

Droperidol Reduces Postoperative Nausea and Vomiting and Supports the Continuation of Intravenous Patient-Controlled Analgesia with Fentanyl

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ABSTRACT- PURPOSE: To examine the impact of adding droperidol to fentanyl-based intravenous patient-controlled analgesia (IVPCA) on the discontinuation of IVPCA use due to postoperative nausea and vomiting (PONV). **METHODS:** Patients who underwent surgeries other than abdominal surgeries and used IVPCA between April 2014 and March 2018 were selected. Patients using IVPCA with fentanyl alone were compared to patients using droperidol added to IVPCA. Patients were allocated to one of two groups depending on the drug used for IVPCA: 1) control group, fentanyl alone; 2) droperidol group, droperidol with fentanyl. The primary endpoint was the discontinuation of IVPCA due to PONV. Secondary endpoints included PONV within 48 hours after surgery, the number of antiemetics used, pain score, and adverse effects. Propensity score matching was used to control the differences in clinical features among patients. **RESULTS:** Among the 793 patients initially enrolled in this study, 145 were excluded via propensity score matching; 364 of the remaining patients received IVPCA supplemented with droperidol. Propensity score matching showed that discontinuation of IVPCA due to PONV was significantly decreased in the droperidol group compared to the control group ($P = 0.01$). Further, compared with the control group, the droperidol group had reduced nausea up to 24 hours after surgery ($P < 0.01$), and the number of vomiting episodes and use of antiemetics decreased within 12 hours after surgery ($P < 0.01$). **CONCLUSIONS:** The addition of droperidol to IVPCA is associated with a decrease in PONV, as well as the improved continuation of pain treatment with fentanyl-based IVPCA, similar to IVPCA with morphine. However, it is necessary to monitor the side effects of this treatment.

KEYWORDS: Droperidol, Postoperative nausea and vomiting, Intravenous patient-controlled analgesia, Postoperative pain

INTRODUCTION

After surgery, many patients experience postoperative pain, as well as postoperative nausea and vomiting (PONV). Intravenous patient-controlled analgesia (IVPCA) with fentanyl is widely used to decrease postoperative pain. However, anesthetic-induced PONV and opioids used for IVPCA often lead to the discontinuation of IVPCA, which compromises postoperative pain management and increases medical care costs (1-5). Commonly used antiemetics include 5-hydroxytryptamine-3 receptor antagonists (5HT3RA) and neurokinin-1 receptor antagonists (NK1RA), which have been shown to combat PONV effectively. However, unpleasant side effects, medical care costs, and off-label usages have been noted with these drugs, which significantly limits available therapeutic options for these patients. Despite droperidol being the most cost-effective antiemetic alternative, its usage has decreased due to a warning

of fatal arrhythmia by the Food and Drug Administration (6-8). In this study, the addition of droperidol to IVPCA reduced PONV and IVPCA discontinuation. Although droperidol has been widely used for a few decades, real-world reports of its use are inadequate, and its efficacy and safety when added to fentanyl are unclear (9-13). Therefore, in this retrospective study, we investigated the impact of adding droperidol to fentanyl-based IVPCA on the discontinuation of IVPCA due to PONV.

MATERIALS AND METHODS

This retrospective cohort study was carried out within

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a single facility, from which we collected information from patients' medical records following validation by two people.

This study complied with the standards of the Declaration of Helsinki and the current ethical guidelines. The design and methodology, including the opt-out method of consent available to all patients, was approved by the Kameda General Hospital Clinical Research Review Committee (Approval number: 18-073) and adhered to the applicable STROBE guidelines.

Study Population

Patients who underwent surgeries other than abdominal surgeries and received IVPCA between April 2014 and March 2018 were retrospectively enrolled. Patients were allocated to one of two groups depending on the drug used for IVPCA: 1) control group, fentanyl alone; 2) droperidol group, droperidol with fentanyl. Patients were excluded if they met the following criteria: 1) had Alzheimer's disease or were using antedementia drugs before surgery; 2) had difficulty understanding the numerical rating scale (NRS); or 3) had a poor understanding of the IVPCA education provided by the pharmacist.

