






# Postoperative Analgesic Efficacy of Nefopam after Anorectal Surgery: A Retrospective Observational Study

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## Abstract

**Objective** To examine the effectiveness of nefopam on postoperative pain control after anorectal surgeries.

**Methods** We retrospectively reviewed the electronic medical records of patients who underwent anorectal surgeries from January 2019 to March 2022 at two medical centers. The data were divided into nefopam and conventional groups. The primary outcome was the number of patients who requested additional opioids in the 24-h postoperative period. The secondary outcomes were numeric rating pain scores (NRPS) within a 24-h postoperative period and analgesic drugs-related side effects.

**Results** Eighty-seven patients in the conventional group and 60 in the nefopam group were recruited. The nefopam group reported less additional opioid consumption than the conventional group in all dimensions of analysis, including overall, adjusted to anesthetic techniques and types of surgery. However, these did not reach statistical significance ( $P = 0.093$ ). Only patients in the nefopam group who underwent hemorrhoidectomy under TIVA or spinal anesthesia significantly required fewer additional opioids ( $P = 0.016$ , 60% mean difference). Similarly, the 24-h postoperative morphine consumption was lower in the nefopam group (mean difference =  $-3.4$ , 95%CI: 0.72, 6.08). Furthermore, significantly lower NRPS were reported in the nefopam group during the 12-18 h postoperative period ( $P = 0.009$ ). On the other hand, analgesic drugs related side effects were similar in both groups.

**Conclusions** The administration of nefopam after major anorectal surgery is beneficially evident in reducing postoperative opioid requirements.

## Keywords

- ▶ anorectal surgery
- ▶ hemorrhoidectomy
- ▶ nefopam
- ▶ postoperative pain
- ▶ opioid requirements

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## Introduction

Anorectal surgery consists of various procedures, varying from minor to major operations. Even though most of them are seemingly minor operations, some can be excruciating procedures. Several studies are trying to determine an effective analgesic technique to control postoperative pain, but no regimen has been accepted as the best protocol. The decision on postoperative analgesic regimens is widely based on the preference of individual surgeons.

Nefopam, a non-opioid and non-steroidal analgesic drug, is a benzoxazocine derivative. It was developed in the early 1970s and is known to act as an N-methyl D-aspartate (NMDA) receptor antagonist and a monoamine reuptake inhibitor.<sup>1,2</sup> The analgesic mechanism of nefopam is the inhibition of serotonin, norepinephrine, and dopamine reuptake. This action results in the reduction and prevention of central sensitization, leading to decreased nociceptive responses. In addition, it has an indirect modulating effect on NMDA receptors. Nefopam 20 mg is equianalgesic to 7-12 mg of morphine, 50 mg of meperidine, and 10 mg of ketamine.<sup>3-5</sup> A trend toward multimodal opioid-sparing analgesia is a pivotal element in ERAS protocols. Thus, nefopam has gained popularity as an analgesic adjunct in various surgeries. Some recent studies have shown that nefopam can significantly reduce postoperative opioid consumption in many surgeries, namely, laparoscopic gastrectomy, laparoscopic cholecystectomy, breast surgery, and gynecological surgery.<sup>6-8</sup> Nevertheless, there is currently no research on nefopam as an analgesic adjunct in anorectal surgery.

Regardless, some of the colorectal surgeons in our hospital have been prescribing this medication for surgical pain control. We have interestingly been observing their clinical benefits. Hence, this study aims to examine the effectiveness of nefopam on postoperative pain control after anorectal surgeries. We hypothesized that nefopam would reduce additional postoperative opioid requirements.

## Materials and Methods

This study was approved by the Institutional Review Board of Chulalongkorn University, Bangkok, Thailand (IRB No. 806/64) and registered with the Thai Clinical Trials Registry (<https://www.clinicaltrials.in.th/TCTR20220405003>). We retrospectively reviewed the electronic medical records of patients who underwent anorectal surgeries (e.g., hemorrhoidectomy, fistulotomy, fistulectomy, sphincterotomy) from January 2019 to March 2022 from two medical centers, King Chulalongkorn Memorial Hospital (KCMH) and Bangkok Christain Hospital (BCH). Patients 18 to 65 years old with an American Society of Anesthesiologists physical status classification I to III were included in the study. Written informed consent was waived by the IRB, as this was a retrospective study. Exclusion criteria include day-case surgery, incomplete medical record, and chronic opioid use.

