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Original Article

An investigation on influential factors of patient-controlled epidural analgesic requirement over time for upper abdominal surgeries

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Abstract

Background: Patient-controlled epidural analgesia (PCEA) is commonly used to relieve postoperative pain for upper abdominal surgeries. However, there is still a lack of studies exploring factors associated with PCEA consumption over time after upper abdominal surgery; our study intended to provide further elucidation about this issue.

Methods: This study retrospectively evaluated postoperative PCEA consumption over time after upper abdominal surgery. Cumulative PCEA consumption in the first four 12-hour intervals was directly retrieved from the data recorded by infusion pumps. Potentially influential factors of PCEA requirements, including demographic variables and infusion pump settings, were also collected. A linear mixed model was applied to investigate the relationships between these factors and PCEA consumption over time. A backward elimination strategy was used to select independent factors significantly associated with PCEA consumption.

Results: A total of 1001 patients were included in the analysis. On average, PCEA consumption after upper abdominal surgery peaked during the 2nd 12-hour interval and then decreased gradually over time. After the model selection processes were completed, four independent factors were identified to have significant effects on PCEA consumption. Surgery for malignant disease and background infusion rate were positively associated with PCEA consumption and did not interact with time. Additionally, female patients tended to consume less and less PCEA over time relative to males. Age had a negative effect on PCEA consumption, which peaked during the 2nd 12-hour interval and then decreased gradually over time. The final selected model exhibited acceptable predictive power relative to the observed data.

Conclusion: Our analyses provided valuable information about the factors associated with PCEA consumption over time after upper abdominal surgery. However, the mechanism of how these factors interact over the course of time awaits further investigation.

Keywords: general anesthesia; linear mixed model; patient-controlled epidural analgesia; upper abdominal surgery

1. Introduction

Postoperative pain management promotes patient comfort, improves postoperative outcome, and can be regarded as one of the most important parts of perioperative care.[1–5] Patient-controlled epidural analgesia (PCEA) has been effectively used for postoperative pain management for decades.[6] It appears that postoperative pain management with PCEA has the advantage of better analgesia,[7–10] fewer side effects and less complications,[3,10] reduced suppression of lymphocyte proliferation, as well as attenuation of the proinflammatory cytokine response in the postoperative period.[11] Many studies have demonstrated that, compared with postoperative intravenous patient-controlled analgesia (IVPCA), PCEA has vigorous benefits and superior analgesic effects,[7,12,13] particularly after upper abdominal and thoracic surgery.[12–14] Mann et al[12] have reported that after major abdominal surgery in elderly patients, PCEA using local anesthetics and an opioid provided better pain relief and improved mental status and bowel activity than IVPCA. Meierhenrich et al[14] also demonstrated that in patients undergoing lung surgery, PCEA is superior to IVPCA

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with respect to postoperative pain control and restoration of pulmonary function.

Nevertheless, there are still some risks involved with PCEA, such as catheter-associated neurological complications and potential respiratory depression, hypotension, and motor blockade, which may compromise postoperative mobilization or delay patient recovery.[10,15,16] These side effects are considered to be principally attributable to skill technique problems, drug overdose, and drug interactions.[10] In order to avoid these drawbacks, judicious determination and adjustment of PCEA dosage during the course of administration is essential. Although some studies had investigated factors associated with postoperative PCEA demand,[17–20] there is still a lack of studies that examine how these factors interact with time on PCEA demand, particularly in patients receiving upper abdominal surgery. Accordingly, this retrospective study aimed to investigate PCEA consumption over time after upper abdominal surgery and explore how influential factors of PCEA consumption interacted with time. A more comprehensive picture of and dynamic features involved with the relationships between PCEA consumption over time and its influential factors could be provided through our analyses.