Anesthesia Method and IVPCA Education

From the clinical records, we recorded the method and type of anesthesia, analgesics, and prophylactic antiemetics administered during surgery by an anesthesiologist. In Japan, medical care is covered by the National Health Insurance System, and by policy, the clinical use of certain drugs is not permitted. We were unable to use the expensive 5HT₃RA and NK₁RA for PONV. Therefore, anesthesiologists provided one or more prophylactic antiemetics, such as dexamethasone, droperidol, prochlorperazine, and metoclopramide to patients with PONV risk ≥ 2 as a routine treatment. None of the patients received premedication. IVPCA was initiated immediately before the end of surgery with a Coopdech[®] Syrinjector[®] PCA mobile disposable infusion pump (Daiken Medical Corporation, Osaka, Japan). The IVPCA comprised of a solution containing 40 mL of 0.9% physiological saline and 1 mg of fentanyl citrate (0.5 mg/10 mL), to which 2.5 mg of droperidol was added per 60 mL of solution. Surgeons were given discretion on whether to add droperidol to the IVPCA. The continuous infusion rate was usually fixed at 1.0mL/h. However, the surgeon could change it to 0, 0.5, 1, or 1.5mL/h depending on the pain and side effects; the rescue dose was set as 1 mL, the lockout time was 10 min, and 6 rescue doses were allowed per hour. During the abstraction period, the policy of our hospital was to use prochlorperazine first and

metoclopramide afterward. The selection and administration rate of drugs postoperatively, including droperidol or an antiemetic, was determined at the surgeon's discretion. Physicians continued treatment with IVPCA until patients completed the prescribed course or experienced no pain. If the patients revealed symptoms of severe PONV, side effects, or device errors, the use of IVPCA was discontinued. The use of the disposable IVPCA device was not resumed after discontinuation due to these reasons.

Per the standard protocol, all patients received information about anesthesia and IVPCA from the anesthesiologist before their surgery. Patients undergoing scheduled surgery received standardized education by pharmacists trained in the use of IVPCA, which was conducted at the patient's bedside and included instructions on the use of IVPCA, the effects and side effects of the medication, and the use of additional analgesics and antiemetics. The pharmacist assessed the patients' depth of understanding and asked them to demonstrate their capability to press the rescue button on the device. Patients who required urgent IVPCA after emergency surgery received a similar education from the pharmacist within 24 hours post-surgery. These evaluations were obtained from available medical records.

Endpoints

Patients using IVPCA with fentanyl alone were compared to those using IVPCA with droperidol. The primary endpoint was the discontinuation of IVPCA use due to PONV, as described in the medical records. Secondary endpoints included PONV, the number of antiemetic agents used, pain score, and adverse effects within 48 hours after surgery. The adverse events investigated were drowsiness, delirium, dizziness, hypotension, extrapyramidal disorder, restlessness, and arrhythmias. Age and operation time were categorized based on PONV risk according to a consensus guideline, and body mass index (BMI) was categorized based on the World Health Organization classification. The reasons for IVPCA discontinuation were obtained from the medical records (1). Pain scores according to the NRS (rating 0–10) were evaluated at rest in the morning, afternoon, and evening by a nurse trained in pain evaluation. These scores were also obtained from the medical records.

STATISTICAL ANALYSIS

The Fisher's exact test was used for the analysis of categorical data, and the Mann-Whitney's *U* test was used for the analysis of continuous variables. Targeting the available population, missing data were addressed by a full analysis of all cases. Propensity

score matching was carried out to control for any differences in clinical features between patients receiving IVPCA with and without added droperidol. These propensity scores were based on sex, age, BMI, the American Society of Anesthesiologists physical status (ASA-PS), history of PONV or motion sickness, smoking history in the past month before surgery, anesthesia method, operation time, number of PONV preventive drugs used, and pre-operative education by pharmacists. Patients with or without droperidol were matched 1:1 based on propensity scores and were not replaced. The matching caliper was set to a 20% standardized difference. This matching was confirmed using the standardized mean difference (SMD). To eliminate residual confounding factors in the groups after matching, all variables were entered into a generalized linear model, and dual-robust estimations were performed. All data were analyzed by a statistician using R (version 3.4.1). The significance level was set at $P < 0.05$.

