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Serial Analgesic Consumptions and Predictors of Intravenous Patient-controlled Analgesia with Cluster Analysis

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Objectives: To elucidate the dynamics of analgesic consumption regarding intravenous patient controlled analgesia (IVPCA) during postoperative period is rather complex partly due to between-patient variation and partly due to within-patient variation. A statistical method was proposed to classify serial analgesic consumption into different classifications that were further taken as the multiple outcomes on which to explore the associated predictors.

Methods: We retrospectively included 3284 patients administrated by IVPCA for 3 days after surgery. A repeated measurement design corresponding to serial analgesic consumption variables defined as six-hour total analgesic consumptions was adopted. After determining the numbers of clusters, serial analgesic consumptions were classified into several homogeneous subgroups. Factors associated with new classifications were identified and quantified with a multinominal logistic regression model.

Results: Three distinct analgesic classifications were aggregated, including "high", "middle" and "low" level of analgesic consumption of IVPCA. The mean analgesic consumptions on 12 successive analgesic consumptions at 6-hour interval of each classification consistently revealed a decreasing trend. As the trends were almost parallel with time, this suggests the time-invariant proportionality of analgesic consumption between the levels of analgesic consumption of IVPCA. Patient's characteristics, like age, gender, weight, height, and cancer status, were significant factors associated with analgesic classifications. Surgical sites had great impacts on analgesic classifications.

Discussion: The serial analgesic consumptions were simplified into 3 analgesic consumptions classifications. The identified predictors are useful to recognize patient's analgesic classifications before using IVPCA. This study explored a new approach to analysing dynamic changes of postoperative analgesic consumptions.

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Acute postoperative pain management is one of the important components of postoperative care.[1] Adequate postoperative pain control helps patients to undergo early rehabilitation and reduce the length of stay in hospital.[2,3] Despite efforts to improve pain management, 80% of patients still experience intense pain after surgery.[4]

Among all the management, intravenous patient-controlled analgesia (IVPCA) is a useful and well-established approach to relieving acute postoperative pain.[5–7] Patients are allowed to self-administrate small dose of opioid by pressing the button of the IVPCA to reach their timely analgesic demands. This self-controlled mechanism becomes an important biofeedback to the nature of acute postoperative pain and the serial of analgesic consumptions are worthy of study. However, studying analgesic consumptions is difficult, analgesic consumptions of acute pain differ across not only the patients but also time.[8,9] Although the evidence showed patterns of morphine reduction from postoperative day 1 to day 3 and a possible biological rhythm pattern existing,[5,10,11] studies to reveal the analgesic patterns are very rare.[10,11]

The objective of the study was to identify distinct analgesic consumption patterns among the serial analgesic consumption of postoperative acute pain. We proposed a statistical method to classify the postoperative analgesic consumption patterns as a new classification system. We also identified significant predictors in association with the new classifications.

MATERIAL AND METHODS

Participants

This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (IRB: 2011-03-037IC). We conducted a retrospective cohort study with a balanced repeated measurement between January 2005 and December 2010. Patients who met the following criteria were recruited in the study: age from 15 to 90 years-old, able to understand and self-operate IVPCA pump, the administration of general anaesthesia without any neuraxial techniques, and the use of IVPCA for postoperative pain control at least 3 days. We excluded patients who required additional sedative agents or ventilator support in intensive care units beyond 24 hours due to the disease consideration.

Study Design

IVPCA Setting and Adjustment

All patients followed the same protocol of IVPCA management in the study. IVPCA was prepared with standard solution of 1 mg/mL morphine in normal saline. IVPCA pumps were initiated after patients completed their surgical procedures in the postanesthesia care unit (PACU). A 0.05 mg/kg loading dose was first given for immediate acute postoperative pain management. IVPCA were programmed to administrate bolus dose of 0.5 to 1.5 mg morphine with lockout interval between 5 to 10 minutes when patients activated the demand button.

