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ORIGINAL ARTICLE

Postoperative continuous intravenous infusion of fentanyl is associated with the development of orthostatic intolerance and delayed ambulation in patients after gynecologic laparoscopic surgery

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Abstract
Purpose Early ambulation is essential for rapid functional recovery after surgery; however, orthostatic intolerance may delay recovery and cause syncope, leading to potential serious complications such as falls. Opioids may contribute to orthostatic intolerance because of reduced arterial pressure and associated reduction in cerebral blood flow and oxygenation. This study aimed to examine the effect of postoperative continuous infusion of fentanyl on orthostatic intolerance and delayed ambulation in patients after gynecologic laparoscopic surgery.
Methods In this retrospective cohort study, data from 195 consecutive patients who underwent gynecologic laparoscopic surgery were analyzed to evaluate the association between postoperative continuous infusion of fentanyl and the incidence of orthostatic intolerance or delayed ambulation. The primary outcome was defined as delayed ambulation, an inability to ambulate on postoperative day 1. The secondary outcome was defined as orthostatic intolerance and symptoms associated with ambulatory challenge, including dizziness, nausea and vomiting, feeling hot, blurred vision, and eventual syncope. Multivariate logistic regression was used to determine the independent predictors of delayed ambulation and orthostatic intolerance.
Results There were 24 cases with documented orthostatic intolerance and 5 with delayed ambulation. After multivariate logistic regression modeling, postoperative continuous infusion of fentanyl was found to be significantly associated with both orthostatic intolerance [adjusted odds ratio (95 % confidence interval), 34.78 (11.12–131.72)] and delayed ambulation [adjusted odds ratio (95 % confidence interval), 8.37 (1.23–72.15)].
Conclusion Postoperative continuous infusion of fentanyl is associated with increased orthostatic intolerance and delayed ambulation in patients after gynecologic laparoscopic surgery.

Keywords Orthostatic intolerance · Gynecologic laparoscopic surgery · Opioids · Ambulation · Analgesia

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Introduction

Early ambulation after surgery is considered to be essential for enhanced recovery because bed rest increases muscle loss and weakness, impairs pulmonary function, and predisposes patients to venous stasis and thromboembolism [1]. Protocols for enhanced recovery after surgery are designed to reduce the surgical stress response and support basic body functions by use of optimized analgesia, by early ambulation, and by early return to normal diet [2, 3]. These interventions have been shown to improve postoperative outcomes [4, 5]. Although adequate pain relief is thought to be important in early convalescence, effective pain relief does not always lead to increased ambulation and reduced hospital stay [6].

Early mobilization may be hindered by factors such as pain and orthostatic intolerance (OI). OI represents an inability to maintain an upright posture because of symptoms of cerebral hypoperfusion, including dizziness, nausea, and vomiting, feeling hot, blurred vision, and eventual

syncope [7]. Postoperative patients may be particularly vulnerable to OI after ambulation because blood and fluid losses during surgery aggravate postural reduction in central blood volume in the upright position. Transient inability to ambulate is observed after ambulatory surgery and is a major cause of prolonged hospital stay [8], and a high incidence of OI during early postoperative mobilization has been reported in patients after major surgery [9, 10]. However, the incidence of OI during early ambulation after gynecologic laparoscopic surgery is unknown, and the predisposing factors associated with failed orthostasis are not fully understood.

Drugs used for postoperative analgesia, including opioids, may contribute to OI because of reduced arterial pressure and associated reduction in cerebral blood flow and oxygenation. Because postoperative use of opioids is associated with increased risk of postoperative nausea and vomiting [11], it may increase the incidence and severity of OI. Although postoperative continuous infusion of fentanyl is commonly used in Japan, its efficacy and impact on early ambulation are unclear. We hypothesized that postoperative continuous infusion of fentanyl causes OI during the ambulation challenge and delayed ambulation.

The primary aim of this study was to determine the relationship between postoperative continuous infusion of fentanyl and delayed ambulation. We also examined the relationship between postoperative continuous infusion of fentanyl and OI during the ambulation trial.

