Dynamic analysis of variations in postoperative pain trajectories over time in patients receiving epidural analgesia using latent curve models

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Abstract

Background: Although epidural analgesia (EA) provides reliable pain relief after major operations, few studies have explored how postoperative pain trajectories change over time in patients receiving EA and the associated factors. This study aimed to model the dynamic features of pain trajectories after surgery and investigate factors associated with their variations using latent curve analysis.

Methods: This retrospective study was conducted at a single medical center in Taiwan, and data were obtained from patients receiving perioperative EA by electronic chart review. Mean numeric rating pain scores were recorded daily in the first five postoperative days. Patient demographics, surgical sites, and infusion pump settings were also collected. Latent curve models using two latent variables, intercept and slope, were developed to explain the variations in postoperative pain scores over time. The influences of potential predictors of postoperative pain trajectories were further evaluated for the final model determination.

Results: Of the 1294 collected patients, the daily pain scores averaged 2.0 to 2.9 for different surgical sites. Among the nine significant factors influencing pain trajectories, chest and lower extremity surgery tended to induce less and more baseline pain, respectively, than those with abdomen surgery (both $p < 0.001$). In addition, male patients and those with a shorter anesthesia time had less baseline pain ($p < 0.001$ and $p = 0.016$, respectively). The older and lighter patients and those with chest surgery or American Society of Anesthesiologists class ≥ 3 tended to have milder decreasing trends in pain trajectories. A higher infusion rate was associated with an elevated baseline level and smoother decreasing trend in pain trajectory. The final model fit our data acceptably (root mean square error of approximation = 0.05, comparative fit index = 0.97).

Conclusion: Latent curve analysis provided insights into the dynamic nature of variations in postoperative pain trajectories. Further studies investigating more factors associated with pain trajectories are warranted to elucidate the mechanisms behind the transitions of pain scores over time after surgery.

Keywords: Epidural analgesia; Latent curve model; Pain trajectory; Surgery

1. INTRODUCTION

Epidural analgesia (EA) remains a ubiquitous analgesic technique, and the main indications for EA include thoracotomy, obstetric analgesia, open abdominal surgery, and lower extremity surgery.[1] EA attenuates a patient's stress response to surgery by reducing sympathoadrenal activity and neuroendocrine cytokine release, and thereby lowers the risk of thromboembolic, pulmonary, and gastrointestinal complications after major surgery.[2] Compared with systemic opioids, EA not only improves the quality of postoperative analgesia but also promotes gastrointestinal motility and postoperative pulmonary function.[3] Furthermore, EA also facilitates early recovery and accelerates patient rehabilitation programs after surgery.[4]

Traditional continuous epidural infusion of highly concentrated local anesthetic agents has disadvantages such as increasing the possibility of systemic toxicity and motor weakness.[5]

Patient-controlled EA (PCEA) used to be administered through an infusion pump programmed for several parameters, including loading dose, infusion rate, demand dose, and lockout interval. Although the effectiveness of EA on postoperative pain is well established, how pain trajectories vary over time after surgery in patients receiving PCEA and what effect these trajectories have remain unclear. Accordingly, we conducted this retrospective study to investigate variations in postoperative pain trajectories over time in patients receiving PCEA and investigate the factors associated with these trajectory changes. We hypothesized that a combination of patient attributes, surgical type, and infusion pump settings would alter the postoperative pain trajectories over time. To achieve the study aims, we used

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 89-94.

Received July 22, 2019; accepted July 25, 2019.

doi: 10.1097/JCMA.0000000000000200.

latent curve analysis to characterize postoperative pain trajectories in patients undergoing PCEA and incorporated multiple predictors into the latent curve models to evaluate the effects of miscellaneous factors on the pain trajectories after surgery and their interaction with time. Clinical prediction models were also developed to provide more quantitative insights into the nature of changes in postoperative pain trajectories.

