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Orthostatic intolerance during early mobilization following video-assisted thoracic surgery

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Abstract

Purpose: Early postoperative mobilization is crucial for early ambulation to reduce postoperative pulmonary complications after lung resection. However, orthostatic intolerance (OI) may delay patient recovery, leading to complications. It is therefore important to understand the prevalence of and predisposing factors for OI, which have not been established following video-assisted thoracic surgery (VATS).This study evaluated the incidence of OI, impact of OI on delayed ambulation, and predisposing factors associated with OI in patients after VATS.

Methods: This retrospective cohort study consecutively analyzed data from 236 patients who underwent VATS. The primary outcome was defined as OI with symptoms associated with ambulatory challenge on postoperative day 1 (POD1), including dizziness, nausea and vomiting, feeling hot, blurred vision, or transient syncope. Multivariate logistic regression was performed to identify independent factors associated with OI.

Results: Of the 236 patients, 35.2% (83) experienced OI; 45.8% of these could not ambulate at POD1, compared with 15.7% of patients without OI ($P < 0.001$). Factors independently associated with OI included advanced age [odds ratio 2.83 (1.46‑5.58); $P = 0.002$], female gender [odds ratio 2.40 (1.31–4.46); $P = 0.004$], and postoperative opioid use [odds ratio 2.61 (1.23–5.77); $P = 0.012$]. Use of thoracic epidural anesthesia was not independently associated with OI [odds ratio 0.72 (0.38–1.37); $P = 0.318$].

Conclusion: Postoperative OI was common in patients after VATS and significantly associated with delayed ambulation. Advanced age, female gender, and postoperative opioid use were identified as independent predisposing factors for OI.

Introduction

Early ambulation following surgery is essential for early patient recovery. Otherwise, prolonged 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, such as optimized analgesia, early ambulation, and early return to normal diet, have been shown to improve postoperative outcomes in patients undergoing colorectal surgery [2–3]. However, postoperative orthostatic intolerance (OI) may delay ambulation and is characterized by symptoms such as dizziness, nausea and vomiting, feeling hot, blurred vision, and eventual syncope due to failed orthostatic cardiovascular regulation leading to a decrease in the arterial pressure, and cerebral hypoperfusion during standing [4]. Patients may be particularly vulnerable postoperatively to OI after ambulation because blood and fluid losses during surgery aggravate postural reduction in central blood volume while in the upright position. Transient inability to ambulate is observed after ambulatory surgery and is a major cause of prolonged hospital stay [5], and a high incidence of OI during early postoperative mobilization has been reported in patients after major surgery [6–8].

In thoracic surgery patients, postoperative pulmonary complications, including atelectasis, pulmonary infection, and respiratory failure, remain to be major clinical problems despite advances in surgical procedures and perioperative care [9]. A fast-track approach, such as early ambulation after lung resection, has been proposed in order to reduce postoperative pulmonary complications in patients undergoing lung resection [10]. Preventing OI and facilitating early ambulation are crucial components of the fast-track approach, but the incidence of OI during early ambulation and its impact on delayed ambulation after lung resection is unknown, and the predisposing factors associated with failed orthostasis are not

fully understood.

In a previous study [8], we identified continuous postoperative intravenous infusion of fentanyl as an independent predisposing factor for OI following gynecologic laparoscopic surgery. However, we could not examine the effect of gender and epidural anesthesia on OI in the previous study. Although thoracic epidural anesthesia is commonly considered the “gold standard” for post-thoracotomy analgesia [11] and is widely used in thoracic surgery, epidural administration of local anesthetics may theoretically induce OI through sympathectomy-induced vasodilation. The effect of thoracic epidural anesthesia on the incidence of OI has not been clarified.

The primary aim of this study was to determine the incidence of OI during early postoperative mobilization and its impact on delayed ambulation in patients undergoing video-associated thoracic surgery (VATS) for lung tumor resection. In addition, we examined the predisposing factors associated with OI. We were especially interested in evaluating the effect of epidural anesthesia on the incidence of OI.

Materials and Methods

This retrospective cohort study included patients who underwent VATS for lung tumor resection at Kyoto University Hospital from November 1, 2010 to October 31, 2011. Approval was obtained from the ethics committee of Kyoto University Hospital. Exclusion criteria were conversion to open thoracotomy (any incision extending beyond 15 cm) and postoperative admission to the intensive care unit. Data on patient characteristics (age at surgery, gender, height, body mass index, history of postoperative nausea and vomiting (PONV) or motion sickness, smoking status, and American Society of Anesthesiologists physical status), surgery (type of lung tumor, duration of surgery, and blood loss), anesthesia or analgesia (anesthetic agents and use of thoracic epidural anesthesia, intercostal nerve block, and postoperative opioids), and recovery profile (pain score and adverse events) were retrieved from the medical records of these patients.