The PCA team frequently evaluated and adjusted IVPCA regiment at PACU until verbal rating pain score less than 3 (no pain: 0; worse pain:10). After that, PCA team regularly visited patients at least once a day for IVPCA evaluation and adjustment. Any inadequate pain relief and side effects complained by the patients would trigger additional reevaluation program by PCA team members at any time during 3 postoperative days.

Data Collection

We used IVPCA machine to collect patients' serial changes of analgesic consumption in 3 postoperative days. The microprocessor of IVPCA real-time records any dose changes and demand counts information. However, as analgesic consumptions varied with time we classified the continuous analgesic consumption variable into discrete variables every 6 hours. Because all patients have observed for completing 3 postoperative days, they equally had successive 12 analgesic consumption variables to represent their postoperative analgesic behaviours. The concept of the serial analgesic consumptions for each patient is shown in Figure 1.

All analgesic consumptions dose and bolus counts were retrieved from log profile of infusion pumps (Aim® plus system; Abbott Laboratories, North Chicago, IL). Other patient characteristics data were collected from medical record and IVPCA worksheet.

Statistical Analysis

These panel data were analysed in steps. The first step was the application of cluster analysis to classify patients' serial analgesic consumptions according to 12 serial analgesic consumption variables denoted by C_1-C_{12} to aggregate the similar subject into the same group based on the Ward's minimal variance method with the 4 criteria of minimizing within-group variance and maximizing the between-group variance (see Appendix).[12,13] In the light of the criteria, patients were similar within group, but were dissimilar between groups. Therefore, we could cluster patients' serial analgesic consumptions into 3 distinct groups and form a simpler new classification.

As far as the Ward's minimal variance method is concerned, we determined the numbers of clusters with the following 4 criteria, Cubic Clustering Criteria (CCC),[14] R-square (R^2), root mean square standard derivations (RMSSD) and semi-partial R-square (SPRSQ).[15] The Cubic Clustering Criteria, which measured the inflation of the within group sum of squares, has been widely used in determining the optimal number of cluster in many situations.[16] In general, higher values indicate better clustering. A good clustering can be indicated by CCC >3. Three other criteria can be used to assess the validity of clustering

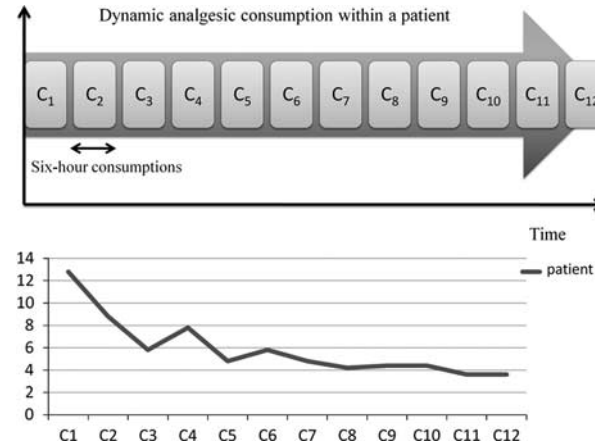

FIGURE 1. Concept of dynamic change of analgesic consumptions of one patient.

with a larger R-square and small RMSSTD and SPRSQ. It should be noted that as 12 consecutive analgesic consumption variables were analysed and they were correlated within the same individual the unit of analysis was based on each 6-hour analgesic consumption rather than individual. The correlation structure across 12 variables (C_1 to C_{12}) would be taken into account when the cluster analysis was implemented using the algorithm for merging the same kind of analgesic consumption (see Appendix).

The second step was to evaluate the possible predictors responsible for new classifications identified from the first step. We transformed age in a continuous variable into 4 levels, >60, 60 to 69, 70 to 79, and ≥ 80 years-old. Others variables included weight, height, age, cancer (0 for non-cancer and 1 for cancer), gender (0 for female and 1 for male), surgical sites, and surgical types. Surgical site variables were characterized by 10 levels (upper abdomen, lower abdomen, spine, extremity, chest, head & neck, genitourinary, obstetrics, gynecology, and others), which represent 10 different surgical areas. All continuous variables are expressed as the mean $\pm$ SD, and discrete variables are presented as the absolute number (percentage). One-way ANOVA was used to compare age and weight across 3 classifications. When there were significant differences among groups, *post hoc* analysis was conducted with Scheffé multiple comparison procedure. Categorical variables, like gender and cancer status were tested with chi-square test. P value less than 0.05 was considered statistically significant. When more than 2 outcomes were involved, the multinomial logistic regression model was proposed to test the association between predictors and analgesic consumption classifications.[17] The effects of predictors were expressed as odds ratio.