2. METHODS

2.1. Setting and patient selection

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (IRB-TPEVGH No. 2015-11-010CC). The need for written informed consent was waived as all study materials were anonymized and de-identified before analysis. The inclusion criteria were patients undergoing chest, abdomen, and lower extremity surgery and receiving postoperative EA at our hospital in 2012. All data were obtained from the institutional electronic medical record system.

2.2. Anesthesia and analgesia management

All patients included in this study were given balanced general anesthesia or spinal anesthesia. For general anesthesia, most patients received fentanyl 1 to 2 μg/kg and propofol 1 to 2 mg/kg for induction and a nondepolarizing neuromuscular blocker to facilitate tracheal intubation with rocuronium 0.8 mg/kg or cisatracurium 0.2 mg/kg. General anesthesia was maintained with sevoflurane 2 to 3 vol%, desflurane 6 to 8 vol% in a mixture of oxygen and air. Only some of the patients undergoing lower extremity surgery received spinal anesthesia with 10 to 16 mg of 0.5% bupivacaine solution. All of the patients had an implanted epidural catheter which was typically placed in the lumbar or middle or lower thoracic region, and its function was assessed with a test dose of local anesthetic preoperatively. EA was started intraoperatively with a combination of local anesthetic (bupivacaine 0.25% or 0.5%) and 5 μg/mL fentanyl, and continued postoperatively for at least 72 hours. Catheters were assessed daily for proper function by the acute pain service team. An ambulatory infusion pump (Gemstar™ Yellow; Hospira, Lake Forest, IL, USA) was used postoperatively and programmed to deliver a combination of local anesthetic solution with bupivacaine 0.0625% and 5 μg/mL fentanyl with an infusion rate of 0 to 7 mL/h, a demand dose of 0 to 6 mL and a lockout time of 6 to 20 minutes.

2.3. Data retrieval

The medical records of the recruited patients were extracted by specialist anesthesiologists who were not involved in data analysis. Random samples of the extracted data were thoroughly checked by the authors to ensure the quality of data. Patient characteristics and daily pain score recordings using an 11-point numeric rating scale with response options from "no pain" to "the worst pain" were retrieved during the first five postoperative days (PODs) from the electronic medical record system and served as the endpoints in the following latent curve analysis. Other collected variables included gender, age, weight, height, body mass index, and surgical site (chest, abdomen, and lower extremity as the reference group).

2.4. Statistical analysis

Patient characteristics and mean daily pain scores during the first five postoperative were expressed as mean ± SD or count with percentage. Latent curve analysis was performed to model the changes in daily mean pain scores over time and evaluate how patient characteristics affected the pain score trajectories. Three kinds of latent curve models, basic, single predictor, and multiple predictor models were used to explore the transitions of daily pain scores over time.[6,7] The basic model was applied to estimate baseline intercept and slope parameters, and then the single predictor model was used to evaluate univariate effects of collected variables on the intercept and slope parameters. The backward model selection strategy was performed to identify independent explanatory factors of the intercept and slope parameters and determine the final multiple predictor model. Details of the latent curve model (LCM) statistical technique have been reported previously.[8,9] The goodness of fit was assessed using root mean square error of approximation (RMSEA) and comparative fit index (CFI), and values of RMSEA < 0.1 and CFI > 0.9 implied an acceptable data fit.[10,11] All latent curve analyses were performed using AMOS 18.0 (SPSS Inc, Chicago, IL, USA). Other statistical analyses were conducted using SPSS 18.0 (SPSS Inc).

3. RESULTS

In total, 1294 patients and 6034 mean pain score observations from POD 1 to POD 5 were included in the analysis. Table 1 shows the patients' characteristics and that 42.6%, 33.9%, and 23.5% of the patients underwent abdomen, chest, and lower extremity surgery, respectively. The daily mean pain scores after surgery ranged between 2 and 2.9 at distinct surgical sites.

