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Original Article

Survival analysis of postoperative nausea and vomiting in patients receiving patient-controlled epidural analgesia

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Abstract

Background: Postoperative nausea and vomiting as well as postoperative pain are two major concerns when patients undergo surgery and receive anesthetics. Various models and predictive methods have been developed to investigate the risk factors of postoperative nausea and vomiting, and different types of preventive managements have subsequently been developed. However, there continues to be a wide variation in the previously reported incidence rates of postoperative nausea and vomiting. This may have occurred because patients were assessed at different time points, coupled with the overall limitation of the statistical methods used. However, using survival analysis with Cox regression, and thus factoring in these time effects, may solve this statistical limitation and reveal risk factors related to the occurrence of postoperative nausea and vomiting in the following period.

Methods: In this retrospective, observational, uni-institutional study, we analyzed the results of 229 patients who received patient-controlled epidural analgesia following surgery from June 2007 to December 2007. We investigated the risk factors for the occurrence of postoperative nausea and vomiting, and also assessed the effect of evaluating patients at different time points using the Cox proportional hazards model. Furthermore, the results of this inquiry were compared with those results using logistic regression.

Results: The overall incidence of postoperative nausea and vomiting in our study was 35.4%. Using logistic regression, we found that only sex, but not the total doses and the average dose of opioids, had significant effects on the occurrence of postoperative nausea and vomiting at some time points. Cox regression showed that, when patients consumed a higher average dose of opioids, this correlated with a higher incidence of postoperative nausea and vomiting with a hazard ratio of 1.286.

Conclusion: Survival analysis using Cox regression showed that the average consumption of opioids played an important role in postoperative nausea and vomiting, a result not found by logistic regression. Therefore, the incidence of postoperative nausea and vomiting in patients cannot be reliably determined on the basis of a single visit at one point in time.

Keywords: epidural analgesia; logistic models; patient-controlled analgesia; postoperative nausea and vomiting; survival analysis

1. Introduction

Postoperative nausea and vomiting and postoperative pain are two major concerns in patients receiving surgeries and anesthetics.[1] Frequently, postoperative nausea and vomiting occurs in patients receiving general, regional, or local anesthesia and causes significant suffering.[2–4] Sometimes, patients prefer to endure postoperative pain rather than receive opioids that may result in postoperative nausea and vomiting,[5] and

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may even voluntarily pay more to obtain effective antiemetic therapies.[6]

Previous studies attempted to investigate the incidence and risk factors of postoperative nausea and vomiting using different predictive models.[7–10] However, the incidences of postoperative nausea and vomiting explored in previous studies ranged from 10% to 30% in general anesthesia[2,11–14] and from 3.2% to 34% in patients receiving patient-controlled epidural analgesia.[15–21] This disparity may be attributable to the different time points used when the patients were visited. Postoperative nausea and vomiting could occur several minutes, hours, or even days after anesthesia. If the investigation of postoperative nausea and vomiting is limited to a specified time point, the analysis will be confounded.

In this study, we analyzed the information obtained by repeatedly visiting the patients to explore the risk factors and incidence of postoperative nausea and vomiting, and assessed the effects of time points, which have rarely been discussed in the literature. When considering the effects of time, survival analysis was applied to analyze the occurrence of postoperative nausea and vomiting. We compared the results obtained by logistic regression to those determined by survival analysis to elucidate the differences between the two statistical methods. This research may contribute to a clearer understanding of the incidence of postoperative nausea and vomiting.

2. Methods

In this retrospective, observational, uni-institutional (a medical center in central Taiwan) study, we analyzed the results of 229 patients receiving postsurgical patient-controlled epidural analgesia from June 2007 to December 2007. Ethical approval was obtained from the Institutional Review Board of Taichung Veterans General Hospital. The data were reviewed for patients receiving general anesthesia for the following surgeries: (1) upper abdomen surgery; (2) lower abdomen surgery; and (3) chest surgery. The composition prescription in patient-controlled epidural analgesia consists of bupivacaine (0.1%) and fentanyl (1.5 μg/mL) in normal saline (500 mL). We collected data including age, sex, body mass index, types of surgery, the setting of patient-controlled analgesia pumps, total dosage (mL) and average dosage (mL/hour) of patient-controlled epidural analgesia, and the time point of postoperative nausea and vomiting occurrence.

In our institution, patients were visited five times over a 3-day period of patient-controlled epidural analgesia use, and the five time points were as follows: (1) the first visit on operation day (OPD-1); (2) the second visit on operation day (OPD-2); (3) the third visit on the 1st postoperative day (POD-1-1); (4) the fourth visit on the 1st postoperative day (POD-1-2); and (5) the fifth and final visit on the 2nd postoperative day (POD-2). If the patient had used patient-controlled epidural analgesia on the first visit, the zero time point was backtracked by calculating the average dosage on the first visit.