All statistical analyses were performed with SAS software (V9.2; SAS Institute Inc., Cary. NC. USA.).

RESULTS

Patient Characteristic, Surgical Site, and Analgesic Consumption

There were total 3284 patients enrolled in the analysis during January 2005 and December 2010. The mean age of IVPCA users was 60.7 years old, including 47.7% of those aged 65 years or older. Male gender accounted for 51.5% of

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all patients. The majority of patients received general anaesthesia (94.6%). Total analgesic consumption of IVPCA for 3 days was 64.2 mg. In addition to demographic features, anthropometric variables (such as weight and height), and surgical site are also presented in Table 1.

Results of Analgesic Consumption Classifications

We chose the number of clusters with the consideration of 4 criteria (CCC, R^2, RMSSD and SPRSQ). We present a plot of Cubic Clustering Criteria (CCC) versus number of clusters for serial analgesic consumption data in Figure 2 consistent with the criteria of the optimal number of cluster indicated by CCC. Three other criteria such as larger R^2 and small RMSD and SPRSQ also suggest the same number of clusters. After the application of Ward's minimal variance method, 3284 patients were aggregated into 3 groups high, middle, and low serial analgesic consumption with the numbers of patients corresponding to 846, 1316 and 1122 patients, respectively. The mean and cumulative doses of 3 groups over time are diagrammed in Figure 3, reflecting different levels of morphine requirements. Therefore, 3,284 patients were clustered into 3 homogeneous groups ("High", "Middle", and "Low"). The decreasing time trend, notably 12-hour since the administration, was consistently noted for each group. As 3 curves were in parallel this suggests time-invariant proportionality on serial analgesic consumption between any of two groups. Other statistics of serial analgesic consumptions for three classifications are shown in Table 2.

Predictors Associated with Three Classifications of Analgesic Consumptions

Predictors can be sorted into 2 major categories: patients' characteristics and surgical site. Table 3 shows the comparisons of each variable in each category across 3 groups of analgesic consumptions. All variables on patient characteristics were statistically significant. The majority of surgical sites were significant different among classifications except three surgical sites (thoracic, head & neck and genitourinary).

The results of multivariate analysis are presented as adjusted odds ratio in Table 4. The independent predictors

TABLE 1. Baseline Characteristics of IVPCA Patients

Variable	Value
Characteristics (n = 3284)	
Age (y)	60.7 (17.6)
Gender (Male:Female)	1691:1539
Weight (kg)	61.4 (12.5)
BMI (kg/m^2)	23.8 (4.1)
Cancer (%)	54.7
General anaesthesia	94.6%
Regional anaesthesia	5.4%
Surgical Site	
Upper abdomen surgery (%)	27.7
Lower abdomen surgery (%)	34.3
Spine surgery (%)	12.6
Extremity surgery (%)	6.4
Thoracic surgery (%)	5.5
Head & neck surgery (%)	2.0
Genitourinary surgery (%)	4.3
Obstetrics surgery (%)	1.5
Gynecology surgery (%)	4.7
Analgesic consumption	
Start time (6:00-13:00)	2029
Start time (13:00-19:00)	1000
Start time (19:00-24:00)	255
Day 1 analgesic consumption (mg)	29.96 (15.48)
Day 2 analgesic consumption (mg)	19.00 (11.48)
Day 3 analgesic consumption (mg)	15.21 (9.93)
Total analgesic consumption (mg)	64.2 (33.2)

Values are expressed as Mean (SD).

