and safety of nefopam for pain control after laparoscopic cholecystectomy. A total of 215 patients, they revealed that patients receiving nefopam infusion had significantly lower postoperative pain scores, less opioid consumption at 6, 12 and 24 hr, and less opioid-related side-effects.

Nefopam has more favorable safety profile compared to NSAIDs and opioids as it has minimal effects on platelet aggregation, and no central nervous system depression. Additionally, the concomitant administration of nefopam is aimed to lessen the adverse effects of opioids use for postoperative pain control (Moon et al., 2016; Jin et al., 2016). However, other studies revealed that the nefopam administration related to minor adverse effects such as tachycardia, nausea, vomiting, sweating and dry mouth (Moon et al., 2016; Kapfer et al., 2005; Lee et al., 2013; Mimoz et al., 2001; Evans et al., 2008; Son et al., 2017; Jin et al., 2016; Park et al., 2018). Nausea, vomiting and tachycardia may be caused by nefopam's anticholinergic and adrenergic activities, and the escalation of plasma levels (Djerada et al., 2014). Nefopam is thereby suggested to be better tolerated with infusion duration more than 45 minutes for the standard dose of 20 mg (Djerada et al., 2014). Some studies have used antiemetic drugs, such as ondansetron 8 mg (Na et al., 2016) or ramosetron 0.3 mg, 30 minutes prior to surgery completion to reduce postoperative nausea and vomiting in laparoscopy and laparotomy of gynecologic surgery (Dordoni et al., 1994). Some previous studies demonstrated a significant association of

the risk of tachycardia (NNH 7) (RR 3.12: 95% CI 1.11 – 8.79) and increased sweating (NNH 13) (RR 4.92: 95% CI 2.0–12.1) with nefopam (Evans et al., 2008). Also, Kapfer et al. (2005) reported that patient who underwent major surgery and was given 20 mg of nefopam IV infused over a 12-minute period had significantly less morphine consumption in the first hour at PACU. Nevertheless, the patient receiving nefopam experienced tachycardia and profuse sweating more frequently than the control group. Tachycardia may be a common side effect of nefopam, and thus caution is extremely necessary when administering the drug to patients with cardiovascular complication (Heel et al., 1980; Evans et al., 2008). In this study, there was no significant difference in terms of nausea, vomiting, tachycardia or pain on injection site between groups even faster injection time (10 seconds) than usual and without antiemetic drug prophylaxis. The previous studies reported that patient could experience dry mouth if nefopam more than 10 mg was administered at postoperative phase (Moon et al., 2016; Lee et al., 2013; Jin et al., 2016). In our study, we observed higher incidence of dry mouth in the N group compared to the P group, but the difference was not statistically significant.

Additionally, the N group did not feel pain during low dose nefopam diluted with 10ml of NSS injection, whereas 2 patients in the P group felt pain during injection due to malposition of IV catheter. Therefore, low dose nefopam administered by slow IV injection could be a safe alternative approach to control acute pain after laparoscopic abdominal surgery. Furthermore, slow IV injection of nefopam at the PACU may be more convenient for nurses and physician, and also tended to have a higher patient satisfaction.

There were some limitations to this study. First, the sample size is small. Second, we studied only a single low dose of nefopam injection and assessed the outcomes during the PACU admission. Further studies with a larger sample size, multiple doses of nefopam administration with longer follow up period may help confirm our findings.

Conclusion and Suggestions

In conclusion, additional low dose nefopam administered by slow IV injection could reduce acute pain intensity after laparoscopic abdominal surgery, while this approach did not increase the risk of adverse effects. Hence, low dose nefopam may be considered as an adjunctive analgesic in a multimodal analgesia. For future studies, we recommend increasing the sample size to provide stronger confirmation of our results. Additionally, extending the follow-up period and assessing NRS pain scores at rest and during movement would allow for further exploration of the long-term efficacy and safety outcomes associated with low-dose nefopam administration.

Author Contributions

Rawee Jongkongkawutthi: contributed to conceptualization, design of methodology, providing of materials subjects or patients, collection of data, manuscript review, and critical revision of important intellectual content

Surachart Pojanasupawun: contributed to conceptualization, design of methodology, providing of materials subjects or patients, responsible as the anesthesiologist

Supatcharee Khlibsi: contributed to providing materials to subjects or patients, collection of data

Artit Laoruengthana: contributed to data analysis and interpretation, manuscript writing, and critical revision of important intellectual content

Siriluk Toolyodpun: contributed to conceptualization, design of methodology, providing of materials subjects or patients, responsible as an anesthesiologist, manuscript writing, and critical revision of for important intellectual content

All authors have read and approved the manuscript.

Conflict of Interests

All authors declare that they have no conflicts of interest.

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