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DISCRIMINATION OF PAIN INTENSITY LEVEL AND SIDE EFFECTS OF POSTOPERATIVE PAIN USING PARAMETERS EXTRACTED FROM THE EVOKED PAIN PATTERN

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ABSTRACT

The value of evoked potentials (EPs) in the clinical assessment of physiological function has been recognized for some time by those with specialized neurophysiological interests. Based on this concept, we have applied this novel technique for discrimination of pain intensity level and side effects using time-domain parameters extracted from the evoked pain pattern (EPP) in postoperative pain via patient-controlled analgesia (PCA). In conventional PCA systems, each delivery is similar to evoked pain stimulation, and we then count the following demands in a lockout interval. Therefore, the EPP is calculated and averaged from several lockout intervals in a period of time. From this calculation, the evoked parameters of area, latency, and amplitude of each period of time can be easily extracted. A total of 741 cases from 1519 patients at a medical center have been screened and compared with these three parameters using different visual analog scales (VAS) and side effects (SE). The results indicate that the area parameter is a good indicator for higher VAS patients and the variance of latency parameter is a better outcome for interpreting the patients with SE. However, the amplitude parameter shows no significant differences in both VAS and SE groups. Using massive information from clinical trials and a novel technique of evoked pain stimulation algorithm, we demonstrate that evoked parameters (i.e. area and latency) can serve as indicators to assess various clinical evidences, such as VAS and SE associated with postoperative pain.

Keywords: Evoked potentials (EPs); Evoked pain pattern (EPP); Patient-controlled analgesia (PCA); Evoked pain stimulation; Area; Latency; Amplitude; Visual analog scales (VAS); Side effects (SE).

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INTRODUCTION

Pain is inherently subjective and pain measurement relies primarily on the verbal report of patients. Furthermore, pain is a complex, private experience and attempts to make valid assessments of it have been fraught with difficulties.[1] Thus, the wide variation in the pain experience among individuals leads to a large variability in the pain scale ratings of patients who experience similar stimuli or interventions. In addition, pain scale measurements are often interpreted in different ways by different researchers and clinicians, depending on the criteria they choose to apply.[2] Recently, pain has been proposed as "the fifth vital sign" to be entered into a patient's chart along with temperature, blood pressure, pulse, and respiration rates.[3,4] However, there is still no objective measurement for the experience of pain.

In the search for more reliable, objective, continuous, and on-line monitoring of dynamic pain, similar to the other vital signs, our previous research has found that patient-controlled analgesia (PCA) devices are an important means of self-reported pain intensity. Because, the pain pattern of patients stored inside the PCA device may differ from either analgesic drugs or surgical operations and present specific characteristics with clinical implications.[6,7] Hence, how to interpret this pain pattern more objectively and reliably in order to continuously monitor this fifth vital sign is still the most important aspect of the pain measurement.

Auditory evoked potentials (AEPs) are obtained by introducing an auditory signal in the form of clicks to a patient through earplugs. The electrical signals produced by the central nervous system in response to these clicks are recorded by electrodes placed on the scalp. The wave form represents the passage of electrical activity from cochlea and cortex. Every peak in the AEP can be characterized by its amplitude and latency (time coordinate). It has been evaluated that the middle latency auditory evoked potentials (MLAEPs) are associated with depth of anesthesia.[8–11] The amplitudes of the peaks decrease and the latencies increase with the increase in anesthetic level. Using this concept, we have applied these novel techniques for discrimination of pain intensity level and SE using time-domain parameters extracted from evoked pain stimulation.