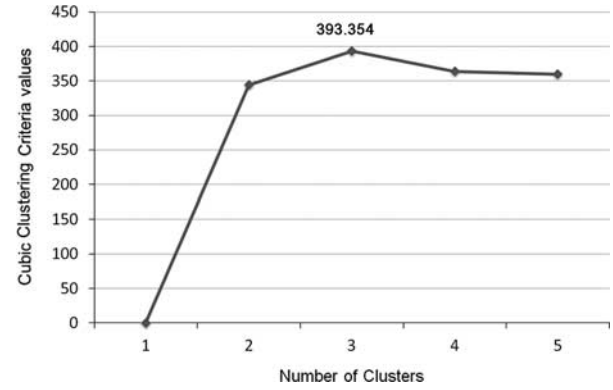

FIGURE 2. Using Cubic clustering criterion (CCC) to determine the optimal number of clusters. CCC has highest value in the three clusters, which indicated three clusters are optimal.

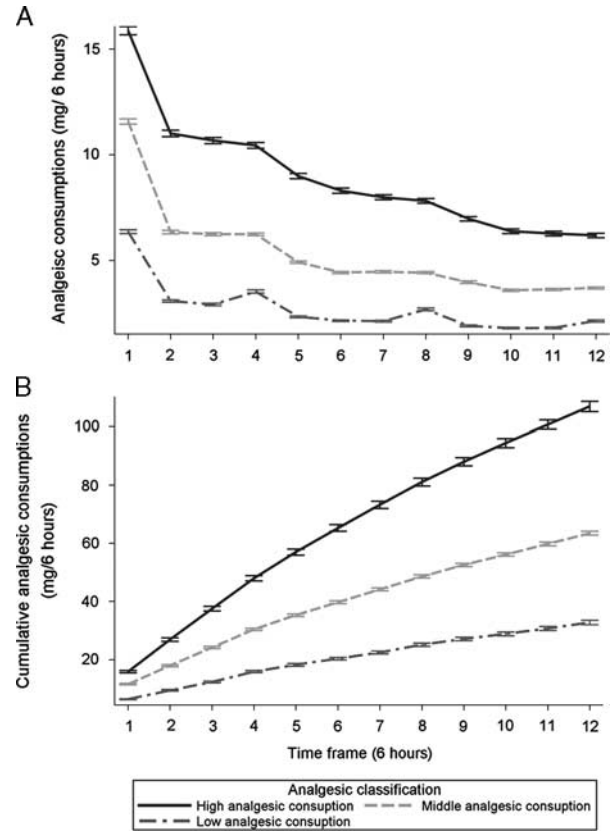

FIGURE 3. Two panel line charts to present analgesic consumption changes of three analgesic classifications. (Upper plot) To show the mean doses change over postoperative three days. (Lower plot) To show the accumulative doses change over three postoperative three days. (Line presented as mean and 95% confidence interval).

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TABLE 2. Results of 3 Analgesic Consumption Classifications (mg/6 h)

Consumption Classifications	Serial Analgesic Consumptions						
After cluster	C_1	C_2	C_3	C_4	C_5	C_6	
High (n = 846)	15.9 ± 5.7	11.0 ± 4.6	10.7 ± 4.1	10.4 ± 3.9	9.0 ± 3.6	8.3 ± 3.6	
Middle (n = 1316)	11.6 ± 4.6	6.3 ± 2.8	6.2 ± 2.6	6.2 ± 2.3	4.9 ± 1.9	4.4 ± 1.8	
Low (n = 1122)	6.4 ± 3.0	3.1 ± 1.9	2.9 ± 1.8	3.5 ± 2.5	2.3 ± 1.4	2.1 ± 1.4	
Before cluster (n = 3284)	10.9 ± 5.8	6.4 ± 4.3	6.2 ± 4.1	6.4 ± 3.9	5.1 ± 3.5	4.6 ± 3.3	
Consumption Classifications	**Serial Analgesic Consumptions**						
After Cluster	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	Total Dose
High (n = 846)	8.0 ± 3.3	7.8 ± 3.3	7.0 ± 3.1	6.4 ± 3.2	6.3 ± 3.1	6.2 ± 3.0	106.9 ± 26.0
Middle (n = 1316)	4.5 ± 2.1	4.4 ± 1.9	4.0 ± 2.3	3.6 ± 1.7	3.6 ± 1.8	3.7 ± 1.8	63.5 ± 12.4
Low (n = 1122)	2.1 ± 1.4	2.7 ± 2.1	1.9 ± 1.2	1.8 ± 1.2	1.8 ± 1.2	2.1 ± 1.8	32.8 ± 13.0
Before cluster (n = 3284)	4.6 ± 3.2	4.7 ± 3.1	4.0 ± 3.0	3.7 ± 2.7	3.7 ± 2.7	3.8 ± 2.7	64.2 ± 33.2