RESULTS

During the study period, 793 patients underwent surgeries other than abdominal surgeries with IVPCA

at our institution. Of these patients, 145 were excluded based on the exclusion criteria outlined above. Of the remaining 648 patients, general anesthesia was induced with propofol (an opioid) and a muscle relaxant and was maintained with desflurane or sevoflurane. Of the remaining 648 patients, 364 (56.2%) received IVPCA with droperidol (Figure 1). The droperidol group had lower ASA-PS ($P = 0.02$), more motion sickness ($P = 0.02$), different types of surgery ($P < 0.001$), shorter surgery time ($P < 0.001$), shorter anesthesia time ($P < 0.001$), and received more preventive antiemetics ($P = 0.04$) than the control group. Even after propensity score matching, the SMD was more than 10% for surgery type and anesthetic method (Table 1).

The discontinuation of IVPCA due to PONV was significantly decreased in the droperidol group ($P = 0.01$) compared to the control group. In addition, discontinuation of IVPCA due to the absence of pain was increased in the droperidol group compared to the control group (Table 2). No patients deviated from the standard response in the prevention and treatment of PONV.

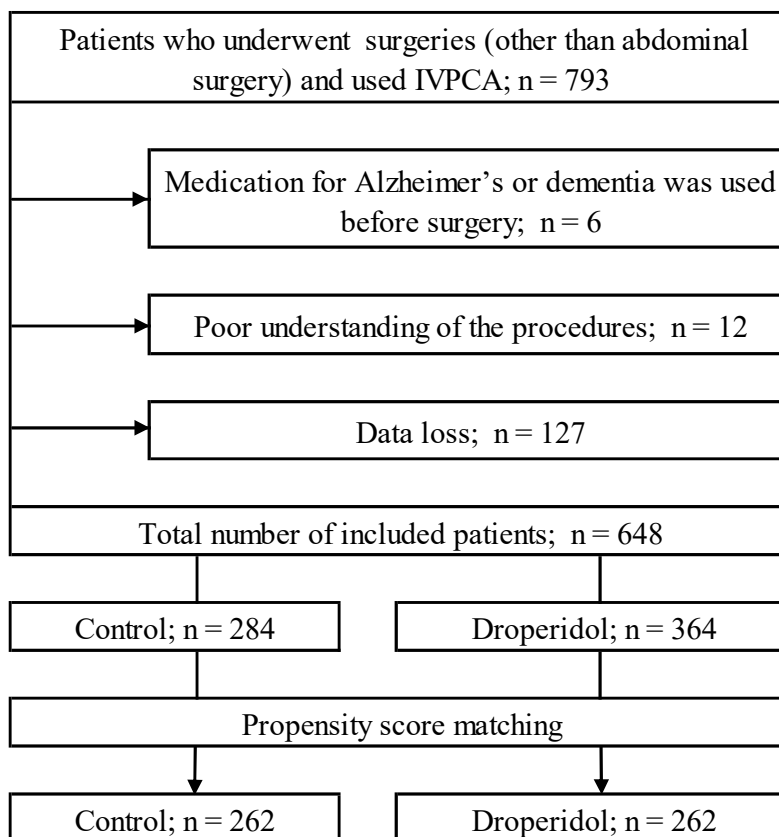


Figure 1. Flowchart of the study population. This figure depicts the study selection process, illustrating the proportion of patients included, as well as the proportion excluded along with the deciding criteria. IVPCA, intravenous patient-controlled analgesia.

Table 1. Patient characteristics.