When patients were receiving patient-controlled epidural analgesia, we followed up the patients and adjusted the depth of the epidural catheter or the dosage of medications according to the patients' pain intensity at rest and in motion after surgeries. Our goal was to keep the patients' pain intensity below 3 at rest and below 5 in motion by using the numeric rating scale (where 0 = no pain and 10 = most intense pain imaginable). When analgesia in the required dermatome failed or was found to be inadequate, the type of pain management would be changed to other regimens such as intravenous patient-controlled analgesia. Consequently, these patients were not included in this study.

IBM SPSS Statistics 20 (IBM SPSS Inc. Chicago, IL, USA) was used to analyze these data. The Cox proportional hazards model (Cox model) was used to determine the correlations between variables and survival time to calculate the odds ratio of the risk factors. When patients suffered from postoperative nausea and vomiting in the following periods, it was defined as the occurrence of an event. Survival time was outlined as the time duration until the occurrence of postoperative nausea and vomiting. If an event did not occur in the following period, then the patient was assumed to be censored. We also applied logistic regression to analyze the correlations between variables and the incidences of postoperative nausea and vomiting at specific time points, and compared the results with those obtained using the Cox model. Both in the Cox model and logistic regression, the forward likelihood ratio was used to identify significant variables. A p value <0.05 was considered significant.

3. Results

A total of 229 patients received patient-controlled epidural analgesia for postoperative pain control between June 2007 and December 2007. The demographic data of the patients are shown in Table 1. The settings of patient-controlled analgesia pumps were as follows: bolus dosage, 4.38 ± 0.94 mL; continuous infusion dosage, 4.25 ± 1.18 mL; lockout time, 17.9 ± 4.6 minutes; and 4-hour upper limit dosage, 46.8 ± 11.25 mL. In patients with and without postoperative nausea and vomiting, the average total dosage of patient-controlled analgesia was 106.5 ± 91.73 mL versus 279.2 ± 98.85 mL and the duration of patient-controlled analgesia use was 16 ± 14.4 hours versus 46.7 ± 6 hours, respectively. The overall incidence of postoperative nausea and vomiting was 35.4% (Table 1), and ranged from 5.5% to 17.6% at five different time points (Table 2). The highest incidence of postoperative nausea and vomiting was noted at the third visit on postoperative Day 1 (POD-1-1); the lowest was found at OPD-1 (Table 2).

Before logistic regression was applied to explore the risk factors for incidence of postoperative nausea and vomiting in patients with patient-controlled epidural analgesia, univariate analysis of candidate variables was performed. These results, as provided in Table 3, revealed that age, sex, height, and surgical sites may play significant roles in predicting the occurrence of postoperative nausea and vomiting in POD-1-1, POD-1-2, or POD-2.

At three time points (POD-1-1, POD-1-2, and POD-2), sex was found to have a significant influence on the occurrence of

Table 1
Demographic data.

Characteristic	Sex (M/F)	143/86
	Age (y)	58.71 (16.88)
	Height (cm)	161.71 (8.14)
	Weight (kg)	60.3 (10.53)
	BMI	23.02 (3.36)
Event	(1/0)[a]	81/148
Surgical site	Chest	102
	Thoracotomy	40
	Esophageal surgery	16
	Thymus surgery	2
	Thoracoscopic surgery	8
	Other chest surgery	36
	Upper abdomen	95
	Esophageal surgery	1
	Liver surgery	43
	Gastric surgery	18
	Open cholecystectomy	8
	Other upper abdomen surgery	25
	Lower abdomen	32
	Colorectal surgery	13
	Nephrectomy	8
	Cystectomy	3
	Other lower abdomen surgery	8

Numbers found in parentheses represent standard deviations.
BMI = body mass index; F = female; M = male.
[a] Event: 1 = the occurrence of postoperative nausea and vomiting in the following periods; 0 = no occurrence of postoperative nausea and vomiting in the following periods.

postoperative nausea and vomiting (Table 4). Female patients appeared to be more likely (3.013, 2.790, and 3.015 times) to suffer from postoperative nausea and vomiting than male patients at these three time points. In addition, the surgical sites of the patients were noted to have an effect on the occurrence of postoperative nausea and vomiting at POD-1-2 and POD-2 (Table 4). Patients undergoing surgeries in the upper abdomen may have a higher risk of developing postoperative nausea and vomiting than those receiving surgeries in the chest, and the odds ratios were 4.490 and 4.834, respectively, at the above mentioned time points.

