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수술 후 통증조절 목적으로 펜타닐과 병용되는 네포팜 vs. 케토롤락의 사용현황

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Concurrent Use of Nefopam vs. Ketorolac with Opioid Analgesic for Post-operative Pain Management

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ABSTRACT

Objective: To compare the analgesic effects and adverse drug reactions (ADRs) of fentanyl intravenous patient-controlled analgesia (ivPCA) with nefopam, a centrally acting analgesic agent with demonstrated opioid sparing activity, as compared to ketorolac in a tertiary teaching hospital. **Methods:** A retrospective evaluation of electronic medical records was conducted on patient records including either nefopam or ketorolac with opioid ivPCA for post-operative pain management in general surgery department from January to December 2014. The status of pain control and ADRs were collected. **Results:** Out of 6,330 general surgery cases, nefopam was given in 153 prescriptions (6.9%) and ketorolac in 81 prescriptions (3.6%). The level of pain control was not different between two groups (70.9% vs. 75.3%; $p = 0.51$), but ADRs were more frequently reported in nefopam group (9.8% vs. 2.5%; $p < 0.05$). New ADRs of hot flushes (n = 1) and paresthesia in hands (n = 1) were reported in nefopam group and they were unlisted in the approved package insert. No serious ADRs were reported in both groups. **Conclusion:** Our findings presented that nefopam showed a similar analgesic effect and higher ADR rates compared to ketorolac as an adjuvant to fentanyl iv PCA for post-operative pain management in general surgery patients in South Korea.

KEY WORDS: Nefopam, ketorolac, postoperative pain management, analgesic effects, drug safety, adverse events, opioid analgesics

Optimal pain management represents a priority, as well as a clinical challenge, for healthcare professionals, since inadequate pain control following surgery may result in delayed patient recovery and subsequent discharge, as well as poor clinical outcomes.[1-4] Although opioids have been reported as the main analgesics used in post-operative pain management[3] despite their associated adverse drug reactions (ADRs), multimodal analgesia including the use of various analgesic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) has been recommended.[5]

Nefopam, a benzoxazocine analgesic and an analogue of diphenhydramine, was developed for the treatment of spasticity

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in the early 1970s.[6] As a centrally acting analgesic agent, nefopam exerts its action by inhibiting the reuptake of serotonin, noradrenaline, and dopamine[6]. Although nefopam has demonstrated opioid-sparing effects when used in combination with opioid analgesics[6-11] and a better safety profile in terms of renal function and platelet aggregation as compared with NSAIDs[8,10], the approved package insert of nefopam (Acupan®) currently includes a warning of insufficient data supporting its concurrent use with opioid analgesics.[12]

Nefopam is approved for use in acute pain, especially post-operative pain and lists the following adverse drug reactions (ADRs) in the approved package insert: gastrointestinal side effects, anorexia, nausea, vomiting, somnolence, dizziness, nervousness, sleep disturbance, insomnia, excitability, irritability, hallucinations, convulsions, headache, blurred vision, fatigue, hyperhidrosis, sweating, tachycardia, palpitations, thirst, pain at injection sites, etc.[12]

The current study was designed to estimate the rate of concurrent use of nefopam with fentanyl intravenous patient-controlled analgesia (ivPCA) and to compare the analgesic effects and ADRs between nefopam vs. ketorolac with fentanyl ivPCA groups in post-operative patients using electronic medical records (EMRs) from a tertiary teaching hospital.

METHODS

Study design and study population

A retrospective evaluation of EMRs was carried out at a tertiary teaching hospital in South Korea which provides care for approximately 1.2 million outpatients and more than 60,000 inpatients annually. EMR of the hospital was supported by a proprietary healthcare information system which houses clinical data and built-in clinical decision tools to provide patient care services and hospital management. All hospitalized patient records in general surgery department from January to December 2014 were retrospectively identified and data on patient characteristics (age, body weight and height) and clinical characteristics (length of stay, type of surgery, duration of surgery, medications, the status of pain control, and associated ADRs) were collected by reviewing patient profiles, prescription records, and nursing charts available from EMRs.