In order to validate the model of pain pattern more precisely, we use a method which pain researchers accept as important for pain assessment. The visual analog scales (VAS) is an established, validated, self-report measure of pain intensity usually consisting of a 10 cm line on paper with verbal anchors labeling the ends.[12] VASs have been used in many studies to measure a number of constructs including pain, asthma, dyspepsia, mood, appetite, ambulation, and vitality.[13] The VAS has been shown to have advantages over verbal rating scales and numerical scales in sensitivity to changes in pain intensity and in capacity to provide ratio scale measures of experimental pain.[14] They are particularly useful for populations with language barriers[15] and can be presented in various forms.[16] Additionally, clinical observations indicate that patients often find SE, particularly nausea and vomiting, more distressing than the postoperative pain for which they are being treated.[17] When using PCA, some patients seem willing to endure pain rather than suffer unpleasant side-effects, and it has been proposed that patients may in fact balance pain against SE.[18] From clinical point of view, we add two clinical evidences collected by VAS scores and SE through patient–clinician interviews to our previous research of a multilayer hierarchical structure of *i*-pain system.[19] Hence, the present study proposes a novel technique derived from evoked potentials in order to obtain time-domain parameters extracted from evoked pain stimulation. We wish to determine whether or not these parameters can distinguish the clinical evaluation parameters of VAS and SE at different ranges.

EVOKED PARAMETERS EXTRACTED FROM EVOKED PAIN PATTERN

In traditional PCA systems, consenting patients are provided with a hand-held pushbutton and are instructed to trigger the button (i.e. demand) when patients require pain relief. A bolus of constant size (e.g. 1 ml of morphine) is given in response to each legitimate pushing of the button. However, the size of the bolus is set by the medical staff and there is a "lockout" period following each bolus administration, during which time no further bolus can be delivered. Therefore, demand was the patient made a request by pushing the PCA button. And, delivery was the successfully completed demand that was met by administration of the drug. Since each delivery is like an evoked pain stimulation, we count the following demands in a lockout period (e.g. 10 or 15 min) which is called one sweep. Then, the evoked pain pattern (EPP) is calculated and averaged from several sweeps. For example, if we choose a time window of 1 h at a 10 min lockout interval of the PCA machine, the EPP will be calculated from approximately 6 sweeps because the patients may have some

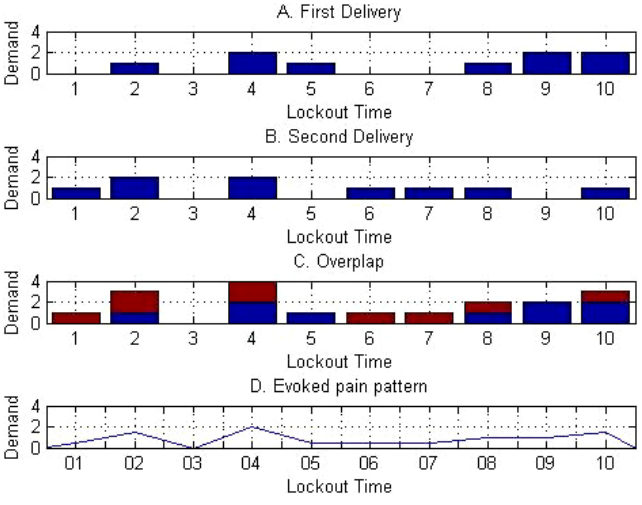


Fig. 1 Example of evoked pain pattern at 10 min lockout interval **(A)** first sweep: the demand number of each minute after first delivery; **(B)** second sweep: the demand number of each minute after second delivery; **(C)** sum of the number of demands for each minute from first and second sweeps; **(D)** averaged and plotted number of demands for each minute to a curve.

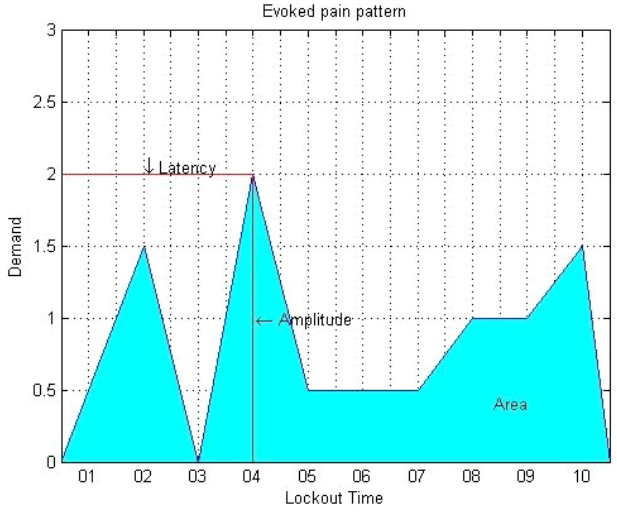


Fig. 2 Evoked parameters of area, latency, and amplitude extracted from evoked pain pattern.