2. Methods

After the approval of our institutional review board was obtained (VGHIRB No.: 2011-03-037-IC), this retrospective study was conducted at Taipei Veterans General Hospital, Taipei, Taiwan. Data were collected from patients receiving PCEA after upper abdominal surgery with laparotomy from 2007 to 2009. Those who had unstable postoperative condition or major complications and used PCEA for less than 48 hours owing to miscellaneous causes were eliminated from the analysis. A 20-gauge epidural catheter was placed at a selective lower thoracic intervertebral space using an 18-gauge Tuohy needle and a loss-of-resistance technique to most effectively identify the epidural space prior to surgery. The depth of implanted epidural catheters in the epidural space ranged from 5 cm to 8 cm along the patient's back. All epidural catheters were securely affixed with skin adhesive, tested for loss of sensation in corresponding dermatomes with 2 mL of 2% lidocaine, and further preclude the possibility of intrathecal or intravascular migration prior to surgery. All patients received endotracheal intubation under combined general and epidural anesthesia with epidural loading dose of 10 mL bupivacaine (0.25%) and fentanyl (5 μg/mL) mixture. Anesthesia was maintained with inhalation anesthetics and additional epidural bolus doses of 0.25% bupivacaine. After the completion of surgery, a patient-controlled infusion pump (Aim Plus system; Abbott Laboratories, North Chicago, IL, USA) was used to deliver the standardized PCEA infusate composed of bupivacaine (0.0625%) and fentanyl (1 μg/mL). The pump settings included a background infusion rate between 3 mL/h and 7 mL/h, a patient-controlled bolus dose of 1.5–4 mL, and a lockout interval of 15–30 minutes. In order to ensure data quality, cumulative doses of the first four 12-hour intervals were calculated using the recordings directly retrieved from the infusion device. Pain relief was assessed indirectly by the demand/delivery (*D*/*D*) ratio, and values less than 2 usually imply adequate analgesia.[21] Other collected variables included patient gender, age, weight, height, body mass index (BMI), and confirmation of surgery for malignant disease of the stomach, pancreas, gall bladder, or liver (coded as 0 for nonmalignancy and 1 for malignancy).

2.1. Statistical analysis

Continuous data are expressed as mean with standard deviation, and categorical data are presented as count with percentage. The *D*/*D* ratios are exhibited as median with interquartile range (IQR). Linear mixed models with first-order autoregressive covariance structure were used to evaluate within-subject time effects and other between-subject effects on PCEA consumption over time. A random intercept model was also used to account for the unexplained variance at the subject level. The candidate factors consisted of patient characteristics, including gender, age, height, weight, BMI, and surgery for malignant disease, and PCEA pump settings, including bolus dose, background infusion rate, and lockout interval. The effects of these factors interacting over time were also examined. A stepwise backward elimination strategy based on likelihood ratio change was used to select factors and interaction effects significantly associated with PCEA consumption over time. Scatter plots for predicted PCEA consumption from the selected model against observed PCEA consumption during different time intervals were illustrated, and corresponding correlation coefficients were calculated to check the goodness of fit to data. The Bonferroni adjustment was used for multiple comparisons, and a p value less than 0.05 was considered statistically significant. According to Peat and Barton,[22] the minimum number of cases for multiple regression analysis should be at least 100. This criterion was met because the sample size of this study was 1001. All statistical analyses were conducted using the SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 1001 patients were included in our analysis. The baseline characteristics of the recruited patients are presented in Table 1. Among them, female patients accounted for nearly one-third of the study population. The mean age was 63.3 years, and 82.2% of these patients received upper abdominal surgery for a malignant disease. With respect to the PCEA pump settings, the mean bolus dose, background infusion rate, and lockout interval were 2.2 mL, 5.0 mL, and 20.5 min, respectively. A significant difference in the mean PCEA consumption during the first four 12-hour intervals was noted ($p < 0.001$, linear mixed model analysis). When compared with the mean PCEA consumption during the 1st 12-hour interval, more PCEA solution was consumed during the 2nd 12-hour interval ($p = 0.039$), but less PCEA consumption was noted during the 3rd and 4th 12-hour intervals (both $p < 0.001$). The *D*/*D* ratios of the first four 12-hour intervals

Table 1
Baseline characteristics of patient receiving upper abdominal surgery.

	n (%)	Mean	SD
Gender			
Female	325 (32.5)		
Male	676 (67.5)		
Age (y)		63.3	14.7
Height (cm)		163.6	33.5
Weight (kg)		63.2	19.5
BMI (kg/m^2)		23.7	3.6
Malignancy [a]	823 (82.2)		
Bolus dose (mL)		2.2	0.8
Infusion rate (mL/h)		5.0	0.6
Lockout interval (min)		20.5	3.0
PCEA consumption (mL)			
0–12 h		74.2	17.4
12–24 h		75.5	19.2
24–36 h		70.1	18.2
36–48 h		69.9	18.0

BMI = body mass index; PCEA = patient-controlled epidural analgesia; SD = standard deviation.
[a] Patients received surgery for malignant disease.

were 1.85 (IQR = 1.33–2.83), 1.6 (IQR = 1.2–2.33), 1.47 (IQR = 1.09–2) and 1.5 (IQR = 1–2.12).