This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (IRB no. B-1508/312-117) and was granted a waiver of informed consent and documentation of consent for all patients.

Data on medications, ADR assessment, and pain control

Of two opioid medications delivered in ivPCA, i.e., fentanyl and oxycodone namely, the study focused on fentanyl as it is the most commonly prescribed in our clinical setting. As nefopam was first introduced in late 2013 the hospital, all prescription records for hospitalized patients were retrieved between January 1, 2014 and December 31, 2014 to describe a patterns of nefopam use as compared to ketorolac, i.e., the most frequently used analgesic agent with opioid ivPCA before the introduction of nefopam. We considered concurrent use of nefopam with fentanyl ivPCA (ivPCA-N) or ketorolac with fentanyl ivPCA (ivPCA-K) if these agents were prescribed on the same day, respectively.

Data on ADRs and causal inferences were retrieved from relevant 'ADR' sections in the EMRs, including documented patient-reported ADRs or symptoms recorded on nursing charts. ADR causality was assessed using tools such as the Naranjo Algorithm and the Korean Algorithm version 2.[13-15] A nefopam-related ADR was defined when causality assessment concluded an association with nefopam use was possible, probable, or certain, and the assessment was made by two independent pharmacists trained in causality assessment.

The study considered that pain was controlled if the nursing charts from EMRs included descriptions about reduced pain after nefopam or ketorolac administration and no subsequent prescriptions of analgesic agents were issued.

Statistical analysis

For estimating the rate of concurrent use of nefopam with fentanyl ivPCA and comparing the rates for nefopam vs. ketorolac use, descriptive statistics were used. Differences between ivPCA-N group and ivPCA-K group were evaluated using Chi-square test, Mann-Whitney *U*-test, or *t*-test. All analyses were performed using IBM SPSS Statistics version 21.0 (SPSS Inc, Chicago, IL, USA). A p-value <0.05 was considered as statistically significant.

RESULTS

Patterns of use of nefopam in post-operative pain management

A total of 6,330 general surgery cases in 2014 were identified, of which 2,315 (36.6%) cases involved the use of one or more injectable opioid analgesics as ivPCA. Of these 2,315 cases, fentanyl ivPCA was administered in 2,225 (35.2%) cases (Fig.