delay in pushing the button in each 10 min lockout interval. Figure 1 shows an example of how to calculate an EPP. Figures 1(A) and 1(B) are the first and second sweep counted by the demand number of each minute after first and second delivery. Then, the demand number of each minute is summed from first and second sweeps, as shown in Fig. 1(C). Finally, the demand number for each minute is averaged and plotted to a curve, as shown in Fig. 1(D). This average response is called the EPP, and it always has some peaks and troughs although the area and latency of these are variable. Then, the following evoked parameters extracted from EPP were defined as follows and as shown in Fig. 2.

(a) Area: Total area of the EPP to measure the number of times a patient pushes the button.
(b) Latency: Time from starting delivery until the maximum average amplitude demand value of the EPP; in order to know the variation of latency, we also calculate the variance of latency for this parameter.
(c) Amplitude: Maximum average demand value of the EPP to measure the highest demand.

PATIENTS AND METHODS

This study was approved by the Shin Kong Wu Ho-Su Memorial Hospitals Ethics Committee. A total of 741 cases from 1519 patients had been screened and compared with these three parameters using different ranges of VAS and SE. The VAS was divided into two groups for scores less than or equal to 3 (i.e. VAS_3) and greater than or equal to 5 (i.e. VAS_5). Furthermore, the SE were divided into two groups for total score equal to 0 (i.e. SE_0) and total score greater than or equal to 1 (i.e. SE_1) which were counted for a total score of nausea plus vomiting. Patients were excluded from the study if they were morbidly obese, unable to understand the use of the PCA or had a history of allergy to morphine. According to routine clinical practice, patients were instructed on the correct use of the PCA pump and given standardized PCA education by a PCA team nurse.

PCA instrument devices (i.e. Abbott AIM Plus pump) collected all the patients' demands and delivered a bolus to a patient when pain relief was required. In order to understand in more detail how to collect information from PCA devices, please refer to description of our previous research given in Ref. 19. Moreover, VAS scores and SE through a patient–clinician interview module were also recorded. VAS was obtained by having patients rate their pain from "no pain" to "pain as bad as it can be" on 100 mm lines.[20] The degree of patient side effects was graded on a 3-point scale: 0 = no side effect, 1 = little side effects, 2 = heavy side effects, 3 = serious side effects (i.e. difficulty enduring). Then, the patients' basic information, postoperative records of PCA device, and VAS and SE were transmitted to personal computer (PC) to create a comprehensive file in the PC-based *i*-pain system. For statistical analysis, the data was compared using the unpaired Student's *t*-test, with $P < 0.01$ considered significant.

RESULTS

Table 1 shows the demographic details of these screened patients. In order to analyze the difference of

Table 1. Demographic Details of a Total of 741 Cases from 1519 Patients.

Groups	Patient Cases	Gender	Age (yr)	Weight (Kg)	PCA Duration (Day)	Lockout Time (Min)
VAS_3	287	204F, 83M	47.9±17.3	63.0±12.1	4.2±2.5	10
VAS_5	44	27F, 17M	53.3±18.8	65.0±11.9	4.6±1.9	10
SE_0	390	267F, 123M	48.7±16.9	64.5±11.63	4.2±2.3	10
SE_1	20	18F, 2M	48.8±20	59.2±11.2	3.9±1.8	10

Note: VAS_3 means VAS score less than or equal to 3; VAS_5 means VAS score greater than or equal to 5; SE_0 means the total score of side effects equal to 0, which are counted as the total score of nausea plus vomiting; SE_1 means the total score of side effects greater than or equal to 1; Values are expressed as mean ± S.D.