In the basic latent curve model, the estimated factor loading of slope parameters (Fig. 1) of POD 2, POD 3, and POD 4 was 1.047, 0.577, and 0.108, respectively. The estimated values of intercept and slope parameters of the basic LCM were 2.337 and 0.091, respectively. As a result, the daily mean pain score between POD 1 and POD 5 could be estimated as follows:

$$\text{POD 1: } 2.337+(1)\times 0.091=2.428,\ \text{POD2:} 2.337+(1.047)\times 0.091=2.432,\ \text{and so on.}$$

Of note, the maximal difference between the predicted and observed daily mean pain score was <0.1 unit of the numeric rating scale (on POD 1).

Table 2 presents the results of single predictor LCM analysis and shows that lockout interval did not exert any significant effect on the intercept or slope parameter of longitudinal pain scores and that anesthesia time had a borderline significant

Table 1

Patient characteristics (N = 1294)

	Abdomen (n = 551)	Chest (n = 439)	Lower extremity (n = 304)
Age, y	50 ± 18	58 ± 16	72 ± 11
Sex, female	338 (61.3%)	187 (42.6%)	225 (74.0%)
Body height, cm	162 ± 8	163 ± 9	155 ± 9
Body weight, kg	66 ± 12	63 ± 11	66 ± 12
Body mass index, kg/m^2	25.0 ± 4.1	23.8 ± 3.5	27.3 ± 4.3
ASA class ≥ 3	120 (21.9%)	113 (25.9%)	65 (21.7%)
Anesthesia time, min[a]	8.29 ± 0.99	8.24 ± 0.59	7.37 ± 0.41
Demand dose, mL	2.0 ± 0.4	2.2 ± 0.5	2.0 ± 0.3
Background infusion rate, mL/h	3.7 ± 1.3	4.9 ± 0.5	3.7 ± 0.7
Lockout interval, min	15.2 ± 1.5	15.4 ± 1.5	15.4 ± 1.6
Mean NRS pain score			
POD 1	2.7 ± 1.3	2.0 ± 1.2	2.9 ± 0.9
POD 2	2.5 ± 1.1	2.1 ± 1.2	2.7 ± 0.8
POD 3	2.3 ± 1.0	2.1 ± 1.1	2.6 ± 0.9
POD 4	2.4 ± 1.2	2.4 ± 1.3	2.6 ± 0.9
POD 5	2.2 ± 1.0	2.5 ± 1.2	2.6 ± 1.1

Values are presented as mean ± SD or count (%).
[a]On base-2 logarithmic scale.
ASA = American Society of Anesthesiologists; NRS = numeric rating scale; POD = postoperative day.

