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Nefopam Vs Fentanyl in Female Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Nefopam is a non-opioid drug that inhibits reuptake of serotonin, norepinephrine, and dopamine. Nafopam is equipotent with opioids (morphine andmeperidine) and can decrease postoperative nausea and vomiting (PONV) by morphine sparing effect. So, we compared postoperative pain and PONV between female patients who received nefopam and fentanyl after laparoscopic cholecystectomy (LC).

Methods

Patients were randomly assigned to two groups: those who received fentanyl 1 μg/kg at skin closure (Group F, n=31) and those who received nefopam 30 mg mixed with normal saline 500 ml for 30 minutes during surgery (Group N, n=31). General anesthesia was induced with lidocaine 40 mg, propofol 2 mg/kg, and rocuronium 0.6 mg/kg and was maintained with desflurane and remifentanil 0.5 -1.5 μg/kg/min. Postoperative pain is assessed using visual analogue scale (VAS). VAS, rescue analgesics (fentanyl and ketorolac doses), and PONV were evaluated for 0-2 hr, 2-6 hr, 6-12 hr, and 12-24 hr after surgery.

Results

Age-adjusted VAS significantly decreased during the four assessment time periods in both groups ($p < .0001$). There were no significant differences between the two groups in fentanyl ($p = 0.163$) and ketorolac ($p = 0.676$) doses and PONV.

Conclusion

The analgesic effects of nefopam and fentanyl administered after LC in female patients were not significantly different. Nefopam is not inferior to fentanyl for pain control of LC.

Keywords

Laparoscopic cholecystectomy; Nefopam; Pain; Postoperative nausea; Vomiting

Abbreviations

ASA: American Society of Anesthesiologist; ANCOVA: Two-Way Repeated Measurement Analysis of Covariance; LC: Laparoscopic Cholecystectomy; PACU: Postanesthetic Care Unit; PCA: Patient Controlled Analgesia; PONV: Postoperative Nausea and Vomiting; VAS: Visual Analogue Scale

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Introduction

Laparoscopic cholecystectomy (LC) has many advantages over open laparotomy cholecystectomy, including improved postoperative pain and healing time [1]. Although LC is performed via minimal incisions, patients often complain of severe postoperative pain. Bisgaard et al. [2] reported that 5% of all LC patients had chronic moderate-to-severe pain 1 year after LC and that the intensity of acute postoperative pain can be a predictor of its transition into a chronic pain. Acute severe pain after LC in early postoperative periods increases the risk of chronic pain, so acute pain control is important.

Intravenous opioids have been used to manage moderate to severe pain during acute postoperative periods. Although opioids provide effective pain relief, they are frequently associated with side effects, such as postoperative nausea and vomiting (PONV) as well as respiratory complications.Morphine is associated with an increasing incidence of PONV than fentanyl in ambulatory surgery [3]. Younger female patients undergoing LC are at high risk of PONV [4].

Nefopam was developed in the early 1970s and has been used in many countries for the treatment of postoperative pain.Nefopam 20 mg is equipotent to morphine 6-12 mg [5] or to meperidine 50 mg [6]. In systematic review article, cumulative 24 h morphine consumption was significantly decreased by almost 30% - 50% with nefopam [7].

This study is aimed to compare postoperative pain intensity and rescue analgesics dose between nefopam and fentanyl when administered after LC in female patients. We hypothesize that the use of nefopam will decrease postoperative opioid use and incidence of PONV.

Methods and Materials

We enrolled a total of 62 female patients who were ASA physical status 1 or 2, aged 16-60 yr, and scheduled for elective LC under general anesthesia between February 2012 and November 2012. Ethical approval for this study (Ethical Committee Number 2011-109) was provided by the Ethical Committee of our hospital. Consent was given by each patient after complete description of the protocol. Exclusion criteria included patient desire to undergo intravenous patient-controlled analgesia (PCA), psychiatric disorders, and severe cardiovascular, renal, or hepatic disease as well as histories of chronic pain, substance abuse or long-term medication of analgesics.

A computer-generated randomization was used. The random numbers sequence was generated by an internet site program (http://www.random.org). Patients were randomly assigned to two groups: those who received fentanyl 1 μg/kg at skin closure (Group F, n=31) and those who received nefopam 30 mg mixed with normal saline 500 ml for 30 minutes during surgery (Group N, n= 31). These drugs were administrated by a nurse who is blinded to this study.

No patients were premedicated. The followings were monitored in the operating room: noninvasive blood pressure, lead II electrocardiography, pulse oximetry (SpO_2), and bispectral indices (BIS, Aspect Medical System, Norwood, MA, USA), and end-tidal carbondioxide concentration ($EtCO_2$).

General anesthesia was induced with lidocaine 40 mg, propofol 2 mg/kg, and rocuronium 0.6 mg/kg and was maintained with desflurane 5-7 vol%, medical air (FiO_2 0.5), and remifentanil 0.5-1.5 μg/kg/min. $EtCO_2$ and BIS remained in the 30-35 mmHg and 40-60, respectively. Desflurane and remifentanil were discontinued at the end of surgery. The pressure of CO_2 insufflation was kept under 12 mmHg. CO_2 was evacuated by manually compressing of the abdomen at the end of surgery. Total anesthetic and surgical time were recorded.