Each of the patients received one of the anesthetic techniques, including spinal anesthesia (SA), total intravenous anesthesia (TIVA), or local anesthesia (LA), as deemed appro-

priate by the surgeon. This was mainly based on the patient's condition, diagnosis, and surgical procedures. After the surgery, pain control was prescribed according to the surgeon's preferences. They usually used multimodal analgesic regimens comprising opioids and non-opioid analgesia. Every patient would receive oral paracetamol, as needed, in addition to intravenous opioids for the first-line analgesic rescue therapy. Some patients might be prescribed other analgesics such as nefopam, NSAIDs (etoricoxib), and gabapentin if moderate to severe postoperative pain is expected.

We divided the data into two groups. The Nefopam group included patients who received nefopam postoperatively as an adjuvant to an analgesic regimen. The conventional group was comprised of patients who did not receive nefopam postoperatively. The primary outcome was additional postoperative opioid consumption measured by the number of patients who requested additional opioids for breakthrough pain in the 24-h postoperative period. The secondary outcomes were as follows: numeric rating pain scores (NRPS) at 6-12 h, 12-18 h, and 18-24 h postoperative period, analgesic drugs related side effects. We did not record NRPS during the first 6-h after surgery because various anesthetic techniques undoubtedly influenced them.

All data analysis was executed in STATA 15.1 statistical software (StataCorp LP, College Station, TX). Continuous variables were analyzed with the independent t-test reported as mean and standard deviation for patient demographic information and regression analysis. All categorical variables were analyzed with the Exact probability test. Regarding the effects of different anesthetic techniques on postoperative pain, we did a subgroup analysis to prove its effects on the 24-h postoperative additional opioid requirement. Also, each surgical procedures cause a different degree of tissue trauma and postoperative pain. Among anorectal procedures, hemorrhoidectomy is renowned as an excruciating procedure. We thereby, in addition, show subgroup analysis adjusted to types of surgery. Furthermore, we evaluated the effects of other analgesic drugs that were commonly prescribed to our patients.

## Results

A total of 150 patients were included in this study. Three were excluded due to chronic opioid usage and incomplete data record. Therefore, 147 patients were analyzed and divided into the conventional group (87 patients) and the nefopam group (60 patients). ►Table 1 shows baseline demographics and clinical characteristics. There was no significant statistical difference between the groups, except for the anesthetic techniques.

Patients in the nefopam group reported lower additional opioid requirements compared to the conventional group in all dimensions of analysis, including overall, adjusted to anesthetic techniques and types of surgery. Nevertheless, none of the analyses did reach a statistical significance, except for those who underwent hemorrhoidectomy under TIVA or spinal anesthesia ( $P=0.016$ , 60% mean difference, ►Table 2).

**Table 1** Baseline demographics and clinical characteristics

Patient characteristics	Nefopam (n = 60) n (%)	Conventional (n = 87) n (%)	P-value <sup>†</sup>
- Age (years) <sup>a</sup>	46.50 ± 11.65	44.46 ± 11.79	0.302 <sup>‡</sup>
- Sex			0.388
Male	40 (66.7)	51 (58.6)	-
Female	20 (33.3)	36 (41.4)	-
- BMI (Kg/m <sup>2</sup> )			0.096
Underweight (BMI ≤ 18)	3 (5.0)	2 (2.3)	-
Normal (BMI 18-24.9)	33 (55.0)	47 (54.0)	-
Overweight (BMI 25-29.9)	20 (33.3)	21 (24.1)	-
Obese (BMI ≥ 30)	4 (6.7)	17 (19.5)	-
- ASA physical status			0.557
I	43 (71.7)	60 (69.0)	-
II	14 (23.3)	25 (28.7)	-
III	3 (5.0)	2 (2.3)	-
- Type of surgery			0.057
LIFT/Fistulotomy	30 (50.0)	50 (57.5)	-
Hemorrhoidectomy	23 (38.3)	20 (23.0)	-
Strictulotomy/Anoplasty	0 (0)	2 (2.3)	-
LIS/Sphincterotomy	0 (0)	6 (6.9)	-
Combined (>1 operation)	7 (11.7)	9 (10.3)	-
- Operation time (min) <sup>a</sup>	60.38 ± 28.13	71.72 ± 30.89	0.023 <sup>‡</sup>
- Anesthetic technique			0.009
Spinal anesthesia	29 (48.3)	48 (55.2)	-
Total intravenous anesthesia (TIVA)	16 (26.7)	7 (8.1)	-
Local anesthesia	15 (25.0)	32 (36.8)	-
- Intraoperative morphine use (mg) <sup>a</sup>	2.65 ± 3.24	2.55 ± 2.75	0.843 <sup>‡</sup>