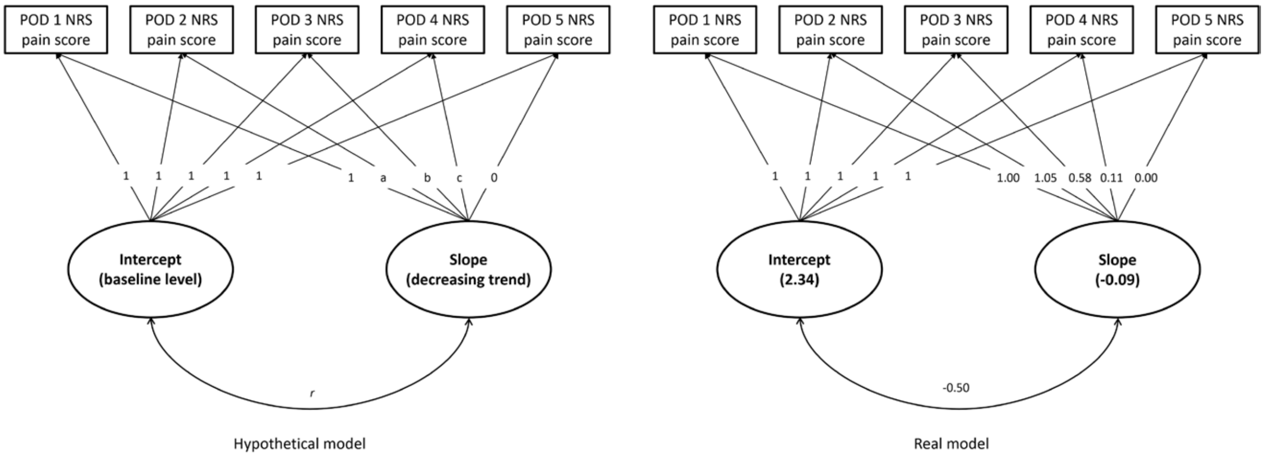

Fig. 1 Basic latent curve models before and after parameter estimation. Left part: hypothetical basic latent curve model; right part: basic model with parameter estimates. The figure illustrates the basic latent curve models (before and after parameter estimation) with two latent factors, intercept and slope, to characterize the variations in postoperative pain trajectories over time in patients receiving PCEA after surgery. The "intercept" represents a constant baseline of mean NRS from POD 1 to POD 5, and the corresponding factor loading (on the directed lines) on each POD is fixed at 1. In contrast, the "slope" implies the linear rate at which mean NRS changes over time. Note that factor loading of the slope parameter on POD 1 and POD 5 was constrained to be 1 and 0, respectively, and the remaining three (a, b, and c) were unspecified and could be estimated from the data. The double-headed arrow between the intercept and slope reflects the correlation (*r*) between the two latent variables. Accordingly, the mean NRS at a specific POD could be estimated using the following equation: POD *t* NRS = intercept + λ_t × slope, where λ_t specifies the factor loading of the slope parameter on POD *t* (1, a, b, c, or 0). The estimated parameters are showed in the right side of the figure. NRS, numeric rating scale of daily pain score; PCEA, patient-controlled epidural analgesia; POD, postoperative day.

effect on the slope parameter (p = 0.05). Other variables had significant effects on either intercept or slope parameter or both.

Table 3 shows the results of multiple predictor LCM analysis after model selection. Four independent predictors were identified to affect the intercept parameter. Female gender, longer anesthesia time, higher background infusion rate, and lower extremity surgery were significantly associated with higher baseline pain scores. In contrast, patients receiving chest surgery had lower baseline pain scores postoperatively. With respect to the slope parameters, older age, American Society of Anesthesiologists (ASA) physical status classification (ASA class) ≥ 3, higher demand dose and infusion rate, and receiving chest surgery were associated with slower pain resolution following surgery. In contrast, the heavier patients had faster pain resolution after surgery. The RMSEA and CFI values of the final model were 0.05 and 0.97, respectively, and its graphic presentation is illustrated in Figure 2. Moreover, the pain scores on various PODs could be predicted using the estimated parameters from the latent curve analysis. For example, for a 60-year-old female patient with a body weight of 50 kg and ASA class 3, who underwent chest surgery with PCEA (demand dose: 2 mL, infusion rate: 5 mL/h) and anesthesia time of 200 minutes, her estimated mean pain score on POD 2 could be calculated using the following formula:

$$
\begin{aligned}
&(0.026+0.167\times \text{female gender } +0.072\times \log_2(\text{anesthesia time})\\
&+0.126\times \text{ infusion rate}-0.261\times\text{chest}+0.325\times\text{lower extremity})\\
&+0.719\times (1.657-0.005\times \text{ age}+0.004\times \text{ body weight}\\
&-0.152\times\text{ASA}\geq 3-0.145\times \text{ demand dose}\\
&-0.083\times \text{ infusion rate}-0.252\times\text{chest}) = 1.56.
\end{aligned}
$$

Table 2

Effects of collected variables on the intercept and slope parameters in the single predictor model analysis