Cox regression was used to analyze the risk factors of postoperative nausea and vomiting incidence in patients with patient-controlled epidural analgesia based on the time to occurrence of events (Table 5). The result in step 1 shows that the greater the total dosage of opioids, the lower the risk of postoperative nausea and vomiting with a hazard ratio of 0.988. In the final steps, a higher average dose of opioids consumed was correlated with a higher incidence of postoperative nausea and vomiting, with a hazard ratio of 1.286. Furthermore, female patients were more likely (a hazard ratio of 2.501) to suffer from postoperative nausea and vomiting than male patients, and patients with a higher body mass index were at a higher risk of suffering from postoperative nausea and vomiting, with a hazard ratio of 1.103.

4. Discussion

In this study, the overall incidence of postoperative nausea and vomiting was 35.4%, which was higher than the results found by previous studies.[2,11–14] The incidence of postoperative nausea and vomiting varied with time and ranged from 5.5% to 17.6% at five different time points (Table 2). We explored the total occurrence of events through five time points, which would make the investigation more comprehensive than by only following up the patients at a single time point, and thus a higher incidence of postoperative nausea and vomiting was obtained. The disparity between the incidences of postoperative nausea and vomiting at five time points may reflect the inconsistent results from previous investigations owing to the different visiting time points used in each study.[2,11–14]

Results of analyses by logistic regression showed that female patients were more likely (approximately 3 times more) to suffer from postoperative nausea and vomiting than male patients at three time points (Table 4). The total doses and the average dose of opioids were not found to have a significant effect on the occurrence of postoperative nausea and vomiting. The results support the notion that the risk factors of postoperative nausea and vomiting identified by logistic regression could be affected by different time points and may therefore result in conflicting findings.[7–10,22]

Although other statistical techniques such as generalized estimating equation or mixed model could be applied to analyze the data collected repeatedly, our focus was on the occurrence of postoperative nausea and vomiting and the duration until the occurrence of the first event. Therefore, we applied the Cox proportional hazards model to analyze the factors with respect to time to occurrence of postoperative nausea and vomiting. The results showed that in addition to sex, which was found by logistic regression, body mass index and the average and total dose of opioids were also found to play significant roles in the occurrence of postoperative nausea and vomiting (Table 5).

Several studies have shown that consumption of postoperative opioids was one of the risk factors related to the occurrence of postoperative nausea and vomiting[23,24]; however, other studies did not support this conclusion.[7,25,26] Very few studies have investigated the relationship between the dosage of opioids and the occurrence of postoperative nausea and vomiting, factoring in the time effects.[27] The inconsistent findings may be attributable to the limitations of logistic regression and the use of different visiting time points. The results showed that patients requiring larger doses of opioids were less likely to suffer from postoperative nausea and vomiting (Table 5), which may be attributable to the time factor. Therefore, the average dose of opioids instead of the total dosage of opioids consumed by patients could account for this phenomenon.

The above results indicate that investigations of risk factors and the incidence of postoperative nausea and vomiting may be influenced by the visiting time points and the use of statistical methods. Analysis of the data to predict postoperative nausea and vomiting by logistic regression focuses on the finding of the risk factors at a definite time point. In this study, we found that the risk factors and incidence of postoperative nausea and vomiting investigated by logistic regression

Table 2
Incidences of postoperative nausea and vomiting at different time points.

Time point	%
OPD-1	5.5
OPD-2	14.2
POD-1-1	17.6
POD-1-2	11.0
POD-2	9.8

OPD-1 = the first visit on operation day; OPD-2 = the second visit on operation day; POD-1-1 = the third visit on the 1st postoperative day; POD-1-2 = the fourth visit on the 1st postoperative day; POD-2 = the fifth and final visit on the 2nd postoperative day.

changed between different time points. Using the predictive models established by logistic regression, we may suggest to a patient that there is no need for prophylaxis for postoperative nausea and vomiting at a specific time point such as the 1st postoperative day. However, the patient may experience postoperative nausea and vomiting on the 2nd postoperative day because the condition of the predictive models changed.

If we hope to survey the risk factors of postoperative nausea and vomiting during the entire course of follow up, and not only at any one time point, application of the Cox regression model may be more optimal than the conventional logistic regression. By using this approach, we may achieve a more comprehensive prophylaxis of the postoperative nausea and vomiting. Cox regression has seldom been used to investigate the occurrence of postoperative nausea and vomiting, but it has presented a different viewpoint that did not conflict with the results found in previous studies analyzed with logistic regression.[23,28]

The average consumption of opioids was proven to be an important factor in the occurrence of postoperative nausea and vomiting during the following course of treatment, and this finding may further support the use of multimodal pain control. Use of gabapentin or nonsteroidal anti-inflammatory drugs would reduce the consumption of opioids and may lead to a decreased occurrence or severity of postoperative nausea and vomiting.[29,30] There is reason to believe that these strategies would offer better postoperative care.