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

<sup>a</sup>Data expressed as mean ± standard deviation.

<sup>†</sup>Exact probability test.

<sup>‡</sup>Independent t-test.

**Table 2** Number of patients reported rescue opioid in 24-h postoperatively

Analgesic requirement	Nefopam (n = 60) n (%)	Conventional (n = 87) n (%)	P-value <sup>†</sup>
- Opioid requirement	26 (43.3)	51 (58.6)	0.093
- Anesthetic technique			
Spinal anesthesia	12 (41.1)	26 (54.2)	0.349
Total intravenous anesthesia (TIVA)	6 (37.5)	5 (71.4)	0.193
Local anesthesia	8 (53.3)	20 (62.5)	0.751
- Type of surgery			
LIFT/Fistulotomy	13 (43.3)	27 (54.0)	0.356
Hemorrhoidectomy (Overall)	9 (39.1)	13 (65.0)	0.090
Hemorrhoidectomy (Spinal anesthesia or TIVA)	3 (23.1)	5 (83.3)	<b>0.016</b>

(Continued)

**Table 2** (Continued)

Analgesic requirement	Nefopam (n = 60) n (%)	Conventional (n = 87) n (%)	P-value <sup>†</sup>
Strictulotomy/Anoplasty	0 (0)	2 (100.0)	–
LIS/Sphincterotomy	3 (50.0)	3 (50.0)	–
Combined (>1 operation)	4 (57.1)	6 (66.7)	0.696

Significant p values are in bold ( $p < 0.05$ ).

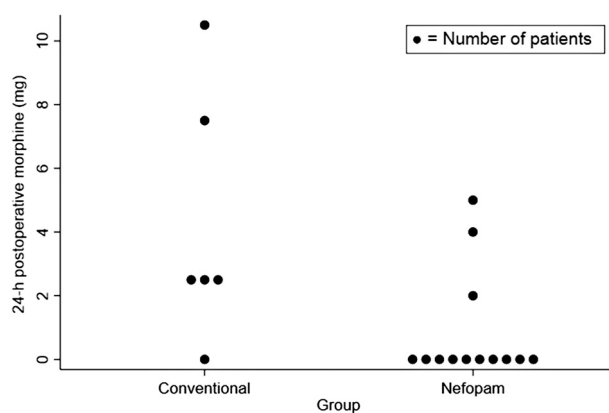
<sup>†</sup>Exact probability test.

**Table 3** 24-hr postoperative morphine consumption (mg)

Analgesic requirement	Nefopam (n = 60)	Conventional (n = 87)	Mean difference	95% CI of mean difference
Overall of anorectal surgery <sup>a</sup>	1.83 ± 2.65	2.32 ± 2.38	–0.48	–0.34, 1.31
Hemorrhoidectomy (Spinal anesthesia or TIVA) <sup>a</sup>	0.85 ± 1.72	4.25 ± 3.92	–3.40	0.72, 6.08*

<sup>a</sup>Data expressed as mean ± standard deviation.

\*Significance < 0.05.



**Fig. 1** Dot plot graph represent 24-h postoperative morphine requirement in patients undergoing hemorrhoidectomy under spinal anesthesia or TIVA technique.