The effects of factors included in the analysis on PCEA consumption after upper abdominal surgery over time are presented in Table 2. Most factors included in the analysis had significant effects on PCEA consumption, except lockout interval. Female gender and older age were negatively associated with PCEA consumption over time, but the other significant factors (including height, weight, BMI, surgery for malignant disease, and bolus dose and infusion rate of PCEA pump) were positively related to PCEA consumption after upper abdominal surgery. With respect to the interaction effect of candidate factors on PCEA consumption with time, only gender ($p = 0.003$), age ($p < 0.001$), height ($p = 0.019$), and infusion rate ($p = 0.035$) had a significant interaction with time on PCEA consumption after upper abdominal surgery.

Table 3 shows the final results of the model selection processes using a backward elimination strategy. On average, the time effect was still significant, and PCEA consumption after upper abdominal surgery peaked during 12–24 hours and gradually decreased over time thereafter. Four patient factors were kept in the final model, and two of the factors (gender and age) had significant interaction with the time interval (both $p = 0.001$). Female gender tended to consume less and less PCEA solution over time relative to their male counterparts. However, there was no significant difference in PCEA consumption between female and male patients during the 1st 12-hour interval. The age effect resulted in the greatest difference in PCEA consumption after upper abdominal surgery during the 2nd 12-hour intervals. Afterward, the difference in PCEA consumption gradually diminished. Note that the age effect on PCEA consumption during the 2nd and 3rd 12-hour intervals was not significantly different from that during the 1st 12-hour intervals. Both surgery for malignant disease and background infusion rate were positively associated with PCEA consumption, and their relationships did not seem to change over time.

Table 2
Estimated main effects of miscellaneous factors on patient-controlled epidural analgesia (PCEA) consumption over time.

	β	SE	p
Gender (female vs. male)	−2.92	1.04	0.005
Age	−0.34	0.03	<0.001
Height	0.04	0.01	0.003
Weight	0.11	0.02	<0.001
BMI	0.68	0.14	<0.001
Malignancy	3.80	1.27	0.003
Bolus dose	2.10	0.64	0.001
Infusion rate	12.19	0.74	<0.001
Lockout interval	0.17	0.17	0.300

β = regression coefficients estimated from linear mixed model analysis; BMI = body mass index; PCEA = patient-controlled epidural analgesia; SE = standard error of the estimated regression coefficients.

Table 3
Effects of selected factors on patient-controlled epidural analgesia (PCEA) demand over time using a backward model selection strategy.

	β	SE	p
Time			<0.001
Time1 (12–24 vs. 0–12 h)	5.62	2.27	0.013
Time2 (24–36 vs. 0–12 h)	−4.80	2.24	0.032
Time3 (36–48 vs. 0–12 h)	−10.20	2.43	0.000
Age	−0.23	0.04	<0.001
Gender (female vs. male)	−0.72	1.21	0.549
Malignancy	3.23	1.20	0.007
Rate	9.49	0.89	<0.001
Interaction of Time1 and age	−0.05	0.03	0.105
Interaction of Time2 and age	0.03	0.03	0.414
Interaction of Time3 and age	0.11	0.04	0.002
Interaction of Time1 and gender	−2.79	1.05	0.008
Interaction of Time2 and gender	−2.84	1.04	0.006
Interaction of Time3 and gender	−3.85	1.13	0.001

β = regression coefficients estimated from linear mixed model analysis; SE = standard error of the estimated regression coefficients.

Fig. 1 illustrates the scatter plots for predicted PCEA consumption from the selected model against observed PCEA consumption during different time intervals. The correlation coefficients between the observed and predicted PCEA consumption after upper abdominal surgery during the 1st, 2nd, 3rd, and 4th 12-hour intervals were 0.80, 0.88, 0.84, and 0.87, respectively, which implied an acceptable predictive power of the selected model.