C1 to C12 are the variables of serial analgesic consumptions of a 6-hour time frame. All data are presented as mean ± SE.

attributed to the classifications are the following variables: age, gender, height, weight, cancer status, and surgical site. Patients with predictors of older age, female gender and performing head and neck surgery were likely to be classified in the "low" level of analgesic classification. Patients who were younger, taller, heavier, had cancer history, or received upper abdominal, lower abdominal, or extremity surgery tended to use more analgesic consumptions of IVPCA and therefore are more likely to be classified as "High analgesic consumption".

DISCUSSION

In this observational study, we applied Ward's minimal variance method to cluster serial analgesic consumptions in an innovative way and identified significant predictors of them. The results simplified serial analgesic consumptions into three distinct consumption classifications and the predictors help us to discriminant these three new classifications.

Analgesic Consumptions are Dynamic Fluctuation

One of difficulties to setup IVPCA regimen is patient's analgesic demands varying over time. Yen et al has found the heterogeneity of total consumption requirements among patients.[18] In fact, the heterogeneity is not only between patients but also within patients themselves. We know different patients' characteristics affect the analgesic requirements of IVPCA,[9,19–22] but the temporal factor is of paramount importance to the clinicians and researchers.[23] Acute postoperative analgesia requires highest opioid in the first few hours and then decreases dosage over time.[24] The reason may be due to gradually improved postoperative acute pain with time.[25] Otherwise, there are circadian variations in both acute pain intensity and in opioid-induced analgesia.[8,11,26] Fixed IVPCA setting throughout postoperative period can't meet the decreasing trend of analgesic consumption for the patients. A time-scheduled dose setting scheme to reach optimal requirements during postoperative period is needed.

Advantages of Classifications

We introduced 12 serial analgesic consumption variables of a patient to represent the dynamic change of them. The series of analgesic consumptions have more information, such as dose, rate and variability, than total consumptions. All of these significantly affect our decision of pain management during whole postoperative period. However, the serial analgesic consumptions are also difficult to analyze. One of aims to apply Ward's minimal

TABLE 3. Univariate Analysis of Predictors Associated with Three Analgesic Consumption Classifications

	Analgesic Consumption Classification			
Variables	High (n = 846)	Middle (n = 1316)	Low (n = 1122)	*P* value
Age (yr)	55.07 ± 14.91	60.28 ± 16.10	65.43 ± 19.64	< 0.001
Gender (M:F)	575:271	650:666	466:656	< 0.001
Weight (kg)	67.20 ± 12.70	61.38 ± 11.54	56.92 ± 11.48	< 0.001
Height (cm)	163.84 ± 8.02	160.24 ± 8.15	157.40 ± 8.30	< 0.001
Cancer	523	727	547	< 0.001
Surgical site				
Upper abdomen	289	376	245	< 0.001
Lower abdomen	324	443	359	0.012
Spine	66	168	181	< 0.001
Extremity	56	66	89	0.013
Thoracic	38	76	68	0.287
Head&neck	12	31	24	0.309
Genitourinary	28	55	57	0.154
Obstetrics	10	29	9	0.012
Gynecology	18	60	77	< 0.001
Others	4	12	14	0.216

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TABLE 4. Multivariate Analysis of Predictor Associated with Three Analgesic Classifications