For 24-h postoperative morphine consumption, patients in the nefopam group required a compatibly lower dose. They showed a statistically significant difference in patients who underwent hemorrhoidectomy under TIVA or spinal anesthesia accordingly (mean difference = –3.4, 95% CI: 0.72, 6.08, ▶ **Table 3**). The dot plot graph shows that 10 of 13 patients in the nefopam group who underwent hemorhoidectomy under TIVA or spinal anesthesia did not require any additional morphine postoperatively. In comparison, five of 6 patients in the conventional group did (▶ **Fig. 1**).

To evaluate the interfering effects of other analgesic drugs, both groups showed no statistical differences in NSAID-related effects (▶ **Table 4**).

Mean numeric rating pain scores are expressed in ▶ **Table 5**. Patients in the nefopam group reported significantly lower scores in the 12-18 h postoperative period ( $P = 0.009$ ).

Eight of 147 patients in total experienced nausea and vomited. One patient in the nefopam group developed the rash. Nevertheless, the groups had no significant difference in analgesic drug-related side effects (▶ **Table 6**).

## Discussion

The results of this retrospective study established a positive trend reinforcing nefopam as an adjunct that can reduce postoperative opioid requirements in anorectal surgery. Although the overall comparison did not reach a statistical significance between the groups, only the patients who underwent hemorrhoidectomy under TIVA or spinal anesthesia and received nefopam expressed significantly less postoperative opioid requirement ( $P = 0.016$ , mean differ-

**Table 4** NSAIDs effects

Analgesic requirement	NSAIDs (n = 107) n (%)	No NSAIDs (n = 40) n (%)	P-value
Opioid requirement	57 (53.3)	20 (50.0)	0.853 <sup>†</sup>
Morphine consumption <sup>a</sup>	2.11 ± 2.55	2.15 ± 2.38	0.927

<sup>a</sup>Data expressed as mean ± standard deviation.

<sup>†</sup>Exact probability test.

**Table 5** Mean numeric rating pain scores

Mean pain scores	Nefopam (n = 60)	Conventional (n = 87)	P-value	Mean difference	95% CI
- At 6-12 h <sup>a</sup>	2.68 ± 2.61	3.21 ± 2.14	0.185	0.524	-0.25, 1.30
Spinal anesthesia	2.97 ± 3.06	3.46 ± 2.44	0.439	0.493	-0.77, 1.75
Total intravenous anesthesia (TIVA)	1.44 ± 1.26	3.14 ± 1.68	<b>0.013</b>	1.705	0.39, 3.02
Local anesthesia	3.46 ± 2.39	2.84 ± 1.69	0.308	-0.623	-1.84, 0.59
- At 12-18 h <sup>a</sup>	1.45 ± 1.59	2.33 ± 2.23	<b>0.009</b>	0.883	0.22, 1.54
Spinal anesthesia	1.48 ± 1.86	2.52 ± 2.69	0.072	1.038	-0.93, 2.17
Total intravenous anesthesia (TIVA)	0.88 ± 1.02	1.43 ± 0.98	0.240	0.554	-0.40, 1.51
Local anesthesia	2.00 ± 1.36	2.25 ± 1.55	0.595	0.250	-0.69, 1.19
- At 18 -24 h <sup>a</sup>	1.37 ± 1.81	1.52 ± 1.80	0.620	0.151	-0.45, 0.75
Spinal anesthesia	1.17 ± 1.47	1.38 ± 1.79	0.609	0.203	-0.58, 0.99
Total intravenous anesthesia (TIVA)	1.44 ± 2.71	1.43 ± 1.62	0.994	-0.089	-2.31, 2.30
Local anesthesia	1.67 ± 1.23	1.75 ± 1.88	0.877	0.083	-0.99, 1.16

Significant p values are in bold (p < 0.05).

<sup>a</sup>Data expressed as mean ± standard deviation.