	Intercept			Slope		
	Estimate	**SE**	***p***	**Estimate**	**SE**	***p***
Age, y	0.003	0.001	0.042	–0.006	0.001	<0.001
Sex, female	0.117	0.048	0.015	0.156	0.039	<0.001
Body weight, kg	–0.008	0.003	0.001	–0.002	0.002	0.405
Body height, cm	–0.001	0.002	0.57	0.004	0.002	0.018
Body mass index, kg/m^2	0.01	0.006	0.089	0.014	0.005	0.002
ASA class ≥ 3	0.007	0.057	0.896	–0.2	0.047	<0.001
Anesthesia time[a]	0.009	0.028	0.738	–0.041	0.021	0.053
Demand dose	0.02	0.061	0.738	–0.185	0.049	<0.001
Background infusion rate	0.04	0.023	0.081	–0.15	0.022	<0.001
Lockout time	0.009	0.015	0.575	–0.008	0.012	0.491
Surgical site						
Chest	–0.16	0.058	0.006	–0.379	0.055	<0.001
Lower extremity	0.273	0.059	<0.001	–0.1	0.048	0.036
Abdomen (reference)	–	–	–	–	–	–

[a]On base-2 logarithmic scale.
ASA = American Society of Anesthesiologists.

Table 3

Analytic results of multiple predictor latent curve model after backward model selection

	Estimate	SE	p
	Intercept		
Sex (female vs male)	0.167	0.05	<0.001
Anesthesia time[a]	0.072	0.03	0.016
Background infusion rate	0.126	0.026	<0.001
Surgical site			
Chest	−0.261	0.062	<0.001
Lower extremity	0.325	0.065	<0.001
Slope			
Age, y	−0.005	0.001	<0.001
Body weight, kg	0.004	0.002	0.011
ASA class ≥ 3	−0.152	0.05	0.002
Demand dose	−0.145	0.054	0.007
Background infusion rate	−0.083	0.022	<0.001
Surgical site			
Chest	−0.252	0.052	<0.001

[a]On base-2 logarithmic scale.
ASA = American Society of Anesthesiologists.

The predicted mean pain scores of other PODs could also be calculated in a similar manner.

4. DISCUSSION

Most previous studies have focused on the efficacy of a pain interventions with time-specific comparisons of mean pain measurements between treatment and control groups. Surgical patients gradually recover with adequate wound care, nutritional supplements, and rehabilitation, and thus postoperative pain steadily decreases. Latent curve analysis not only characterizes how an intervention alters trajectories of outcomes but also provides more comprehensive insights into the processes of transition through the evaluation of repeated measures of data over time.[12,13] In addition, latent curve models also allow for the application of real intervention data and facilitate the computation of specific power estimates under different conditions and assumption settings.[14] Accordingly, latent curve models can be used to analyze variations in postoperative pain trajectories over time in patients using PCEA.

Severe postoperative pain leads to delayed recovery, immobility, patient displeasure, prolonged hospital stay, and increased incidence of cardiac and pulmonary complications.[15,16] Evidence suggests that inadequate pain management after surgery may lead to the development of chronic postsurgical pain.[17,18] Therefore, it is crucial to identify the factors influencing postoperative pain trajectories to optimize analgesic strategies for acute pain management. However, contradictory findings in different studies make acute pain control a challenging issue for clinicians. In patients undergoing abdominal surgery, Caumo et al reported that moderate to intense acute postoperative pain was associated with an ASA physical status of 3, preoperative moderate to intense pain, chronic pain, high trait anxiety, and depressive mood.[19] In ambulatory and elective surgery, the presence of preoperative pain has been reported to be the most important factor affecting postoperative pain.[20,21] Kalkman et al also found that younger age, female gender, preoperative pain level, incision size, and type of surgery predicted the early