4. Discussion

Although PCEA had been shown to be an efficient clinical technique for postoperative pain management,[8,9] there was still wide variability in the effectiveness of the analgesic effect from patient to patient. Many factors may influence the PCEA efficiency and patient satisfaction. These factors include the anatomical variations, position of epidural catheter, drugs of regimen (different local anesthetics with or without opioids), and patient individual factors (such as age, gender, and height).[17,19] Although influential factors for total PCEA consumption had been inspected,[17–20] there is still a lack of

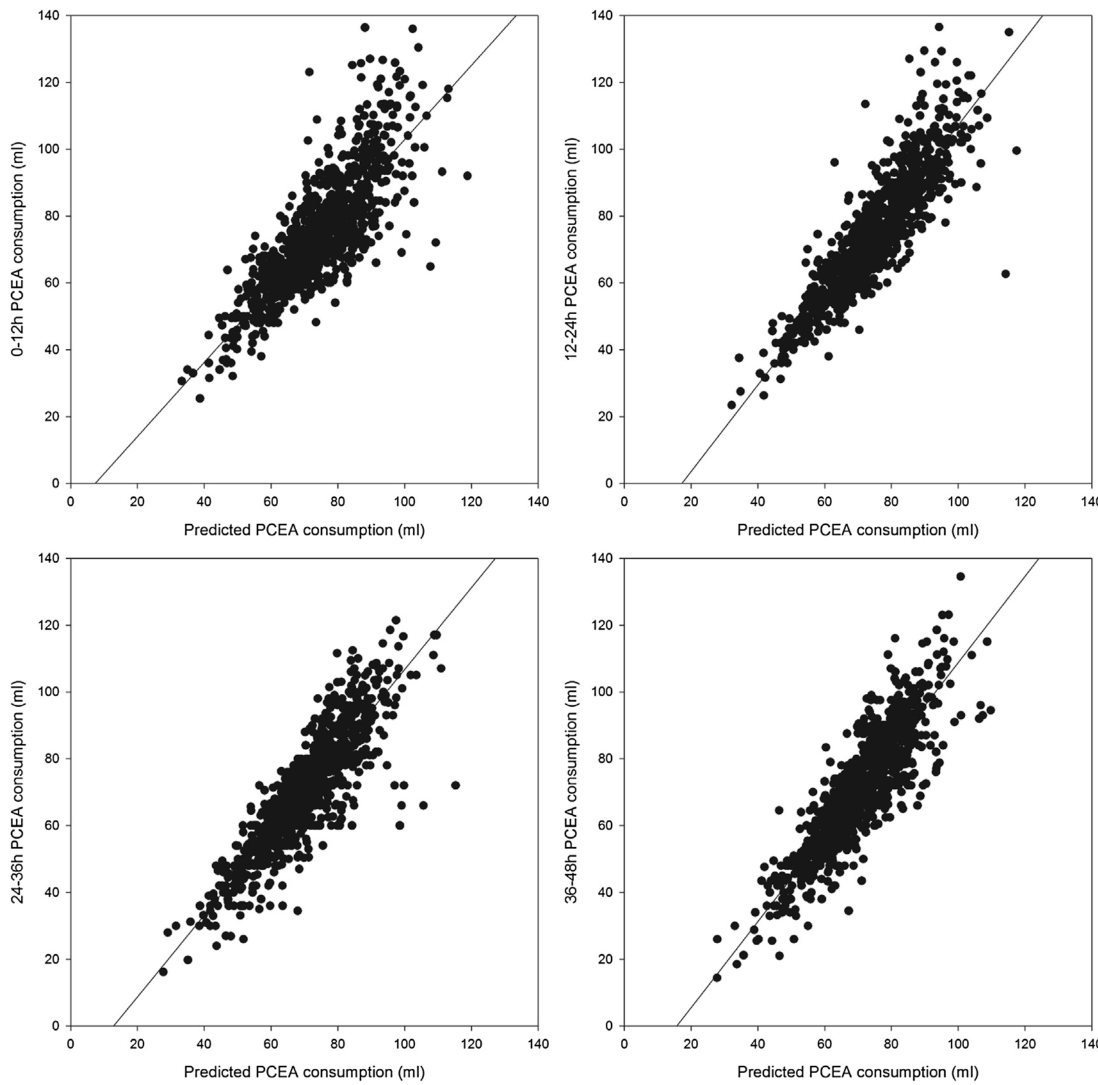

Fig. 1. Scatter plots for predicted patient-controlled epidural analgesia (PCEA) consumption from the selected model against observed PCEA consumption during different time intervals. The predicted PCEA consumption was close to the real PCEA consumption during the four different time intervals.