Selection of anesthetics and use of thoracic epidural anesthesia were left to the discretion of the attending anesthesiologist. Postoperative opioid use included continuous postoperative intravenous infusion of fentanyl and continuous postoperative epidural infusion of fentanyl combined with local anesthetics. For intravenous infusion of fentanyl, a Coopdech Syrinjector PCA Set (Daiken Medical Co., Ltd., Osaka, Japan) was used. Basal infusion rate was 1 ml/h, and bolus volume was 1 ml with a 10-min lockout time. For epidural infusion of fentanyl combined with local anesthetics (ropivacaine 0.2%), a Coopdech Balloonjector (Daiken Medical Co., Ltd.) was used. The infusion rate could be adjusted to 2, 4, and 6 ml/h.

At the institution where the study was conducted, the patients were asked to stand up and walk in the morning and evening of postoperative day 1 (POD1). The patients were encouraged to walk around the ward (approximately 50 meters). A physical therapist recorded

each patient’s walking ability and also the symptoms experienced by the patient during the attempt to stand up and walk.

The primary outcome of interest was defined as OI. 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 POD1. The symptoms as described in previous studies [6–8] were used as the basis for identification of OI; however, we could not use the objective criteria (decrease in systolic arterial pressure > 30 mmHg) as used by Jans et al. [7] because this was a retrospective study. Ambulation was considered to be delayed if the patient could not walk around the ward without assistance on POD1. For patients with delayed ambulation, data on reasons for delayed ambulation were also collected.

Statistical analysis

Data were analyzed using JMP version 8.0 (SAS Institute Japan Ltd., Tokyo, Japan). The data are presented as median (interquartile 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 $P < 0.05$.

The covariates considered in the multivariate models included age (less than 75 years, 75 or more years), gender, body mass index (less than 30 kg/m^2, at least 30 kg/m^2), history of PONV or motion sickness, smoking status, and American Society of Anesthesiologists physical status (1,2, or 3), duration of surgery (less than 4 h, 4 h or more), blood loss (less than 200 ml, at least 200 ml), anesthetics used, use of thoracic epidural anesthesia, and

postoperative opioid use. All covariates were entered into multivariate analysis for which a backward stepwise multivariable logistic regression was performed to seek independent factors associated with OI. All variables maintaining a *P* value of ≤0.1 were included in the final model. Use of epidural anesthesia was forced into logistic models regardless of the statistical significance because this was the primary variable of interest.

Results

A total of 240 patients underwent VATS during the study period. After excluding three patients whose operation was converted to open thoracotomy and one patient who was admitted to intensive care unit after operation, data from 236 eligible patients were analyzed. Patients had a median (range) age of 68 (30–85) years, weight (range) 58 (37–104) kg, and height (range) 167 (138–183) cm, and 99 (41.9%) patients were female.

Eighty-three (35.2 %) patients experienced OI and 62 (26.3 %) patients could not ambulate on POD1; 45.8% of patients with OI could not ambulate at POD1, compared to 15.7% of patients without OI ($P < 0.001$). Among 62 patients who could not ambulate on POD1, 38 (61.3 %) patients experienced OI during ambulation challenge. The reasons for delayed ambulation are described in Table 1. Thirty-three (53.2%) patients failed to ambulate because of OI symptoms (nausea, vomiting, dizziness, or syncope), and seven (11.3%) patients failed to ambulate because of wound pain.

The clinical characteristics of the study population and the univariate association with OI are described in Table 2. After stepwise backward logistic regression analysis, the variables that remained in the final model as independent predictors of OI were advanced age [odds ratio 2.83 (1.46–5.58); $P = 0.002$], female gender [odds ratio 2.40 (1.31–4.46); $P = 0.004$], and postoperative opioid use [odds ratio 2.61 (1.23–5.77); $P = 0.012$] (Table 3). Use of thoracic epidural anesthesia was not independently associated with OI [odds ratio 0.72 (0.38–1.37); $P = 0.318$].