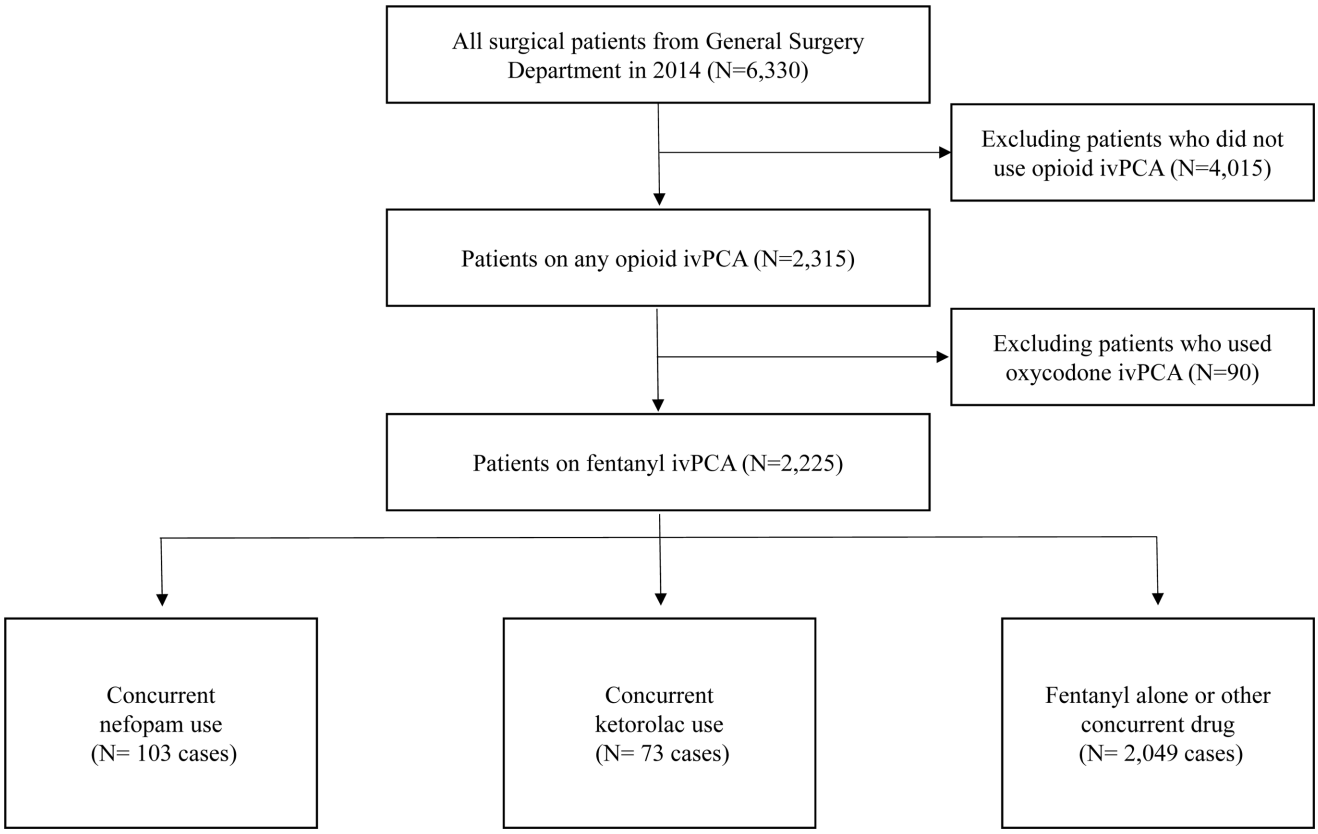

Fig. 1. The process of identifying the study population

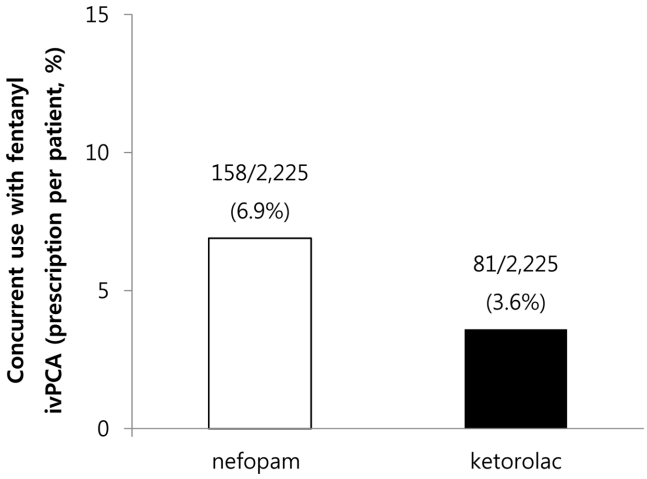

Fig. 2. Prevalence of postoperative pain management with concurrent fentanyl ivPCA use at a tertiary hospital in Korea

1). Following initiation of fentanyl ivPCA, nefopam was given in 103 patient cases (N = 103, 4.6%) with a total of 153 prescriptions (prescription per patient 6.9%) and ketorolac in 73 patient cases (N = 73, 3.3%) with a total of 81 prescriptions (prescription per patient 3.6%) (Fig. 2).

There were no significant differences in patient characteristics between ivPCA-N group and ivPCA-K group as well as clinical characteristics in total operation time, fentanyl infusion rate or the prescribed fentanyl dosage (Table 1). There were no significant differences in the level of pain control (70.9% vs. 75.3%, $p = 0.51$) (Table 1). However, the length of hospitalisation after surgery was significantly longer in ivPCA-N group, compared with ivPCA-K group (mean ± SD 14.5 days ± 13.0 vs 10.0 days ± 8.3, respectively; $p < 0.05$) without significant differences in the operation time or the rate of laparoscopic surgery between the groups. The duration of concurrent analgesic use for ivPCA-N group was longer than ivPCA-K group (mean ± SD 1.5 days ± 1.2 vs 1.1 days ± 0.3, respectively; $p < 0.05$).