literature concerning the influence of these factors on PCEA demand over time. Our study aimed to fill this gap by investigating how potentially influential factors interacted with time on PCEA demand after upper abdominal surgery. In the previous study, findings about the relationships between demographic characteristics and total PCEA consumption in different types of surgery provided several implications for further study.[19] Surgical site is an important influential factor of PCEA demand and patients receiving different types of surgery tended to have different demographic characteristics. In other words, the difference in surgical sites is a major source of heterogeneity that may result in discrepancy in PCEA demand. To reduce the uncertainty from heterogeneous patient groups, we focused on patients receiving upper abdominal surgery to determine the factors that influence PCEA consumption over time.

According to our analysis, PCEA consumption after upper abdominal surgery peaked during the 2nd 12-hour interval and then decreased gradually over time. In general, the most intense pain occurred in the first few days after surgery.[23,24] It is reasonably considered that because of the residual anesthetic effects, postoperative pain may not reach the maximal level until the 1st 12-hour after surgery. Afterward, the surgical pain would become more intense and the patients might demand more analgesic as a result of the subsiding effects of residual anesthetics. The maximal postoperative pain occurred during the 2nd 12-hour period, and PCEA consumption corresponded to the pain intensity. Our results demonstrated how the PCEA demand of patients receiving upper abdominal surgery changed over time.

In our study, it is noted that demographic factors that affected PCEA demand included patient gender, age, surgery for malignant disease, and infusion rate of PCEA. Although we identified that female patients consumed less PCEA solution than their male counterparts, there is still controversy in the literature about gender bias in PCEA consumption.[19] A recent large-scale study revealed that women consumed less PCEA solution and had higher pain scores than men.[18]

However, they concluded that the difference in pain scores was small and not clinically relevant. Gender-related differences in pharmacokinetic and pharmacodynamic handling of analgesics or discrepancy in cognitive pain perception may play some role in gender bias in PCEA consumption.[25,26] We also found that age negatively correlated with postoperative IVPCA use. Most studies that investigated change in the physiology, pharmacodynamics, pharmacokinetics, and processing of nociceptive information that occurs with aging may influence the effectiveness of PCEA and those drugs required to minimize discomfort, and there is a clinically significant reduction in the intensity of pain perception with geriatric patients.[27] Surgery for malignant disease was considered to be a routine pathway for greater surgical damage with a greater extent or likelihood of severe pain, and was also associated with elevated PCEA consumption. In a previous study with 170 patients, a correlation between PCEA requirement and individual characteristics among gynecologic patients was investigated, which showed that patients undergoing procedures for malignant diseases consumed more PCEA solution than those with benign diseases.[20] Such results were consistent with our findings. In addition, we also found that the PCEA infusion rate directly influenced PCEA demand, and this finding is compatible with other reports in the literature.[28] Although the correlation between lockout interval and patients' satisfaction had been investigated in previous studies,[29,30] there was no significant impact on PCEA requirement with the difference in lockout interval.

There are several limitations in this study. First, the retrospective nature of this study limited the data available for analysis, and had potential problems such as selection and misclassification bias. Second, only patients receiving upper abdominal surgery and postoperative PCEA were included in this study, so the generalization of our findings to other surgical types awaits further investigations. Third, the surgical types were not further classified and analyzed as a potential covariate of PCEA demand. Only the factor "malignancy" was used in the analysis. The classification of surgical type can be considered in future analyses on PCEA demand over time whenever the sample size is sufficient.

In conclusion, our analyses provided valuable information about the factors associated with PCEA consumption over time after upper abdominal surgery. PCEA consumption peaked during the 2nd 12-hour interval and then decreased gradually over time. Female gender and older age were negatively associated with PCEA consumption, whereas surgery for malignant disease and background infusion rate were positively associated with PCEA consumption. Our study demonstrated the interaction effects of gender and age with time on PCEA demand. Female patients tended to use less and less PCEA over time relative to male patients. Age had a negative effect on PCEA consumption, which peaked during the 2nd 12-hour interval and then decreased gradually over time. These findings may provide potential implications in clinical practice as determinants of PCEA pump settings or guides to dose adjustment during the PCEA course. PCEA consumption analysis over time provides a more comprehensive view and dynamic features of the relationships between PCEA consumption and its influential factors. However, further investigation is required to unveil the underlying mechanisms and validate our predictive model.

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