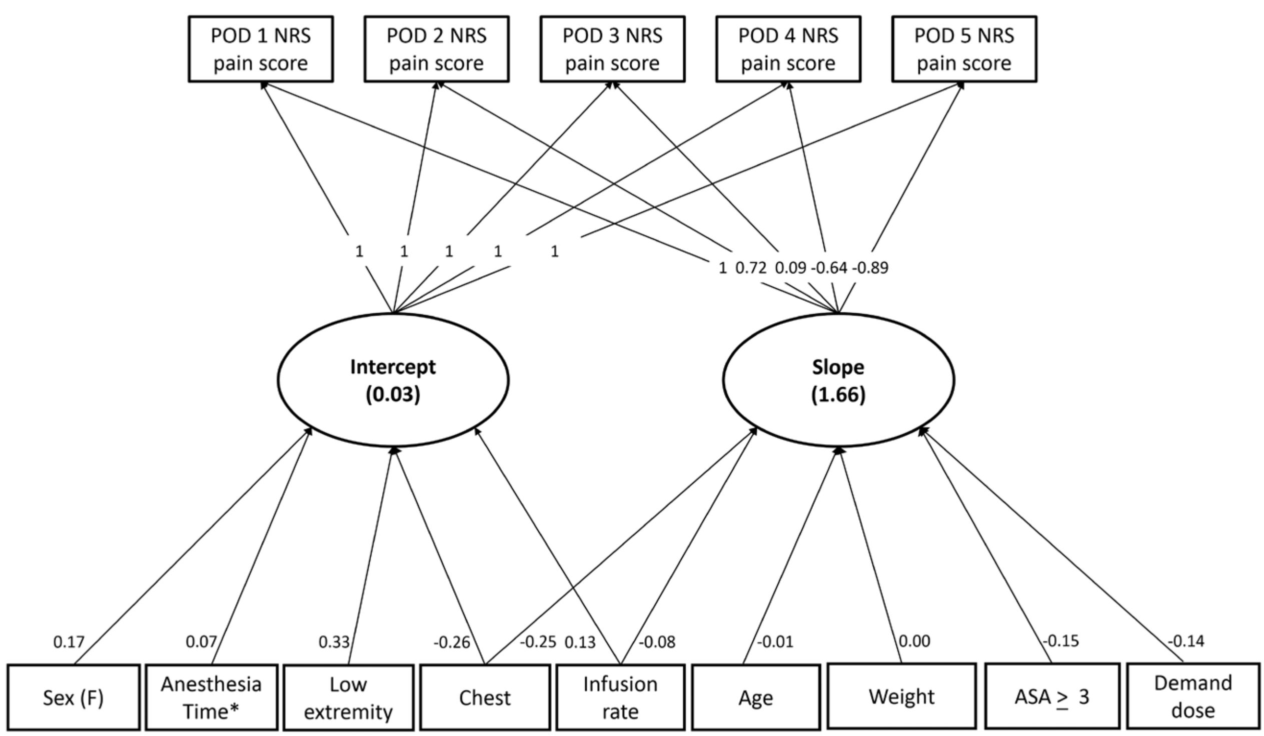

Fig. 2 Multiple predictor model with parameter estimates. *On a binary logarithmic scale. In the multiple predictor latent curve model, several explanatory variables were introduced into the basic model to exert combined effects on the intercept and slope parameters which determined the changes in NRS over time. The NRS at a specific POD could be estimated using the following equation derived from the structural equation modeling analysis including these predictors and latent factors: POD t NRS = (0.026 + 0.167 × female + 0.072 × $\log_2$(anesthesia time) + 0.126 × infusion rate − 0.261 × chest + 0.325 × lower extremity) + λ_t × (1.657 − 0.005 × age + 0.004 × body weight − 0.152 × ASA ≥ 3 − 0.145 × demand dose − 0.083 × infusion rate − 0.252 × chest), where λ_t indicates the factor loading of slope parameter on POD t. All of the related parameter estimates are also illustrated in the figure. ASA, American Society of Anesthesiologists; POD, postoperative day; NRS, numeric rating scale of daily pain score.

occurrence of severe postoperative pain in surgical patients.[22] Another procedure-specific risk factor analysis study reported associations among age, sex, and preoperative chronic pain with postoperative pain intensity.[23] These findings mostly agree with our results, in which age, gender, ASA physical status, and surgical sites were important determinants of the variation in postoperative pain trajectories over time.