Standl et al[3] and Pusch et al[4] discovered that patients receiving general anesthesia were more likely to suffer from postoperative nausea and vomiting than patients receiving regional anesthesia. Wilhelm et al[14] concluded that the sites and types of surgeries may influence the incidence of postoperative nausea and vomiting. In order to decrease the effect of confounding factors, we surveyed the patients receiving general anesthesia for just three types of surgery: upper abdomen, lower abdomen, and chest surgeries. Patients with different surgeries may suffer from various intensities of postoperative pain, but they would optimize their postoperative analgesia by using epidural patient-controlled analgesia.[31,32] Therefore, the occurrence of postoperative nausea and vomiting may be analyzed more discriminatively and predictably by investigating the individualized doses of analgesia regimen consumed than by exploring the effects of different surgeries. Most studies[23,24] that sought to predict the occurrence of postoperative nausea and vomiting comprised only the types of surgeries involved. They frequently lacked information about the detailed surgical methods that would make the analysis results relevant not only for a specific surgery, but also more broadly applicable to more generalized procedures.

Table 3
Univariate analysis of variables predicting the occurrence of postoperative nausea and vomiting by logistic regression.

Time point	POD-1-1	POD-1-2	POD-2
Age (y)	0.243	0.005	0.061
Sex (M/F)	0.004	0.02	0.014
Height (cm)	0.035	0.035	0.013
Weight (kg)	0.73	0.74	0.68
BMI	0.30	0.057	0.204
Surgical site	0.77	0.003	0.022
Dose (mL)	0.177	0.862	0.989
Average dose (mL/h)	0.852	0.98	0.431

The data represent p values from either Student t test or Chi-square test.
BMI = body mass index; F = female; M = male; POD-1-1 = the third visit on the 1st postoperative day; POD-1-2 = the fourth visit on the 1st postoperative day; POD-2 = the fifth and final visit on the 2nd postoperative day.

Table 4
Risk factors of postoperative nausea and vomiting in patients with patient-controlled epidural analgesia analyzed by logistic regression.

Time point	Sex[a]	Surgical site	
		Chest	Upper abdomen
POD-1-1	3.013 (1.451–6.260)*	1	
POD-1-2	2.790 (1.064–7.315)*	1	4.490 (1.394–14.456)*
POD-2	3.015 (1.143–7.952)*	1	4.834 (1.518–15.394)*

Only variables exhibiting significant effects in the occurrence of postoperative nausea and vomiting are exhibited in the table.
The numbers represent odds ratio values; numbers found within parentheses represent 95% confidence intervals.
*$p < 0.05$.
POD-1-1 = the third visit on the 1st postoperative day; POD-1-2 = the fourth visit on the 1st postoperative day; POD-2 = the fifth and final visit on the 2nd postoperative day.
[a] The reference group comprises the male patients.

Table 5
Risk factors of postoperative nausea and vomiting in patients with patient-controlled epidural analgesia analyzed by Cox regression.

	Variables	Hazard ratio*	95% CI
Step 1	Dose (mL)	0.988	0.985–0.990
Step 2	Average dose (mL/h)	1.293	1.214–1.377
	Dose (mL)	0.983	0.980–0.986
Step 3	Sex[a]	2.479	1.495–4.109
	Average dose (mL/h)	1.293	1.213–1.378
	Dose (mL)	0.982	0.978–0.985
Step 4	Sex[a]	2.501	1.507–4.151
	BMI	1.103	1.022–1.189
	Average dose (mL/h)	1.286	1.207–1.370
	Dose (mL)	0.981	0.978–0.985

Only variables exhibiting significant effects in the occurrence of postoperative nausea and vomiting are exhibited in the table.
*$p < 0.05$.
BMI = body mass index; CI = confidence interval.
[a] The reference group comprises the male patients.

The present study was a retrospective investigation, and the patient-controlled epidural analgesia data were collected from the patients' medical records. Previous studies revealed various risk factors for postoperative nausea and vomiting, including a history of smoking, motion sickness, postoperative nausea, and vomiting[7–10] which could not be collected by reviewing the patient charts in the present study. Another limitation in the present retrospective study was that we did not include in the analyses the opioids used in anesthesia and the rescue or extra opioids administered in the ward.

In conclusion, a wide variation of the risk factors and the incidence of postoperative nausea and vomiting may exist because patients were assessed at different time points, coupled with the overall limitation of statistical methods. Visiting patients at different time points and using Cox regression that could factor in the time effects would allow researchers to explore the investigation of postoperative nausea and vomiting more comprehensively. Multimodal pain management and prophylaxis treatment of postoperative nausea and vomiting could offer better postoperative care.

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