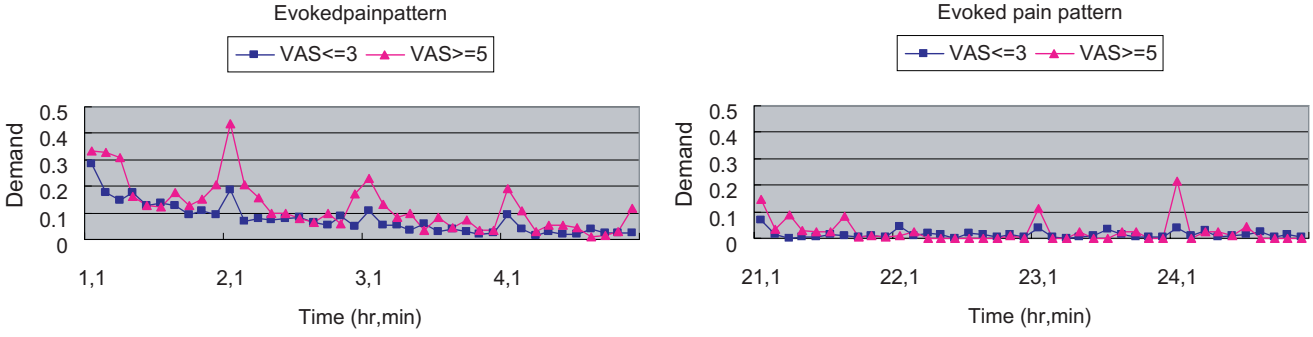


Fig. 3 Evoked pain pattern for two different ranges of VAS at the first 4 h and last 4 h after surgery during one day: **(A)** first 4 h, **(B)** last 4 h. (Notation in the horizontal axis of figures: 1,1: start from 1st min of 1st h; 2,1: start from 1st min of 2nd h; 3,1: start from 1st min of 3rd h; 4,1: start from 1st min of 4th h. The vertical axis shows the average number of demands).

the EPP, we analyzed and averaged all patients' data for four different groups (i.e. VAS_3, VAS_5, SE_0, and SE_1) in the first 4 h after finishing the operation and the last four hours (i.e. 21–24 h) during one day of treatment. Moreover, due to choosing 10 min lockout interval and counting demand number for every 1 min, the 10 points' data can be obtained for every 1 h interval. Figure 3 shows the EPP for two different ranges of VAS at the first 4 h and the last 4 h after surgery. This figure shows that the demand number of the last 4 h is significantly reduced. Moreover, the area value of EPP every hour has shown that large VAS (i.e. VAS_5) is higher than small VAS (i.e. VAS_3). This indicates that the patients like to press the button when they feel more pain. Therefore, the evoked parameters of area, latency, and amplitude can be extracted for two different ranges of VAS at the first 4 h and the last 4 h after surgery as shown in Fig. 4. This figure indicates that the area and amplitude parameters have little differences but the latency parameter has almost no differences when considering the factor of VAS.

Regarding two different ranges of side effects, Fig. 5 shows the EPP at the first 4 h and the last 4 h after surgical operation during one day. Since this figure is the same with Fig. 3, we can see that the demand number over the last 4 h is significantly reduced. Moreover, the latency of EPP has been displayed more regularity with no side effects but less regularity with side effects. This means patients like to press the button when they feel the pain with no side effects. However, with side effects, they seem willing to endure pain rather suffer unpleasant side effects. This was the main reason for the EPP to be randomized. Hence, the evoked parameters of area, latency, and amplitude can be extracted for two different ranges of side effects at the first 4 h and the last 4 h after surgery as shown in Fig. 6. This figure indicates that the latency parameter has large differences but the area and amplitude parameters have only small differences when considering the factor of side effects.

Based on the EPP results in Figs. 3 and 5, we propose that the area parameter is a good indicator for higher VAS patients, and the latency parameter is a better outcome for interpreting the patients with side effects. In order to find the variation of latency according to Fig. 6(b), we calculated the variance of latency for this parameter. Therefore, we first re-analyzed and averaged all patient data for different groups to generate an EPP. Then these three parameters of the area,