In our study, latent curve analysis further revealed that the pain resolution in the patients receiving PCEA was affected by patient characteristics over time. Aging changed the slope of pain resolution, which may have been related to blunted peripheral nociceptive function and the effect of physical changes in geriatric patients, since decreasing proportions of body water composition, muscle mass, and relatively increased fat mass alter drug distribution in the human body.[24] Previous studies have reported that patients with higher body weight tended to call for more analgesics, and our study found that body weight only altered the slope of pain resolution but had no influence on baseline pain intensity.[25,26] The distinct spread of anesthesia in patients with different body weights may partly account for the discrepancies in the trajectories of pain resolution.[27]

Several studies have reported that PCEA with continuous background infusion did not increase the risk of inadequate sensory analgesia or motor block and that the demand dose provided a dose-sparing effect.[28,29] The ideal background infusion rate has been discussed before, and the determinants of total consumption of PCEA have been investigated.[30] Along with background infusion, self-administered bolus doses improved patient satisfaction and alleviated the burden of medical staff.[30] In the current study, we explored the changes in postoperative pain trajectories over time in patients receiving PCEA. The predictors obtained after our analysis may provide valuable information for further investigations and the customization of PCEA settings for patients with miscellaneous combinations of these determinants. We also found that a higher background infusion rate was associated with greater baseline pain and slower pain resolution. This contradictory finding may be due to various causes. The patients undergoing thoracic surgery tended to have a higher background infusion rate (4.9 vs 3.7 of those receiving abdomen or lower extremity surgery) and different age and sex distributions. It is possible that this finding was due to complex interactions among these and other unobserved factors resulting in a combined effect. Further investigations are necessary to elucidate the underlying mechanisms which may be important in postoperative pain management.

Another interesting finding of this study is that worse ASA physical status was not related to baseline pain but was associated with slower pain resolution after surgery. This implies that the sensitivity to pain of debilitated patients undergoing a major operation did not differ from that of healthy individuals, but that the recovery course may have been delayed due to a worse physical condition. However, this phenomenon may be overlooked in clinical practice since these patients are sometimes too weak to express their pain sensation. Therefore, clinicians should pay more attention to these patients with regard to the adequacy of pain management, particularly during the postoperative period. More frequent pain assessments are also encouraged to ensure the quality of pain control after surgery.

There are several limitations to this study. First, we measured postoperative pain in surgical patients treated at a single medical center. Therefore, it was difficult to evaluate cross-regional and cultural influences on pain perception. Second, only observed variables were included in the analysis, and other potentially influential factors such as psychological distress and preoperative pain proposed in other studies were not collected.[22,31–33] Further investigations with more variables should be considered in the future. Third, only three types of surgery were analyzed in this study, and more detailed classifications should be included in future studies to elucidate the relationships between surgical procedures and postoperative pain resolution over time. Fourth, although latent curve models are suitable to investigate interindividual differences in variations over time and to explore influential factors and consequences of change, there are inherent weaknesses in latent curve analysis such as missing data management and difficulty in power estimation.[9] Nevertheless, latent curve analysis can also be applied to extended analyses of postoperative pain trajectories and their influential factors without difficulty from the methodological perspective.

In conclusion, this study demonstrated that latent curve analysis could characterize postoperative pain trajectories over time in patients using PCEA and identify the influential factors. Female gender, longer anesthesia time, higher background infusion, and lower extremity surgery increased the baseline level of postoperative pain. In contrast, aging, ASA > 3, high demand dose, high infusion rate, and receiving chest surgery tended to be associated with slower pain resolution. Body weight accelerated pain resolution over time through a positive effect on the slope parameter. Latent curve analysis provided insights into the dynamic nature of variations in postoperative pain trajectories over time, and more explanatory variables should be considered in future studies to further elucidate the mechanisms behind the transitions of pain scores over time after surgery.

ACKNOWLEDGMENTS

This work was supported by grants from Taipei Veterans General Hospital (V104C-096), Yen Tjing Ling Medical Foundation (CI-108-27), Anesthesiology Research and Development Foundation (ARDF10601), and the Ministry of Science and Technology (MOST104-2314-B-075-015), Taipei, Taiwan, ROC.

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