Adverse drug reactions

Of 153 nefopam prescriptions in ivPCA-N group, ADRs occurred in 15 cases (9.8%) (Table 2), which included 12 documented ADRs (nausea n = 5, dizziness n = 3, tachycardia n = 2, and sweating n = 2) [15] and 3 ADRs that are not listed in the approved package inserts (vomiting n = 1, hot flushes

Table 1. Characteristics of the study population with the concurrent fentanyl ivPCA use*

Characteristics	Nefopam (n = 103 cases)	Ketorolac (n = 73 cases)	*p*-value
Total number of prescriptions	153	81	-
Age, years	57.4 ± 14.6	53.0 ± 15.9	0.06[a]
Body weight, kg	60.9 ± 15.9	60.6 ± 9.9	0.84[b]
Height, cm	162.5 ± 8.5	161.6 ± 7.5	0.50[b]
Length of hospitalization, day	14.5 ± 13.0	10.0 ± 8.3	<0.05
Total operation time, minute	246.9 ± 157.6	215.6 ± 114.2	0.31[a]
Dosage of fentanyl ivPCA, microgram	1,355.8 ± 317.7	1,356.2 ± 321.0	0.89
Infusion rate of fentanyl ivPCA, mL/hr	1.0 ± 0.3	1.1 ± 0.5	0.40[b]
Duration of the combined therapy, day	1.5 ± 1.2	1.1 ± 0.3	<0.05
Laparoscopic surgery, %	41.7	54.8	0.09[c]
Pain control, %	70.9	75.3	0.51[c]

Data presented as mean ± SD or %.
[a]Mann - Whitney U test.
[b]Student's t-test.
[c]Chi-square test.
ivPCA, intravenous patient-controlled analgesia.

Table 2. Adverse drug reactions with the concurrent fentanyl ivPCA use

	Nefopam (n = 153)	Ketorolac (n = 81)	*p*-value
Number (% prescriptions) of ADRs	15 (9.8)	2 (2.5)	<0.05[b]
ADR descriptions, n (%)			
Nausea	5 (3.3)	1 (1.2)	
Dizziness	3 (2.0)	-	
Palpitation	2 (1.3)	-	
Sweating	2 (1.3)	-	
Vomiting	1 (0.7)	-	
Hot flushing[a]	1 (0.7)	-	
Paresthesia on hands[a]	1 (0.7)	-	
Bloody drainage	-	1 (1.2)	

[a]ADRs that are not described in the approved package insert.
[b]Chi - square test.
ADRs, adverse drug reactions; ivPCA, intravenous patient-controlled analgesia.

n = 1, and paresthesia in the hands n = 1). The overall prevalence of reported ADRs were significantly higher in ivPCA-N group than ivPCA-K group (9.8% vs. 2.5%; $p < 0.05$). (Table 2) Five out of 6 patients who had experienced gastrointestinal ADRs like nausea or vomiting were recipients of GI surgery. Nausea, vomiting, hot flushes and paresthesia subsided within 30 minutes of discontinuation of nefopam. No report of nefopam-related renal toxicity or serious ADRs were found.

Of 81 ketorolac prescriptions in ivPCA-K group, ADRs occurred in two cases (2.5%) (Table 2), which included: nausea (n = 1) and bloody drainage (n = 1), both of which are listed on the approved package insert.[16] There was no report of ketorolac-related renal toxicity or serious ADRs.

DISCUSSION

Latest practice guidelines on pain management have described the benefits of multimodal pain management combining analgesics with different mechanisms of action, thereby providing more effective pain relief, compared with single-modality pharmacotherapeutic interventions.[5] Although opioids are recognized for effective analgesia in the management of post-operative pain, their usefulness as monotherapy in post-operative pain control is hampered by their ADR profile, including nausea, vomiting, constipation, urinary retention, respiratory depression, drowsiness, dizziness, pruritus, bradycardia and hypotension.[17] NSAIDs are known to potentiate opioid analgesic effectiveness and decrease opioid-related adverse

effects in opioid-based PCA. Due to the safety related limitations of NSAIDs as PCA adjuvants related to their increased risk for GI ulceration and bleeding[11], hypersensitivity reactions[18,19], renal insufficiency in older patients[6], and cardiovascular risks[20], the need for alternative adjuvant analgesics would appear reasonable and justifiable.