Postoperative pain was evaluated with the visual analogue scale (VAS) in which 0 indicated no pain and 10 indicated maximum pain. If the VAS score was $\geq$ 5, the patient was administered fentanyl 50 μg, and when the VAS score was <5, the patient received intravenous ketorolac 30 mg.

In both groups, VAS and PONV were evaluated 0-2 hr, 2-6 hr, 6-12 hr, and 12-24 hr after surgery by an anesthesiologist who was blinded to this study. We used Apfel's simplified score to assess PONV risk factors [8]. Also, other perioperative complications, such as tachycardia, sweating, dizziness, neuropsychiatric symptoms and light-headedness, were recorded. There were 4 levelsof PONV(0-3). "0" is absence of nausea and vomiting. "1" is mild degree and light nausea symptom. "2" is moderate degree and 1-2 gag reflexes without actual vomiting and require of antiemetic (ondansetron 4mg)."3" is severe degree and experience of vomiting and continuous nausea inspite of use ondansetron 4mg.When the level of PONV was 3, metoclopramide 10mg was intravenously injected.

A minimum group size of 62 patients was calculated to achieve a study power of 80% with a type 1 error rate of 0.05 and drop-out rate of 10%, based on a 20% difference of vomiting incidence at post-anesthesia care unit (PACU) between two groups in pilot study.The chi square test was used to compare categorical variables and the independent *t test* was used to compare continuous variables. Two-way repeated measurement analysis of covariance (ANCOVA) was used to compare age-adjusted repeated measurements in the 2 groups and within each group. The Bonferroni procedure was applied in post hoc analysis. A p value of <0.05 was considered significant. All statistical analyses were carried out using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and R version 2.13.2 (The R Foundation for Statistical Computing, Vienna, Austria) statistical software.

Results

The baseline characteristics of the patients are presented (**Table 1**). There were no significant differences in ASA class, body mass index, anesthetic time, surgery duration and Apfel's score. All patients presented $\geq$ 2 Apfel's scores.On arrival at PACU, two groups had similar VAS (**Table 2**). Age-adjusted VAS significantly decreased during the 4 assessment time periods (p<.0001), but this change was not significantly different between the two groups (p=0.429). Post hoc analysis revealed that this significant change in age-adjusted VAS scores stemmed from significant improvements between all assessments.

Interactions between groups and times were not significantly different between the two groups (p=0.753).At each of the 4 assessment time periods, ketorolac and fentanyl were used for the control of postoperative pain.

These rescue analgesic doses were not significantly different (**Table 3**).

No significant differences were observed between the two groups in the occurrence of PONV and use of antiemetics (**Table 4**). PONV frequently occurred during the first 2 hours after surgery. Other complications were not seen.

		Group		
Variable	Overall	F	N	P value
All patients	62 (100.0)	31 (50.0)	31 (50.0)	
Age	44.23±9.93	47.71±9.29	41.74±10.08	0.048
ASA classification				
1	50 (80.6)	26 (83.9)	24 (77.4)	0.520
2	12 (19.4)	5 (16.1)	7 (22.6)	
BMI (kg/m2)	23.31±3.66	22.82±3.03	23.79±4.20	0.300
Anesthesia time (min)	60.40±8.46	61.77±9.97	59.03±6.51	0.204
Surgery duration (min)	30.89±8.27	30.65±9.81	31.13±6.55	0.820
Apfel's score				
2	5 (8.1)	2 (6.5)	3 (9.7)	0.405
3	41 (66.1)	23 (74.2)	18 (58.1)	
4	16 (25.8)	6 (19.4)	10 (32.3)	

Table 1. Patients' baseline characteristics

Values are the mean ± SE. There are no difference between the two groups, except age. ASA classification - American society of anesthesiologists classification, BMI - Body mass index.

F - Fentanyl and N - Nefopam

	Group (n=31)		P value	
Postoperative pain scale	F (mean± SE)	N (mean± SE)	Time	Time x Group
Visual analogue scale				
0-2 hours	7.91±0.32	7.67±0.31	< .0001	0.753
2-6 hours	5.67±0.31	5.77±0.31		
6-12 hours	4.52±0.38	4.02±0.37		
12-24 hours	3.31±0.31	2.96±0.30		
p value	0.429			

Table 2. Age-adjusted Visual Analogue Scale at the four assessment points (F - Fentanyl and N - Nefopam)

Rescue analgesics		Group (n=31) F (mean ± SE)	Group (n=31) N (mean ± SE)	P value Time	P value Time x Group
Ketolorac					
0-2 hours		18.52±3.14	14.98±3.08	0.007	0.298
2-6 hours		27.50±3.89	29.52±3.82		
6-12 hours		12.11±3.25	14.09±3.19		
12-24 hours		8.01±3.32	11.93±3.17		
	p value	0.676			
Fentanyl					
0-2 hours		108.71±6.47	95.21±6.72	NA	NA
	p value	0.163			

Table 3. Age-adjusted analgesics at the postoperative four assessment points (F - Fentanyl and N -Nefopam)