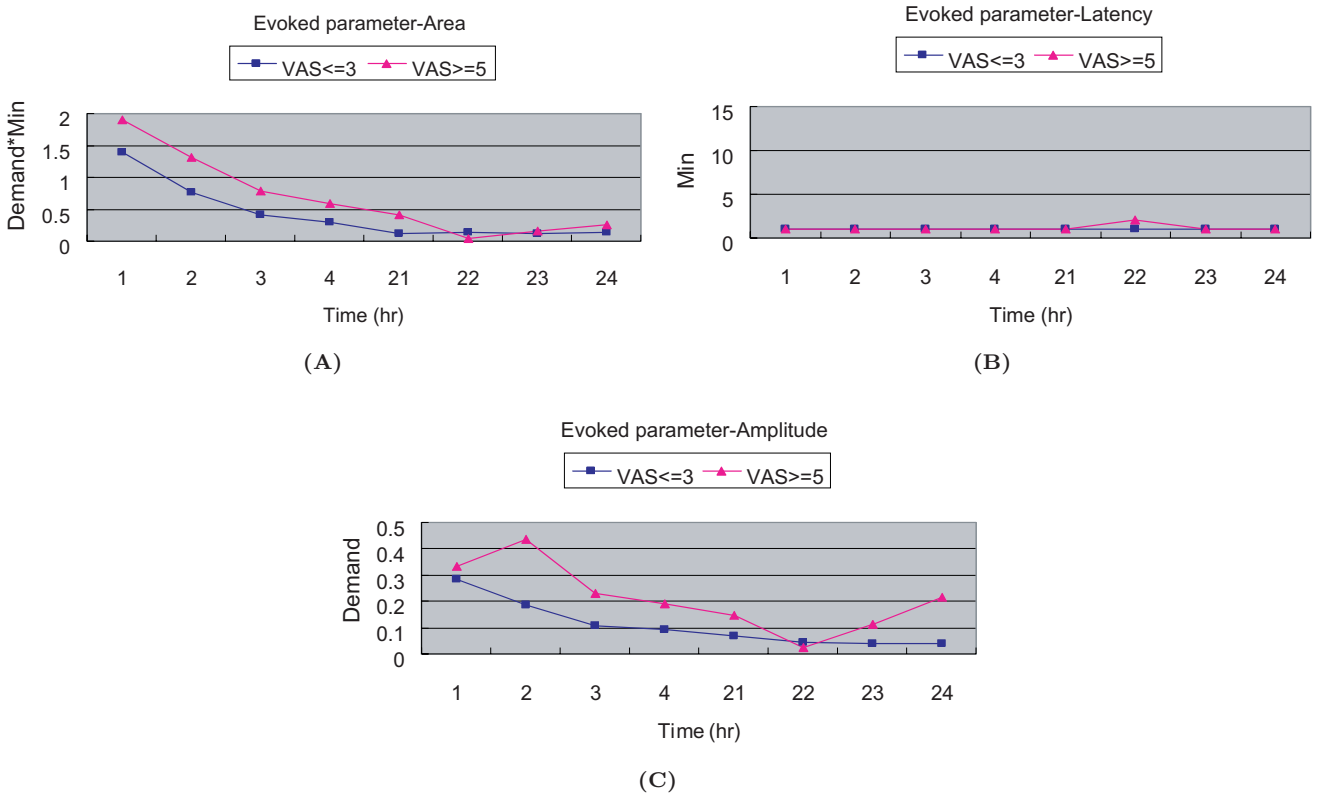


Fig. 4 Evoked parameters for two different ranges of VAS at the first 4 h and last 4 h after surgery during one day: **(A)** area parameter, **(B)** latency parameter, **(C)** amplitude parameter.