	Before propensity score matching						After propensity score matching					
	Control n = 284		Droperidol n = 364		<i>P</i> -value	SMD	Control n = 262		Droperidol n = 262		<i>P</i> -value	SMD
	Count	%	Count	%			Count	%	Count	%		
Sex (female)	141	49.6	200	54.8	0.22	0.10	134	51.1	136	51.9	0.93	0.02
Age (average ± SD), years	58.9	19.0	56.9	18.1	0.18		58.9	19.0	56.9	18.1	0.17	
< 50 years	71	25.0	115	31.5	0.08	0.15	68	26.0	68	26.0	1.00	< 0.001
Body mass index (average ± SD), kg/m ²	24.1	4.4	24.3	3.9	0.54		24.1	4.4	24.3	3.9	0.54	
< 18.5 kg/m ²	21	7.4	14	3.8	0.07	0.18	16	6.1	11	4.2	0.61	0.09
18.5–25.0 kg/m ²	169	59.5	210	57.5			154	58.8	158	60.3		
> 25 kg/m ²	94	33.1	141	38.6			92	35.1	93	35.5		
ASA physical status												
1	53	18.7	100	27.4	0.02	0.23	53	20.2	70	26.7	0.21	0.16
2	196	69.0	234	64.1			180	68.7	167	63.7		
3	35	12.3	31	8.5			29	11.1	25	9.5		
PONV history	16	5.6	26	7.1	0.55	0.06	16	6.1	15	5.7	1.00	0.02
Smoking history within 1 month	44	15.5	59	16.2	0.90	0.02	41	15.6	44	16.8	0.81	0.03
Motion sickness	39	13.7	78	21.4	0.02	0.20	38	14.5	38	14.5	1.00	< 0.001
Pre-operative education by pharmacists	278	97.9	350	95.9	0.23	0.12	256	97.7	256	97.7	1.00	< 0.001
Surgery type												
Spinal	178	62.7	158	43.3	< 0.001	1.04	158	60.3	137	52.3	< 0.001	0.89

Orthopedics	36	12.7	139	38.2			36	13.7	96	36.6		
Oral	57	20.1	2	0.5			55	21.0	1	0.4		
Otolaryngology	12	4.2	62	17.0			12	4.6	27	10.3		
Other ^a	1	0.4	3	0.8			1	0.4	1	0.4		
Anesthesia method												
General	271	95.4	334	91.5	0.13	0.16	249	95.0	245	93.5	0.49	0.11
Spinal	7	2.0	19	5.0			7	2.7	12	4.6		
TIVA	6	2.1	12	3.3			6	2.3	5	1.9		
Anesthesia time (average ± SD), minutes	312.8	140.8	225.2	96.8	< 0.001		312.8	140.8	225.2	96.9	< 0.001	
Surgery time (average ± SD), minutes	242.8	133.7	156.1	81.1	< 0.001		242.8	133.7	156.1	81.2	< 0.001	
> 1.47 h	258	90.8	290	79.5	< 0.001	0.33	236	90.1	231	88.2	0.58	0.06
Number of prophylactic antiemetic drugs ^b												
0	164	57.0	179	49.0	0.04	0.24	143	54.6	140	53.4	0.79	0.09
1	91	32.0	133	36.4			90	34.4	92	35.1		
2	29	10.2	48	13.2			29	11.1	29	11.1		
3	0	0.0	5	1.4			0	0	1	0.4		
Description of prophylactic antiemetics taken by patients												
Dexamethasone	72	25.4	102	28.0	0.48	0.06	72	27.5	62	23.7	0.37	0.09
Prochlorperazine	34	12.0	61	16.8	0.09	0.14	33	12.6	40	15.3	0.53	0.07
Droperidol	30	10.6	59	16.2	0.04	0.17	30	11.5	37	14.1	0.43	0.09
Metoclopramide	13	4.6	22	6.0	0.49	0.07	13	5.0	14	5.3	1.00	0.02

SMD, standardized mean difference; PONV, postoperative nausea and vomiting; SD, standard deviation; ASA, American Society of Anesthesiologists; TIVA, total intravenous anesthesia; iv, intravenously. Data are shown as count and % unless otherwise indicated. ^aOther surgeries include formation and breast surgery. ^bProphylactic antiemetic drug is droperidol 0.625–1.25 mg iv, or prochlorperazine maleate 5 mg iv, or metoclopramide 10 mg iv.