Materials and methods

This was a retrospective cohort study. Patients who underwent gynecologic laparoscopic surgery at Kyoto Medical Center from October 1, 2007 to September 30, 2009 were included in this study. Patients who received prophylactic antiemetics intraoperatively or received nitrous oxide as an anesthetic were excluded from the study. After patient selection, data on patient characteristics (age at surgery, height, weight, and American Society of Anesthesiologists physical status), surgery (procedure conducted and duration of surgery), anesthesia (anesthetics used and intraoperative fentanyl dose), use of postoperative continuous infusion of fentanyl, and recovery profiles (requirements for rescue analgesics, postoperative nausea and vomiting, OI during ambulatory challenge, and delayed ambulation) were retrieved from their medical records.

Use and the rate of postoperative continuous infusion of fentanyl were left at the discretion of the attending anesthesiologist. Fentanyl was intravenously administered at a continuous rate using a Coopdech Syrinjector (Daiken Medical, Osaka, Japan). This device is only used for continuous infusion and not for patient-controlled analgesia. A rescue dose of analgesics (50 mg diclofenac sodium suppository) was administered on patient request. At the institution where the study was conducted, the patients were asked to try to stand up and walk in the morning and evening of postoperative day (POD) 1. A nurse recorded whether the patient could walk and also the symptoms experienced by the patient during the attempt to stand up and walk.

The primary outcome of interest was defined as delayed ambulation, and the secondary outcome was defined as OI. Ambulation was considered to be delayed if the patient could not walk more than 10 steps without assistance on POD 1. The patients were considered to have OI if they experienced signs of cerebral hypoperfusion, defined as having symptoms such as dizziness, nausea, and vomiting, feeling hot, blurred vision, or transient syncope during the ambulatory challenge on POD 1. For patients with delayed ambulation, data on reasons for delayed ambulation were also collected.

Statistical analysis

Data were analyzed using statistical software (JMP version 8.0). The data are presented as median (range) and number (percentage) unless stated otherwise. Differences between groups were compared using the Mann–Whitney U test for continuous variables. For categorical variables, the Pearson chi-square test or Fisher exact test was used where appropriate. All the statistical tests were two tailed. Except for entering multivariate models, statistical significance was set at $P < 0.05$.

All baseline variables were entered into multivariate analysis, for which a backward stepwise multivariable logistic regression was performed to seek independent factors associated with each outcome. All variables maintaining a P value of 0.2 or less were included in the final model. Postoperative continuous infusion of fentanyl was forced into logistic models regardless of statistical significance because this was the primary variable of interest. Results are expressed as odds ratios and their 95 % confidence interval.

Results

In total, 219 patients underwent gynecologic laparoscopic surgery during the study period. After excluding the patients who received prophylactic antiemetics intraoperatively (21 patients) or received nitrous oxide as an anesthetic (3 patients), data from 195 eligible patients were analyzed. Among these, 42 patients received postoperative continuous intravenous infusion of fentanyl whereas 153

did not. The median rate of infusion among the patients who received postoperative continuous infusion of fentanyl was 40 μg/h (range, 25–60 μg/h). Table 1 shows the clinical characteristics of the study population stratified by use of postoperative continuous infusion of fentanyl. The age, height, proportion of emergent surgery, duration of surgery, proportion of total intravenous anesthesia (TIVA), and intraoperative fentanyl dose were significantly different between the groups.

In all, there were five (2.6 %) patients who could not ambulate on POD 1 (Table 2). Of these, three patients received postoperative continuous infusion of fentanyl. Rates of postoperative continuous infusion of fentanyl for these three patients were 50, 55, and 60 μg/h. Four of the five patients who could not ambulate on POD 1 experienced nausea or vomiting during the ambulatory challenge. The clinical characteristics of the study population and the univariate association with delayed ambulation are described in Table 3. After stepwise backward logistic regression analysis, age and the use of a continuous infusion of fentanyl were the variables that remained in the final model as independent predictors of delayed ambulation (Table 4). The adjusted odds ratio for postoperative continuous infusion of fentanyl was 8.37.