	Analgesic Consumption Classification	
	"High"	"Middle"
Predictors	OR	OR
Age (y)		
< 60	reference	reference
60-69	0.67* (0.50-0.90)	1.20 (0.93-1.55)
70-79	0.17† (0.13-0.23)	0.58† (0.46-0.74)
≥ 80	0.02† (0.01-0.03)	0.11† (0.08-0.15)
Gender		
Female	reference	reference
Male	2.43† (1.83-3.24)	1.34* (1.06-1.69)
Weight (kg)	1.07† (1.06-1.08)	1.03† (1.02-1.04)
Height (cm)	1.02* (1.00-1.04)	1.02* (1.00-1.03)
Non-cancer	reference	reference
Cancer	1.80† (1.37-2.37)	1.35* (1.08-1.70)
Surgical site		
Others	reference	reference
Head & neck	0.61† (0.15-2.56)	0.92 (0.34-2.48)
Chest	2.02 (0.56-7.33)	1.31 (0.54-3.20)
Upper abdomen	8.65† (2.53-29.53)	2.67† (1.15-6.18)
Lower abdomen	5.47† (1.61-18.64)	1.89* (0.82-4.37)
Genitourinary tract	1.88 (0.50-7.00)	1.24 (0.50-3.07)
Obstetrics	3.50 (0.75-16.24)	3.22* (1.05-9.92)
Gynecology	1.22 (0.33-4.55)	0.94 (0.39-2.27)
Spine	2.57 (0.73-9.09)	1.50 (0.63-3.54)
Extremities	3.59* (1.00-12.90)	1.18 (0.48-2.88)

"Low" analgesic consumption classification is the reference group.
*P value <0.05.
†P value <0.001.

variance method was to deal with this problem. As a method of clustering, it was designed to aggregate more homogeneous groups and therefore find the pattern of serial analgesic consumptions.[13] The results showed the heterogeneity of the serial analgesic consumptions and can be clustered as 3 classifications (corresponding to high, middle and low level).

It may also suggest that developing 3 IVPCA regimens rather than 1 uniform regimen since they are heterogeneous. Another important result of the study is to use the descriptive data of analgesic consumptions for the corresponding classifications. The mean values are the estimated analgesic requirements of the corresponding groups. 95% confidence intervals are the range of analgesic requirements, which can cover by the bolus dose. Clinicians can understand the dynamic analgesic consumptions during three postoperative days and also know relative change of analgesic consumptions in adjacent period of time and the quantity of analgesic consumptions in every postoperative period within 3 days.

The Predictors of New Analgesic Consumption Classifications

In the new classifications, all postoperative analgesic consumptions can be classified into 3 categories. Analysing predictors helps to identify the patient's analgesic classification before using IVPCA. In our results, patient's characteristics such as age, gender, body weight are important factors responsible for postoperative analgesic consumptions classifications. Age greater than 60 years old was associated with decreased serial analgesic consumptions. In other words, if patients older than 60 years old, they tend to be classified as "low" analgesic consumptions classifications. The age effect is not linear but is polynomial. The findings are similar to most investigators,[27,28] but we considered the serial dynamic analgesic consumptions rather than total dosage. Weight, height and cancer status were associated with increased serial analgesic consumptions. Patients with these factors are more likely to use "high" analgesic consumptions in the postoperative period.

Gender was not identified as a consistent predictor in the literature.[5,29–31] Although the conflicting results were across studies, we found Chinese female used less IVPCA consumptions than male, which is opposite to the finding from Western countries. We had the same finding that female tended to use "low" analgesic consumptions than male after adjusting for other covariates, like weight, age, etc. The "low" analgesic consumptions are also correlated with serial "low" demand counts of IVPCA. We are aware of the fact that Chinese culture of bearing pain in female may influence the behavior of acquiring IVPCA.

Surgery has great impact on analgesic consumptions,[5,31] but great variations make it hard to analyse. Gerbershagen et al analysed the pain intensity of 179 surgical procedures.[32] They found some "minor" or "medium" surgical procedures were not necessarily associated low postoperative pain. Even some with laparoscopic approaches will lead to unexpectedly high levels of postoperative pain. In our study, we found abdominal surgery or orthopaedics surgery for any extremities are the predictors for "high" level of analgesic classification, while head and neck surgery is the predictor for "low" level of analgesic classification.