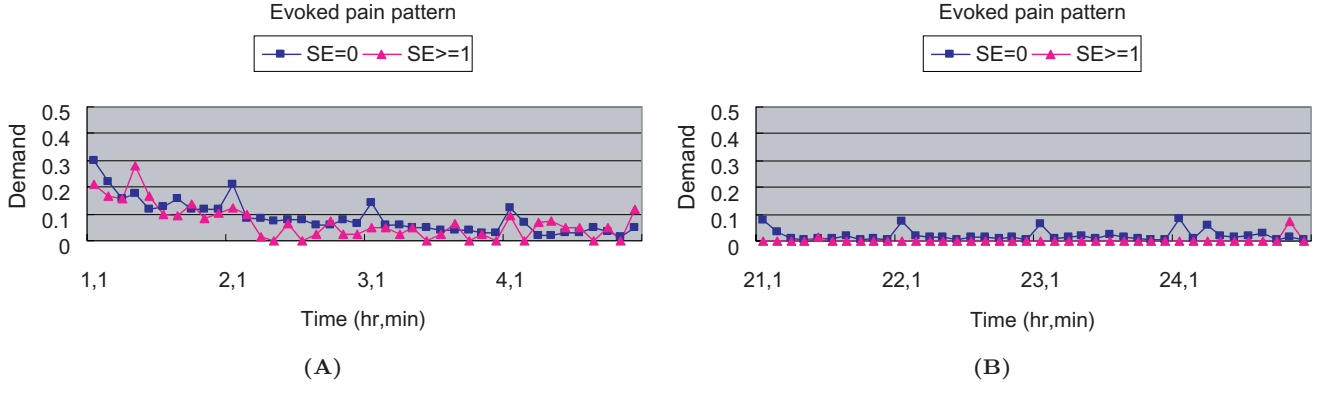


Fig. 5 Evoked pain pattern for two different ranges of side effects at the first 4 h and last 4 h after surgery during one day: **(A)** first 4 h, **(B)** last 4 h. (Notation in the horizontal axis of figures: 1,1: start from 1st min of 1st h; 2,1: start from 1st min of 2nd h; 3,1: start from 1st min of 3rd h; 4,1: start from 1st min of 4th h. The vertical axis shows the average number of demands).

variance of latency, and amplitude from the EPP were extracted using a cumulative method that added 2 h each time from finishing the operation until 24 h, as shown in Table 2. The statistical analysis of these three parameters using different ranges of VAS and SE is also shown in Table 2. Hence, Fig. 7 and Table 2 show that the value of area parameter had significant differences in the VAS group ($P < 0.01$) but there were no significant differences in the SE group ($P > 0.01$). Moreover, Fig. 8 and Table 2 show that the value of variance of latency parameter had significant differences in both VAS and SE groups ($P < 0.01$) but this mean $\pm$ S.D. value in the SE group of SE_1 (i.e. 11.20 ± 2.55) was significantly higher than that in the VAS group of VAS_5 (i.e. 2.05 ± 1.41). In contrast, Fig. 9 and Table 2 show that there were no significant differences in both VAS and SE groups ($P > 0.01$) when compared with the value of amplitude parameter. This indicates that the area