Table 2. Reasons for discontinuation of intravenous patient-controlled analgesia.

	Control (n = 262)		Droperidol (n = 262)		P-value
	Count	%	Count	%	
Total	56	21.4	44	16.8	0.18
PONV	50	19.1	29	11.1	0.01
Side effect	5	1.9	11	4.2	0.20
Device error	0	0.0	3	1.1	0.15
Other	1	0.4	1	0.4	1.00

PONV, postoperative nausea and vomiting.

After eliminating major residual confounders using dual-robust estimation, the addition of droperidol to IVPCA was found to significantly decrease PONV-related discontinuation of IVPCA ($P = 0.01$) (Table 3). A complete dosage of IVPCA was administered in 218 (83.2%) patients in the droperidol group and 206 (78.6%) patients in the control group ($p = 0.18$). Of the

complete dosage patients, 24 (9.1%) in the droperidol group and 11 (4.2%) in the control group discontinued IVPCA due to the disappearance of pain ($p = 0.04$). Among patients who discontinued IVPCA (except for those with no pain), 24 (42.9%) in the control group and 11 (25.0%) in the droperidol group showed an increase in the NRS score by 2 or more points after discontinuation.

Table 3 Doubly robust estimator.

	Odds ratio	95% Confidence interval			P-value
Intercept	0.570	0.045	–	7.250	0.67
Sex (female)	2.340	1.340	–	4.090	<0.01
Age < 50 years	1.060	0.509	–	2.220	0.87
Body mass index	0.808	0.499	–	1.310	0.39
ASA physical status	0.622	0.369	–	1.050	0.07
PONV history	1.270	0.466	–	3.440	0.64
Smoking history within 1 month	0.199	0.060	–	0.665	0.01
Motion sickness	1.700	0.882	–	3.290	0.11
Pre-operative education by pharmacists	1.340	0.246	–	7.260	0.74
Surgery type	0.846	0.585	–	1.220	0.37
Anesthesia method	1.810	0.962	–	3.400	0.07
Surgery time > 1.47 h	0.985	0.382	–	2.540	0.98
Number of prophylactic antiemetic drugs	0.635	0.427	–	0.944	0.02
Addition of droperidol	0.507	0.303	–	0.847	0.01

PONV, postoperative nausea and vomiting; ASA, american society of anesthesiologists.

Concerning secondary endpoints, the droperidol group reported decreased nausea up to 24 hours after surgery compared to the control group ($P < 0.01$). Furthermore, the number of vomiting episodes and the number of times antiemetic drugs required were reduced up to 12 hours after surgery in the droperidol group compared to the control group ($P < 0.01$) (Table 4).

Adverse effects, including drowsiness and extrapyramidal disorder, increased in the droperidol group, although there were no statistically significant differences between the groups in this respect (Table 4). The patients in the droperidol group had higher IVPCA rescue dose use (14 times [7–25] versus [vs.] 13 times [6–23]) ($P = 0.127$) and a longer period of use (38 h [24–48] vs. 30 h [21–42]) than the control group ($P < 0.001$). The pain scores were lower at all times in the droperidol group than in the control group. On the evening of the second day after surgery, the pain score was significantly different from that during the evening of the first day after surgery (Figure 2).

DISCUSSION

In this study, we evaluated the effectiveness and safety of adding droperidol to IVPCA with fentanyl on patients' discontinuation of IVPCA due to PONV using a propensity score matching-based analysis. Adding droperidol to IVPCA with fentanyl was newly shown to decrease IVPCA discontinuation, improve

continuation of pain treatment, and decrease PONV and postoperative pain.

In a previous study, discontinuation of IVPCA due to PONV was reported to be 14%, which was close to the value obtained in the present study (3). Additionally, earlier research has shown that adding droperidol to IVPCA containing morphine was effective against PONV for a limited time (9-13). However, in this study, adding droperidol was effective for up to 24 hours immediately after surgery.