Because intravenous opioid and epidural opioid may have different effects on OI and delayed ambulation, we compared the incidence of OI and delayed ambulation among three groups

(no postoperative opioid, postoperative intravenous opioid, and postoperative epidural opioid) (Table 4). One hundred and twelve patients received continuous postoperative intravenous infusion of fentanyl with the median rate of infusion of 25 μg/h (range: 8.3–48.1 μg/h). The Coopdech Syrinjector PCA Set, the device used for continuous postoperative intravenous infusion of fentanyl, was designed for patient-controlled analgesia, and the bolus dose was requested at median (range) 0 (0–6) times 24 h postoperatively. Fifty-three patients received continuous postoperative epidural infusion of fentanyl with the median rate of infusion of 13.3 μg/h (range: 1.4–30.2 μg/h). The incidence of OI was higher in patients who received intravenous (44.6%) or epidural (35.9%) infusion of fentanyl than in patients who received no postoperative opioids (19.7%).

Discussion

The primary aim of this study was to determine the incidence of OI during ambulation challenge after VATS. We found that as high as 35.2% of patients experienced OI during the ambulation challenge on POD1. The incidence of OI on POD1 in this study was higher than that reported in previous reports (12%–19 %) [6–8]. In addition to the difference in patient characteristics or surgical procedure, continuous postoperative administration of fentanyl may account for the relatively high incidence of OI. We also found that OI was significantly associated with delayed ambulation and that symptoms of OI were the main causes of delayed ambulation after VATS. In contrast, wound pain was not a leading cause of delayed ambulation. Because OI was the major cause of delayed ambulation after VATS, it is essential to ameliorate OI to facilitate recovery.

Although the definition of OI includes PONV during ambulation challenge and PONV is widely used to assess the symptoms among postoperative patients, we used OI instead of PONV to assess symptoms during ambulation challenge in this study. There are two reasons for this. First, the authors considered that the symptoms which are not recognized as PONV (dizziness and blurred vision) are also important because they also make patients discomfort and may delay ambulation. In fact, among 83 patients who experienced OI on POD1, 31 (37.3%) patients were judged not to have PONV. Second, PONV includes nausea and vomiting that is not associated with ambulation (for example, PONV immediately after extubation). The authors considered that identifying ambulation-associated symptoms is important to facilitate ambulation.

We identified postoperative opioid use as an independent predisposing factor for OI after

VATS. This result is consistent with our previous study, which reported that postoperative opioid infusion (median infusion rate: 40 μg/h) is associated with OI in patients after gynecologic laparoscopic surgery [8]. Although the infusion rate of fentanyl in the present study (median infusion rate: 25 μg/h for intravenous infusion, 13.3 μg/h for epidural infusion) was lower than that in the previous study, there was a significant association between postoperative infusion of fentanyl and OI. In contrast to the previous study in which only postoperative opioid infusion was identified as a predisposing factor for OI, advanced age and female gender were also identified as independent predisposing factors for OI in the present study. We suspect that the previous study could not identify advanced age as a predisposing factor for OI because it did not include aged people (the oldest patient was 66 years old, and 96% of the patients were less than 50 years old).

Two of the three predisposing factors for OI identified in this study, viz., female gender and postoperative opioid use, are also known as predisposing factors for PONV [12]. In addition, although it was not statistically significant, history of PONV or motion sickness, which is also one of the well-known predisposing factors for PONV, seemed to be associated with OI (P value = 0.075). We suspect that OI is caused, at least in part, by common mechanism as that of PONV.

Although epidural administration of local anesthetics may theoretically induce OI through sympathectomy-induced vasodilation, the use of thoracic epidural anesthesia itself was not associated with OI during the ambulation challenge in this study. This result suggests that continuous postoperative epidural administration of ropivacaine 0.2% at 2–6 ml/h does not induce clinically significant vasodilation.

The results of this study suggest that epidural as well as intravenous infusion of fentanyl

causes OI. The mechanism of analgesia after epidural administration of fentanyl is considered to be primarily systemic, and epidural administration of fentanyl can cause systemic adverse effects such as sedation, respiratory depression, pruritus, nausea, and vomiting [13]. It is reasonable to consider that epidural infusion of fentanyl has the same effect on OI as intravenous infusion. Although thoracic epidural analgesia with local anesthetics and opioids is recommended for post-thoracotomy analgesia [11], epidural opioids may provide less benefit to the patients undergoing VATS because VATS is associated with less postoperative pain [14]. The balance of benefit and harm needs to be considered when using epidural opioids after VATS.

We found that postoperative opioid infusion is significantly associated with OI and may delay ambulation after VATS. In contrast, it was difficult to determine the analgesic efficacy of postoperative opioid infusion in this study. To the best our knowledge, there are no previous studies that compared the analgesic efficacy of postoperative opioid infusion with that of other reported pain treatments for VATS, i.e., nonsteroidal anti-inflammatory drugs, paravertebral block with local anesthetics, and surgical wound infiltration [15–17]. If one of these pain treatments or their combinations have equivalent analgesic efficacy to postoperative opioid infusion, using them instead of postoperative opioid infusion may reduce OI and facilitate early ambulation. Future studies are required to seek an optimal analgesic strategy after VATS.