Our study showed nefopam was used as a PCA adjuvant in a South Korean tertiary teaching hospital, although it has not been approved for use for this particular indication. Nefopam, a benzoxazocine compound, is a non-opioid, non-steroidal, centrally acting analgesic that has been available in European countries since the mid-1970s.[6,10] Nefopam (Acupan®) exerts its analgesic effects by inhibiting the presynaptic reuptake of monoamine neurotransmitters involved in pain, including noradrenaline, serotonin and dopamine, and its antihyperalgesic effects by inhibiting post-synaptic *N*-Methyl-*D*-aspartate (NMDA) receptor activation.[12,21] Findings from our study also documented that nefopam was more prevalently prescribed soon after its availability in the Korean market as an adjuvant to fentanyl ivPCA for post-operative pain management than ketorolac. Although the level of pain control was not different between two groups, the rate of ADRs were more prevalent in nefopam group.

While studies documented that combination use of nefopam with morphine PCA demonstrated a morphine-sparing effect of approximately 35% without major side effects[8], we believe further studies are needed to document the efficacy and safety of nefopam as part of multimodal analgesia because the approved package insert of nefopam (Acupan®) described about insufficient data supporting its concurrent use with opioid analgesics.[12] Based on clinical judgment or evidence supported by published studies, doctors often prescribe drugs beyond their approved indications by the regulatory agencies. The practice of off-label prescribing is not infrequent as documented in various clinical settings and many countries.[22,23] Off-labeling prescriptions of nefopam or other various alternatives to NSAIDs may be considered in the management of post-operative pain in the form of multimodal analgesia as suggested in the literature.[5]

Our study found 'unlisted' ADRs related to nefopam use as an opioid PCA adjuvant in post-operative pain management, such as body heat sensation and paresthesia of hand. Pyrexia of non-infective etiology within the first 48 hours post-surgery have been previously reported in general surgery patients [24,25], with normal inflammatory host response to surgery[26] or other benign causes cited as the most common causes.[27] Although neuropathies following surgery due to damage to soft and nerve tissues have been described in anaesthetized or sedated patients[28], similar types of ADRs were not found in ivPCA-K group and, therefore, further evaluations of spontaneous reportings or large-scale epidemiological studies are needed to clarify the causal association between nefopam and paresthesia.

Several limitations should be considered in the interpretation of our study findings. This was a retrospective study; hence the efficacy evaluation of analgesics in pain control could lack sufficient details. In addition, there is a potential for random errors because of small sample size. Therefore, further studies with a large scale are needed. As similar to studies using secondary data, only accessible information from the EMRs were used for safety assessment using the Naranjo Algorithm. Continuous use of ketorolac beyond 2 days post-surgery was usually restricted and the drug costs would not be covered by the health insurance. Therefore, the differences of duration of the combined therapy could partially explain the rate of ADRs between two groups. However, we believe that the mean differences of the therapy duration between two groups being 0.4 days could not sufficiently explain the rate differences of ADRs.

In conclusion, this is a first retrospective study which directly evaluated the efficacy and safety of concurrent use of nefopam compared to ketorolac with opioid at clinical setting in South Korea. Our study showed that nefopam was more commonly used than ketorolac as an adjuvant to fentanyl ivPCA for post-operative pain management with similar efficacy in pain control and higher ADR rates were observed in nefopam group at a tertiary teaching hospital in South Korea. We reported three new ADRs not listed in the approved package insert of nefopam. As ketorolac can be used only limited days in South Korea healthcare system, nefopam might be suggested as an alternative analgesic concurrently used with fentanyl. Continuous efforts are needed in monitoring of efficacy and safety outcomes while using nefopam concurrently with opioid analgesic agent.

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DECLARATION OF CONFLICTING INTERESTS

All authors declare that there is no conflict of interest.

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