We believe that previous studies did not adequately verify the influence of the preventive antiemetic agents used. In this investigation, we adjusted for the anesthesia method, preventive antiemetic drugs, and PONV risk by propensity score matching; thus, we showed that adding droperidol to IVPCA is effective for managing PONV. Droperidol has been reported to reduce PONV in a dose-dependent manner (11, 14), and its repeated use during droperidol-supplemented IVPCA can be expected to decrease PONV caused by anesthesia and opioids (9-13).

Lack of education and PONV has been reported to prevent the use of IVPCA (15, 16). The reduction of pain within our study can be explained by the decrease in PONV, which elevated the number of times IVPCA rescue doses were required and prolonged the period of IVPCA use. Therefore, in the droperidol group, the number of cases with discontinuation of IVPCA due to the absence of pain was increased.

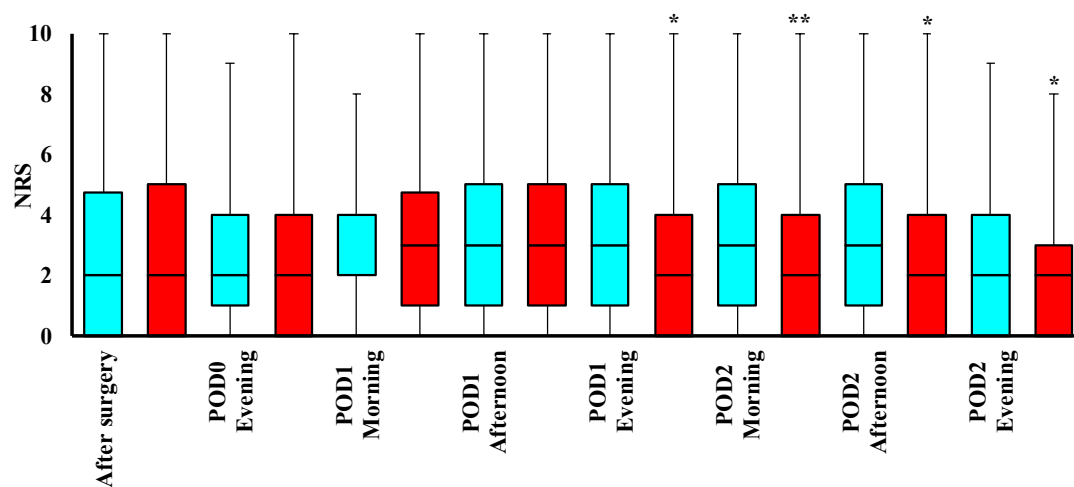


Figure 2. The impact of droperidol on post-surgical pain. The boxes show the changes in the postoperative numerical rating scale (NRS) over time. Cyan indicates the fentanyl-alone control group, and red indicates the droperidol group. POD, postoperative day. *: $P < 0.01$; **: $P < 0.001$.

Table 4 Outcomes

	Control (n = 262)		Droperidol (n = 262)		P value
	Count	%	Count	%	
PONV	128	48.9	82	31.3	< 0.001
Time to end of PONV (average ± SD), h	13.1	16.6	7.97	14.0	< 0.001
Nausea					
< 12 h	89	34.0	50	19.1	< 0.001
12–24 h	88	33.6	50	19.1	0.001
24–48 h	32	12.2	19	7.3	0.08
Total number of vomiting episodes					
Total times, 1/2/3/4/5 times	47/16/2/6/0	17.9/6.1/0.8/2.3/0	28/11/1/1/1	10.7/4.2/0.4/0.4/0.4	0.01
< 12 h	40	15.3	20	7.6	0.01
12–24 h	38	14.5	25	9.5	0.11
24–48 h	9	3.4	1	0.4	0.03
Total antiemetic drugs of the treatments after the surgery ^a					
Total times, 1/2/3/4/5/6/7 times	58/22/3/3/2/1/1	22.1/8.4/1.1/1.1/0.8/0.4/0.4	32/11/5/0/0/2/0	12.2/4.2/1.9/0.0/0.0/0.8/0.0	0.002
< 12 h	66	25.2	34	13.0	0.001
12–24 h	40	15.3	25	9.5	0.06