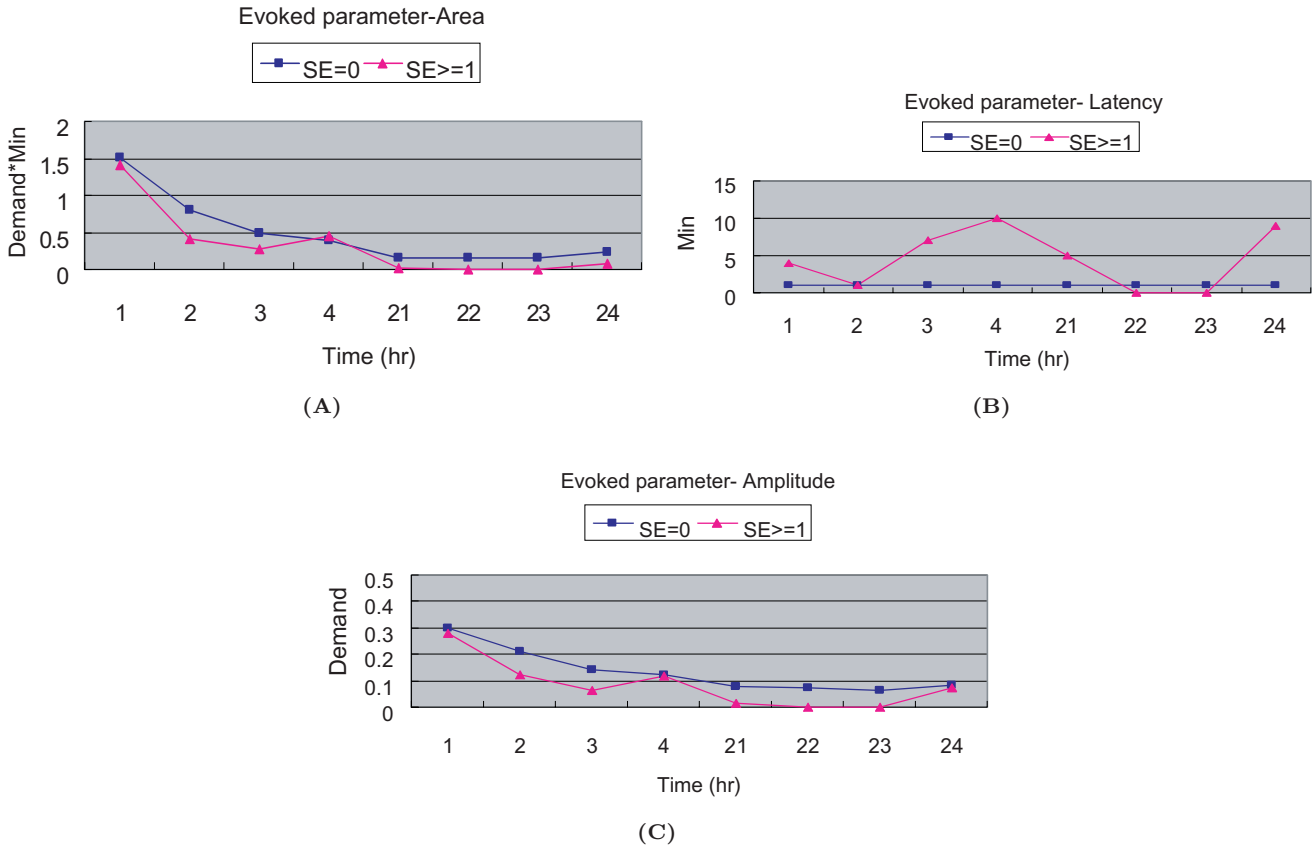
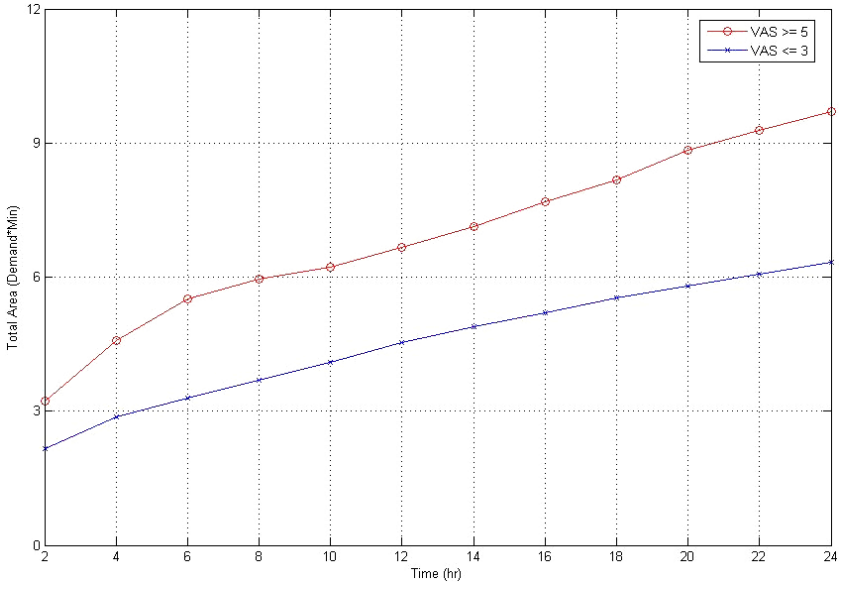


Fig. 6 Evoked parameters for two different ranges of side effects at the first 4 h and last 4 h after surgery during one day: **(A)** area parameter, **(B)** latency parameter, **(C)** amplitude parameter.

Table 2. Statistical Analysis of Three Evoked Parameters from Evoked Pain Pattern Using a Cumulative Method that Added 2 h Each Time from Finishing the Operation Until 24 h.