**Table 6** Analgesic drugs related side effects

Side effect	Nefopam (n = 60) n (%)	Conventional (n = 87) n (%)	P-value <sup>†</sup>
- Nausea and vomiting	4 (6.7)	4 (4.6)	0.716
- Rash	1 (1.7)	0 (0)	0.408

<sup>†</sup>Exact probability test.

ence = 60%), as well as postoperative morphine consumption (mean difference: -3.4, 95%CI: 0.72, 6.08). The explanations for these outcomes are as follows. Anorectal surgery is a wide-encompassing term covering any procedure from simple to extensive surgery. The data in this study also included several anorectal procedures known to result in various degrees of pain ranging from mild to severe pain. The power of each type of surgery was seemingly low and might not be enough to identify the significant differences. Data analysis suggested that surgeons mainly ordered nefopam for the patients who underwent hemorrhoidectomy, LIFT, or fistulotomy (►Table 1). More than 50% of the patients in the nefopam group who underwent hemorrhoidectomy did not require rescue opioids postoperatively (61% for overall analysis, and 77% for under spinal anesthesia/ TIVA, P=0.01, mean difference = 60%, ►Table 2). To decide which anesthetic technique was suitable for each procedure, the surgeons generally evaluated the difficulty and the severity of pathologic lesions. The lesions that needed spinal anesthesia or TIVA seemed more complex; hence, the patients were more likely to experience moderate or severe postoperative pain.

On the other hand, those procedures done under local anesthesia might not be as complicated; therefore, a lower pain level was expected. Hemorrhoidectomy is renowned for being a painful surgery. Several studies are trying to find

effective techniques to relieve post-hemorrhoidectomy pain ranging from topical analgesia (i.e., EMLA, suppository diclofenac) to systemic analgesia.<sup>9-12</sup>

Nefopam is now widely prescribed to treat moderate to severe postoperative pain. The current evidence proposes that nefopam can relieve postoperative pain.<sup>6-8</sup> The analgesic efficacy of nefopam depends on the initial level of pain severity. Annmarie Hedges et al.<sup>13</sup> demonstrated that the effectiveness of nefopam is more apparent in patients with moderate to severe pain than with mild pain. Interestingly, the results of our study also confirm that assumption.

Concerning the analgesic impacts from other analgesic drugs on the primary outcome, we analyzed the impact of NSAIDs on postoperative opioid requirements. Analysis of the Exact probability test shows no significant difference in the 24-h postoperative opioid requirement. 53% of the patients who received NSAIDs still required additional postoperative opioids, slightly higher than those who did not (50%) (►Table 4). Therefore, it could be implied that the administration of NSAIDs in this study did not influence the nefopam effect.

The enhanced analgesic effects of nefopam were demonstrated. The mean numeric rating pain scores (NRPS) in the conventional group were relatively higher than those in the nefopam group (►Table 5). For the time point beyond the first 6-h postoperative, we are concerned about the lasting

effects of spinal anesthesia. Patients in the nefopam group distinctively experienced lower NRPS during 12–18 h postoperatively with a statistical difference ( $P = 0.009$ ). Comparably, in the study of Na HS et al., the NRPS of the nefopam group was significantly lower than that of the control group.<sup>6</sup>

The common side effects of nefopam have been reported as nausea, vomiting, rash, tachycardia, and hypertension. The incidence of these side effects herein was similar in both groups. However, many studies expressed a lower incidence of nausea and vomiting in the nefopam group.<sup>14,15</sup> Moreover, from this study, 6 of 8 patients who had nausea and vomiting were undergoing local anesthesia, and another two were undergoing total intravenous anesthesia technique.

Finally, this study demonstrates that nefopam is beneficial as a part of multimodal analgesia in major anorectal surgery.

Limitations for this retrospective observational study include a lack of controllable factors and an insufficient number of patients in some categories, making it hard to conclude this comparison properly. This study's power of subgroup analysis may not be enough to detect significant differences. Our results illustrate that nefopam can effectively reduce postoperative moderate to severe pain after anorectal procedures, for example, hemorrhoidectomy. For further studies, we suggest conducting randomized controlled trials with appropriate power adjustment, especially in hemorrhoidectomy that requires anesthesia.

In conclusion, prescribing nefopam as part of the analgesic regimen in patients undergoing major anorectal surgery reduces postoperative opioid requirements.

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#### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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