Variables	Grade	Group F (n=31)	Group N (n=31)	P-value
PONV				
0-2 hours	(0/1/2/3)	(19/2/8/2)	(18/5/8/0)	0.425
2-6 hours	(0/1/2/3)	(23/4/4/0)	(23/6/2/0)	0.640
6-12 hours	(0/1/2/3)	(26/5/0/0)	(27/3/1/0)	0.707
12-24 hours	(0/1/2/3)	(28/3/0/0)	(31/0/0/0)	0.238
Ondansetron 4mg				
0-2 hours	(Yes/No)	(10/21)	(8/23)	0.780
Metoclopramide 10mg				
0-2 hours	(Yes/No)	(2/29)	(0/31)	0.492

Table 4. Comparison of difference on postoperative nausea and vomiting, and antiemetics

There were 4 levels of PONV (0-none, 1-mild, 2-moderate, 3-severe). 0: absence of nausea and vomiting, 1: light nausea symptom, 2: 1-2 gag reflexes without actual vomiting and require of antiemetics (ondansetron 4mg) and 3: experience of vomiting and continuous nausea in spite of use ondansetron 4mg. When the PONV was 3, metoclopramide 10 mg was intravenously injected. PONV - postoperative nausea and vomiting. (F - Fentanyl and N - Nefopam)

Discussion

We concluded that nefopam and fentanyl have both similar analgesic efficacy for pain control of LC. There are no significant difference in rescue analgesic dose and incidence of PONV.

Opiates are often required for pain management in immediate postoperative periods and provide rapid pain control. In our institution, fentanyl citrate has widely been used to treat severe acute postoperative pain. Fentanyl, a *pure μ* opioid, is structurally related to meperidine and is formulated as a citrate [9]. Fentanyl is highly lipophilic and onset time is rapid after intravenously injection. Non-opioid analgesics may be useful because opioids have some adverse effects such as PONV, urinary retention and respiratory depression. When anesthesiologists use opioids, a major consideration in early postoperative periods is respiratory depression.Bhatt et al. demonstrated that increasing dose of the oral nefopam did not increase the respiratory depression and nefopam can be an alternative analgesic [10,11].

Nefopam is a centrally acting non-opioid that inhibits reuptake of serotonin, norepinephrine, and dopamine [7]. NMDA receptor activation is related to acute opioid tolerance, and pretreatment with nefopam is useful to prevent pain sensitization induced by opioids [12]. Manoir et al. [13] have documented that nefopam has a significant morphine-sparing effect when combined with PCA morphine. Nefopam is a useful intraoperative non-opioid analgesic that controls postoperative pain.

The usual dose of nefopam based on recommendations from the manufacturer is 20 mg, but Delage et al. [14] have suggested higher doses for successful analgesia (effective dose of nefopam in 50% of patients = 28mg). Effective dose of nefopam in 80% of patients is close to 60 mg with moderate pain [15]. Thus, we used 30 mg of nefopam for postoperative pain management in our study.

The incidence of nausea was lower in the group receiving nefopam with morphine for PCA than in the group receiving morphine alone for PCA [16]. Also, PCA with nefopam was associated with a lower incidence of nausea than PCA with fentanyl alone after cardiac surgery [17].This seems to be due to opioid-sparing effect by nefopam. Risk factors, as assessed by using Apfel's score, are female gender, prior histories of motion sickness or PONV, nonsmoking, and the use of postoperative opioids. This score is simpler and more favorable for predicting the risk of PONV than Sinclair's score [8]. The incidence of PONV is 10%, 20%, 40%, 60% and 80% when Apfel's score is 0, 1, 2, 3, and 4, respectively [4]. All patients who participated in our study had Apfel's scores $\geq$ 2 and there were no significant differences in postoperative fentanyl dose. Thus, it seems to be there are no significant difference between PONV of two groups. PONV is a complex phenomenon and has many etiologies. Anesthesiologists should consider surgery-related risk factors and patient-specific risk factors.

Sweating and tachycardia are the frequent adverse reaction in patients who received nefopam [18].We did not evaluate these complications in this study because it was not clear if any observed sweating and tachycardia was caused by nefopam or anesthesia recovery profile. However, anesthesiologists must keep in mind that more nefopam can lead to more complications [19].

Our study has some limitations. First, patients were younger in Group N despite patient randomization. Younger patients may be more sensitive to noxious stimuli [4]. Second, we needed to collect more data about preoperative patient characteristics. Preoperative neuroticism and sensitivity to cold pressor-induced pain are risk factors of early postoperative pain [20]. Ure et al. [21] have described that the patients with a high intensity of preoperative pain or dyspeptic symptoms (nausea, vomiting, loss of appetite, or feeling of abdominal pressure) need more opioids and have higher postoperative pain levels. Third, further studies about incremental dose of nefopam during various surgeries are needed to manage of postoperative pain and side effects.

The results of this study suggest that nefopamis as effective as fentanyl in management of postoperative pain. Considering that younger age of Group N patients, these results can be meaningful. Nefopam is not inferior to fentanyl for pain control of LC.

Acknowledgments

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