Table 1 Patient characteristics according to use of postoperative continuous infusion of fentanyl

	Group F ($n = 42$)	Group N ($n = 153$)	P value
Age	36 (14–51)	32 (14–66)	0.035
Height (cm)	154.8 (150–172)	155 (146–177.4)	0.039
BMI (kg/m^2)	20.5 (17.5–34)	20.1 (15.8–34.2)	0.326
ASA-PS 1/2/3	31/11/0	115/37/1	0.224
Emergency	1 (2.4)	24 (15.7)	0.022
Type of surgery			0.07
Ovarian cystectomy	26 (61.9)	95 (62.1)	
Salpingo-oophorectomy	2 (4.8)	11 (7.2)	
Myomectomy	9 (21.4)	11 (7.2)	
Cyst enucleation	2 (4.8)	4 (2.6)	
Pelvic adhesiolysis	1 (2.4)	4 (2.6)	
Others	1 (2.4)	5 (3.3)	
Duration of surgery (min)	151 (38–276)	112 (33–218)	0.024
TIVA	15 (35.7)	111 (72.6)	<0.001
Intraoperative fentanyl dose (μg)	50 (0–300)	150 (0–500)	<0.001

Group F represents patients who received postoperative continuous infusion of fentanyl

Group N represents patients who did not receive postoperative continuous infusion of fentanyl

BMI body mass index, *ASA-PS* American Society of Anesthesiologists classification of physical status, *TIVA* total intravenous anesthesia

Table 2 Patients who failed to ambulate on postoperative day 1

Patient	Group	Rate of postoperative continuous infusion of fentanyl (μg/h)	Symptoms associated with ambulation
1	F	50	Nausea, vomiting
2	F	55	Nausea, vomiting, dizziness
3	F	60	Nausea, vomiting, fatigue
4	N	–	Nausea, vomiting, headache
5	N	–	Headache

Group F represents patients who received postoperative continuous infusion of fentanyl

Group N represents patients who did not receive postoperative continuous infusion of fentanyl

In total, 24 (12.3 %) patients experienced OI. The clinical characteristics of the study population and univariate association with delayed ambulation are described in Table 5. After stepwise backward logistic regression analysis, anesthetics and use of continuous infusion of fentanyl were the variables that remained in the final model as independent predictors of OI (Table 6). The adjusted odds ratio for postoperative continuous infusion of fentanyl was 34.78.

In total, 86 (44.1 %) patients required rescue analgesics during the 24 h after extubation, and 19 (9.7 %) patients required rescue analgesics two or more times. The association between postoperative continuous infusion of fentanyl and the proportion of patients who needed rescue analgesics was not statistically significant ($P = 0.376$).

Discussion

The main findings of this study were that postoperative continuous infusion of fentanyl is strongly related to OI and is also related to delayed ambulation in patients after gynecologic laparoscopic surgery. In addition, this study found that OI was the major cause of delayed ambulation on POD 1 after gynecologic laparoscopic surgery. In contrast, we could not confirm the reduction in postoperative analgesic requirements by continuous infusion of fentanyl after such surgery.

Intravenous patient-controlled analgesia (IV-PCA) is commonly used as an option for postoperative pain control. Some studies have demonstrated that the addition of baseline continuous infusion to IV-PCA has no additive analgesic effect [12–14], and routine use of baseline infusion in IV-PCA is no longer recommended [15]. However,

Table 3 Univariate analysis of potential predictors of delayed ambulation

Variables	No delayed ambulation	Delayed ambulation	*P* value
Age	33 (14–66)	26 (14–35)	0.032
Height (cm)	159 (146–177)	165 (153–172)	0.292
BMI (kg/m^2)	20.4 (15.8–34.2)	19.9 (19.4–34)	0.393
ASA-PS 1/2/3	142/47/1	4/1/0	0.957
Emergency	24 (12.6)	1 (20)	0.627
TIVA	124 (65.3)	2 (40)	0.244
Dose of fentanyl (μg)	150 (0–500)	125 (50–200)	0.625
Duration of surgery (min)	120 (36–381)	164 (33–248)	0.788
Postoperative continuous infusion of fentanyl [*n* (%)]	39 (20.5)	3 (60)	0.034

BMI body mass index, *ASA-PS* American Society of Anesthesiologists classification of physical status, *TIVA* total intravenous anesthesia

Table 4 Independent predictors of delayed ambulation

Variables	Coefficient	SE	Adjusted odds ratio	*P* value
Intercept	0.28	1.87		
Age	−0.16	0.07	0.20 (0.043–0.697)	0.019
Postoperative continuous infusion of fentanyl	2.13	0.98	8.37 (1.23–72.15)	0.031

Intercept is a mathematical constant (no clinical interpretation)

Adjusted odds ratios are presented as estimates (95 % confidence interval)

SE standard error

Table 5 Univariate analysis of potential predictors of orthostatic intolerance (OI)