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. [7] for the identification of OI. Despite these limitations, these data provide new information regarding the incidence and predisposing factors for OI

and delayed ambulation in patients after VATS.

In conclusion, the present study found a high incidence (35.2 %) of OI during ambulation challenge on POD1 after VATS and significant association between OI and delayed ambulation. Three independent predisposing factors for OI (advanced age, female gender, and postoperative opioid use) were identified. Multimodal opioid-sparing postoperative pain management may reduce the incidence of OI, and therefore facilitate early ambulation and rapid recovery.

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Tables

Table 1 Reasons for Delayed Ambulation

Symptoms	No. of patients	Proportion (%)
Nausea or vomiting	28	45.2
Wound pain	7	11.3
Dizziness	4	6.5
Fatigue	4	6.5
Dyspnea	2	3.2
Syncope	1	1.6
Other	16	25.8
Total	62	100

Table 2 Univariate Analysis of Potential Predictors of Orthostatic Intolerance

Variable	No OI (n = 153)	OI (n = 83)	*P* value
Age	68 (61–73)	71 (64–77)	0.020
Female gender	54 (35.3%)	45 (54.2%)	0.005
Height (cm)	163.2 (157–168.2)	160 (152–165.3)	0.007
BMI (kg/m^2)	22.1 (20.3–24.7)	22.5 (20.4–24.1)	0.758
ASA-PS (1/2/3)	41/97/15	18/61/4	0.219
Current smoker	22 (14.4%)	11 (13.3%)	0.812
History of PONV or MS	20 (13.1%)	24 (28.9%)	0.003
Metastatic / primary	43/110	11/72	0.010
Duration of surgery (min)	174 (111–234)	183 (143.5–223.5)	0.385
Bleeding (ml)	25 (0–76.5)	30 (0–82)	0.605
TIVA	41 (26.8%)	31 (37.3%)	0.093
Epidural anesthesia	81 (52.9%)	32 (38.6%)	0.035
Postoperative opioid use	96 (62.7%)	69 (83.1%)	0.001

Continuous variables were presented as a median (inter-quartile range), and categorical variables were presented as a number (percentage).

OI, orthostatic intolerance; *BMI*, body mass index; *ASA-PS*, American Society of Anesthesiologists classification of physical status; *PONV*, postoperative nausea and vomiting; *MS*, motion sickness; *TIVA*, total intravenous anesthesia

Table 3 Multivariate Analysis of Independent Predisposing Factors of Orthostatic Intolerance

Variables	Coefficient	SE	Adjusted odds ratio	*P* value
Intercept	−1.96	0.46	-	<0.001
Advanced age	1.04	0.34	2.83 (1.46–5.58)	0.002
Female gender	0.87	0.31	2.40 (1.31–4.46)	0.004
History of PONV or MS	0.65	0.37	1.93 (0.93–4.00)	0.075
Postoperative opioid use	0.96	0.39	2.61 (1.23–5.77)	0.012
Use of epidural anesthesia	−0.33	0.33	0.72 (0.38–1.37)	0.318

Intercept is a mathematical constant (no clinical interpretation). *SE*, standard error; *PONV*, postoperative nausea and vomiting; *MS*, motion sickness

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

Table 4 Recovery Profile by Route of Postoperative Fentanyl Infusion

	No postoperative opioids (n = 71)	Postoperative epidural opioids (n = 53)	Postoperative intravenous opioids (n = 112)
Rate of fentanyl infusion (μg/h)	-	13.3 (10–16.7)	25 (20–30)
Use of epidural anesthesia	58 (81.7)	53 (100)	2 (1.8)
Use of intercostal nerve block	5 (7.0)	0 (0)	47 (42.0)
OI	14 (19.7)	19 (35.9)	50 (44.6)
Delayed ambulation	13 (18.3)	18 (34.0)	31 (27.7)
Pain at rest	1 (0–3)	0 (0–3)	2 (0.25–3)
Pain on movement	3 (1–6)	2 (0–5)	5 (3–6)

Continuous variables were presented as a median (inter-quartile range), and categorical variables were presented as a number (percentage).

OI, orthostatic intolerance

Pain at rest and pain on movement was assessed using 11-point-numeric rating scale on postoperative day 1.