24-48 h	14	5.3	6	2.3	0.11
Description of the antiemetics received by the patients after surgery					
Prochlorperazine	84	32.1	43	16.4	< 0.001
Metoclopramide	24	9.2	14	5.3	0.13
Total of common adverse events	41	15.6	51	19.5	0.30
Drowsiness	18	6.9	32	12.2	0.05
Delirium	9	3.4	8	3.1	1.00
Dizziness	9	3.4	6	2.3	0.60
Hypotension	5	1.9	4	1.5	1.00
Extrapyramidal disorder	1	0.4	4	1.5	0.37
Restlessness	0	0.0	1	0.4	1.00
Arrhythmia ^b	1	0.4	0	0.0	1.00
Other	0	0.0	2	0.8	0.50

PONV, postoperative nausea and vomiting; SD, standard deviation; iv, intravenously.

^a Antiemetic drug is prochlorperazine maleate 5 mg iv or metoclopramide 10 mg iv.

^b Arrhythmias that required treatment.

Adverse events associated with droperidol have been reported in a systematic review; they include drowsiness (12–40% of cases) and extrapyramidal disorders (0.2% of cases) (17). In addition, several studies in which droperidol was added to morphine-based IVPCA showed that drowsiness was increased in the droperidol group (10-13). In this study, adverse effects associated with droperidol included drowsiness and extrapyramidal disorders, as mentioned above, which caused discontinuation of IVPCA in some cases. The increased rate of these adverse effects can be explained by the pharmacological action of droperidol (17). Patients with extrapyramidal disorders in the droperidol group did not use any medications other than droperidol. The symptoms of patients with suspected extrapyramidal disorders were improved by the discontinuation of IVPCA.

On December 5, 2001, the Food and Drug Administration issued a warning about an association between fatal arrhythmias and the use of droperidol (6). In subsequent studies, low doses of droperidol were not associated with increased arrhythmias and could be used safely (18-20). Nevertheless, the use of droperidol declined, and its effects were not studied further. In recent years, 5HT3RA and NK1RA have been widely used instead of droperidol and are recommended in the PONV consensus guidelines (1). However, 5HT3RA and NK1RA are expensive, while droperidol is an inexpensive and useful antiemetic agent in areas with medical resource and system limitations, as well as economic limitations.

Major causes of distress in surgical patients include postoperative pain and PONV, both of which require care (1, 21). However, it has been reported that the management of PONV remains insufficient (22). Not only do drug effectiveness and safety affect the disparity in measures for managing PONV, but cost and availability may also be important factors. Our study showed that adding droperidol to the pain management of fentanyl-based IVPCA could be a satisfactory approach for PONV care.

The study was limited in that it only included patients who underwent surgeries (other than abdominal surgeries); thus, the findings may not be generalizable to patients who undergo body cavity surgery. Second, since this was a retrospective study from a single facility, the treatments, including anesthesia, could not be standardized. Furthermore, a selection bias may exist due to the exclusion of certain patients. In this study, we performed propensity score matching, but we were unable to perform adequate adjustments for the surgical procedures and the anesthesia method. Hence, we performed dual-robust

estimations, adjusting for residual confounding factors and obtained similar results. Third, common drugs for PONV like 5HT3RA and NK1RA could not be evaluated.

One of the strengths of this study was that it evaluated the effect of droperidol using propensity score matching to adjust for risk factors of PONV, such as a history of PONV or motion sickness, and the use of prophylactic antiemetic drugs during surgery.

In conclusion, the addition of droperidol to IVPCA is associated with a decrease in PONV, as well as an improved continuation of pain treatment with fentanyl-based IVPCA, similar to IVPCA with morphine. However, it is necessary to monitor the side effects of this treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest associated with this manuscript.

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