Variables	No OI	OI	*P* value
Age	33 (14–66)	32.5 (14–51)	0.87
Height (cm)	159 (146–177)	161 (151–172)	0.238
BMI (kg/m^2)	20.4 (15.8–34.2)	19.9 (17.5–34)	0.475
ASA-PS 1/2/3	129/41/1	17/7/0	0.806
Emergency	25 (14.6)	0 (0)	0.045
TIVA	113 (66.1)	13 (54.1)	0.253
Dose of fentanyl (μg)	150 (0–500)	100 (0–250)	0.0031
Duration of surgery (min)	116 (33–381)	144 (40–375)	0.0846
Postoperative continuous infusion of fentanyl [*n* (%)]	23 (13.5)	19 (79.2)	<0.0001

OI orthostatic intolerance, *BMI* body mass index, *ASA-PS* American Society of Anesthesiologists classification of physical status, *TIVA* total intravenous anesthesia

Table 6 Independent predictors of orthostatic intolerance

Variables	Coefficient	SE	Adjusted odds ratio	*P* value
Intercept	−4.04	0.67		
TIVA	0.82	0.58	2.27 (0.74–7.54)	0.15
Postoperative continuous infusion of fentanyl	3.55	0.62	34.78 (11.12–131.72)	<0.0001

Intercept is a mathematical constant (no clinical interpretation)

Adjusted odds ratios are presented as estimates (95 % confidence interval)

SE standard error, *TIVA* total intravenous anesthesia

under conditions where a computer-driven IV-PCA device is not available, continuous infusion of fentanyl may be an option for postoperative analgesia. To our knowledge, no previous study has investigated the association of postoperative continuous infusion of fentanyl with OI and delayed ambulation. Increase in the incidence of OI may have serious clinical implications. OI may lead to not only delayed ambulation but also syncope during ambulation, where it may cause falls. In this study, 3 of the 42 patients who received postoperative continuous infusion of fentanyl could not ambulate on POD 1. As the median rate of fentanyl infusion in this study was 40 μg/h, these 3 patients received fentanyl infusion at relatively high rates of infusion (50–60 μg/h). High rates of infusion may be the cause of OI and delayed ambulation. Although the study design cannot elucidate the mechanism of the association between postoperative continuous infusion of fentanyl and the development of OI or delayed ambulation, we speculate that secondary autonomic failure caused by opioids [7] or opioid-induced nausea and vomiting may have a role.

Pain has been recognized as an important limitation in early postoperative ambulation. Therefore, optimal treatment of postoperative pain is mandatory for enhanced recovery. However, use of opioids may also contribute to OI [16] and is associated with side effects, including nausea and vomiting, ileus, and respiration depression, all of which may inhibit ambulation. In this study, four of the five patients who could not ambulate on POD 1 experienced OI during the ambulatory challenge. In contrast, none of the patients failed to ambulate because of wound pain. These findings suggest that OI and not postoperative pain is the major cause of delayed ambulation after gynecologic laparoscopic surgery.

In this study, postoperative continuous infusion of fentanyl did not seem to be effective for prophylaxis of postoperative pain. Although pain scores were not available in this study, the facts that approximately 90 % of the patients needed none or only one rescue analgesic and that no patient failed to ambulate because of wound pain indicate that pain after gynecologic laparoscopic surgery is relatively mild.

The major limitation of this study is its retrospective design. This study represents data from one institution. We could not use the objective criteria (decrease in systolic arterial pressure >30 mmHg) as used by Jans et al. [10] for the identification of OI. In addition, pain scores were not available as an indicator of effectiveness of postoperative continuous infusion of fentanyl. In this study, postoperative continuous infusion of fentanyl was significantly associated with delayed ambulation; however, the number of patients with delayed ambulation was too small to conclude that postoperative continuous infusion of fentanyl is an independent predictor of delayed ambulation. Despite these limitations, these data provide new information regarding the incidence and risk factors for OI and delayed ambulation in patients after gynecologic laparoscopic surgery.

In conclusion, this study demonstrates that postoperative continuous infusion of fentanyl is associated with increased OI and delayed ambulation. Routine use of postoperative continuous infusion of fentanyl is not recommended after gynecologic laparoscopic surgery. Future studies are required to examine whether the results of this study are applicable to other populations or procedures.

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