Strength and Limitations

This is a large-scale survey of consecutively collecting the serial analgesic consumption of over 3000 patients. The proposed statistical method could not only takes into account the correlated measurements of serial analgesic consumption for developing a new classification but the outcomes of new classification can be linked with the postulated predictor to identify who are likely to be classified as high analgesic consumption group.

However, there are some limitations of our study. Our study population were relatively older and had higher proportion of cancer history and of open abdomen surgery compared to other studies. However, several previous studies have also been conducted with similar characteristics of the study population.[18,33] The concern over such kind of population is that study samples may not be representative of the entire population of surgical patients but only a subset of population. The second one is that there are possible unmeasured variables, like opioid medication before operation. However, its influence may be indirectly captured by the variable "cancer" as cancer patients were more likely to take opioid medication than other patients. The third is that Figure 3 not only shows 3 distinct groups of analgesic consumptions with 12 successive measurements but also shows a decreasing time trend, notably from 12 hours since the initiation of IVPCA. By cluster analysis, our results showed there are 3 different levels of analgesic classifications existing for the acute pain phase. We are able to know the level and the trend of patient's analgesic consumptions to have a better regimen of IVPCA. For example, if a patient is in "low analgesic group", the first postoperative day mean morphine usages are 6.4→3.1→

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2.9→3.5 mg, which decrease to half of initial dose. However, a patient in "high analgesic consumption" group will use 15.9→11.0→10.7→10.4 mg, which decrease to two-thirds of initial dose. Those doses are almost 2.5-3 times to the "low analgesic consumption" group. Those variations may come from not only time but also the individual's characteristics effect. In the current manuscript, we only focused on the classification and we did not attempt to elucidate the time-effect by using a formal time-series regression model. It is therefore unlikely to assess the interaction between "time-effect" and "subject-effect" or influences from other unmeasured variables. Therefore, this is a preliminary study of serial analgesic consumptions of IVPCA with Ward's minimal variance method. Further replication and validation of these classifications are needed in the future. Moreover, regarding the part of predictors in association with three levels of serial analgesic consumptions, we are not tempted to build up a predictive model as the variables collected may not be sufficient enough but we only explored the association between some postulated factors and the outcome of analgesic consumptions. For example, we did not collect opioid medication as indicated before. We therefore think our study is also a preliminary study for building up a predictive score for serial analgesic consumption.

CONCLUSION

In this study, we demonstrated the heterogeneity of IVPCA analgesic consumptions come from not only subject's effect but also the time-effect. We applied cluster analysis to explore the analgesic consumption patterns within analgesic consumptions as new classifications. The nature of three classifications help us understand the evolution of postoperative analgesic consumptions and thus improved the IVPCA regimens. Certain predictors associated with 3 analgesic classifications were also explored.

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APPENDIX

Ward's Minimal Variance Method

The key of Ward's minimal variance method is to analyse the error sum of square (ESS) that can be viewed as the measures of similarity within cluster (homogeneity) when merging the same kind of analgesic consumption at each step.

Let D_{AB} denote the distance between cluster A and B, i.e. the loss of similarity within cluster (homogeneity) after each step when merging. ESS_{AB}, ESS_A, and ESS_B represent three error sum of squares when merging cluster A and cluster B. X_A and X_B are the mean vector of cluster A and B, respectively. n_A and n_B are the numbers of observations in cluster A and B. $\| \ \|$ is the Euclidean distance.

$$D_{AB} = ESS_{AB} - (ESS_A + ESS_B)$$
$$= \frac{n_A n_B}{n_A + n_B} \|X_A - X_B\|^2 \qquad ((A-1))$$

Ward's minimal variance method chooses smallest one as the merge criteria. Therefore, this method is also known as the incremental sum of squares approach. In our study, we put multivariate variables (serial analgesic consumptions (C_1-C_{12})) in the Euclidean distance and proceed the algorithm as indicated in (A-1).

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