		Hr													
Parameter	**Group**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**Mean ± S.D.**	***P* Value**
Area	VAS_3	2.15	2.87	3.30	3.69	4.10	4.55	4.89	5.21	5.54	5.81	6.06	6.32	4.54 ± 1.34	$P < 0.01$
	VAS_5	3.23	4.58	5.52	5.96	6.22	6.66	7.13	7.68	8.18	8.83	9.29	9.71	6.92 ± 1.95	$(P = 0.002)$
	SE_0	2.31	3.19	3.65	4.01	4.38	4.84	5.23	5.61	5.98	6.30	6.63	7.02	4.93 ± 1.46	$P > 0.01$
	SE_1	1.83	2.55	2.92	3.86	4.07	4.25	4.43	4.64	4.74	4.90	4.92	4.99	4.01 ± 1.04	$(P = 0.09)$
Variance	VAS_3	0.00	0.00	0.00	0.00	0.90	0.79	0.68	0.60	0.54	0.48	0.44	0.41	0.40 ± 0.33	$P < 0.01$
of Latency	VAS_5	0.00	0.00	0.00	3.13	2.50	2.08	1.79	1.56	3.88	3.52	3.21	2.96	2.05 ± 1.41	$(P = 0.001)$
	SE_0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00 ± 0.00	$P < 0.01$
	SE_1	4.50	15.00	14.17	12.50	11.29	10.61	11.45	11.53	11.18	10.62	10.34	11.26	11.20 ± 2.55	$(P < 0.001)$
Amplitude	VAS_3	0.47	0.20	0.13	0.18	0.14	0.16	0.11	0.11	0.13	0.15	0.11	0.08	0.16 ± 0.10	$P > 0.01$
	VAS_5	0.77	0.42	0.45	0.16	0.11	0.27	0.20	0.29	0.22	0.32	0.16	0.33	0.31 ± 0.18	$(P = 0.023)$
	SE_0	0.51	0.27	0.15	0.16	0.18	0.18	0.13	0.17	0.15	0.15	0.15	0.15	0.20 ± 0.11	$P > 0.01$
	SE_1	0.34	0.14	0.15	0.32	0.05	0.05	0.05	0.15	0.05	0.10	0.02	0.08	0.13 ± 0.11	$(P = 0.108)$

Note: VAS_3 means VAS score less than or equal to 3; VAS_5 means VAS score greater than or equal to 5; SE_0 means the total score of side effects equal to 0, which are counted as the total score of nausea plus vomiting, equal to 0; SE_1 means the total score of side effects greater than or equal to 1; Values are expressed as mean ± S.D. $P < 0.01$ was considered statistically significant using unpaired Student's t-test method.



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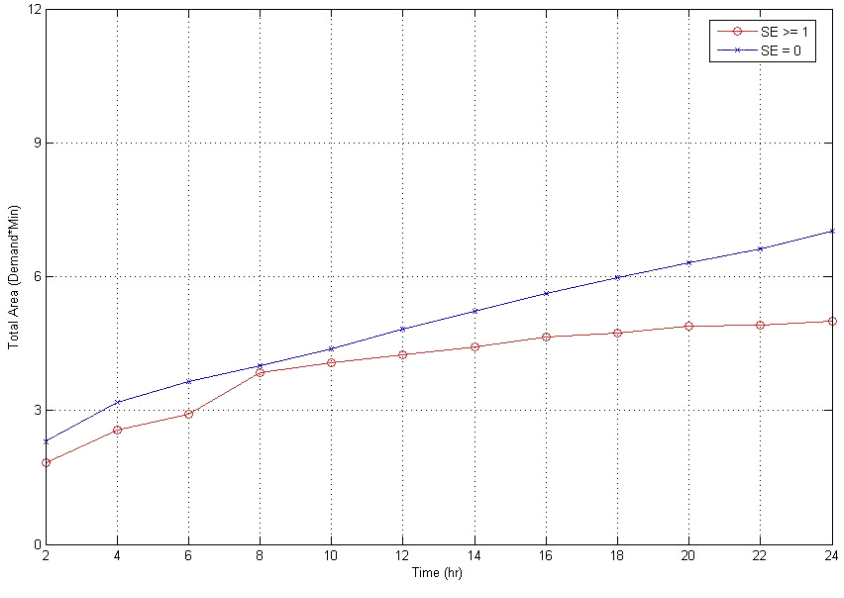


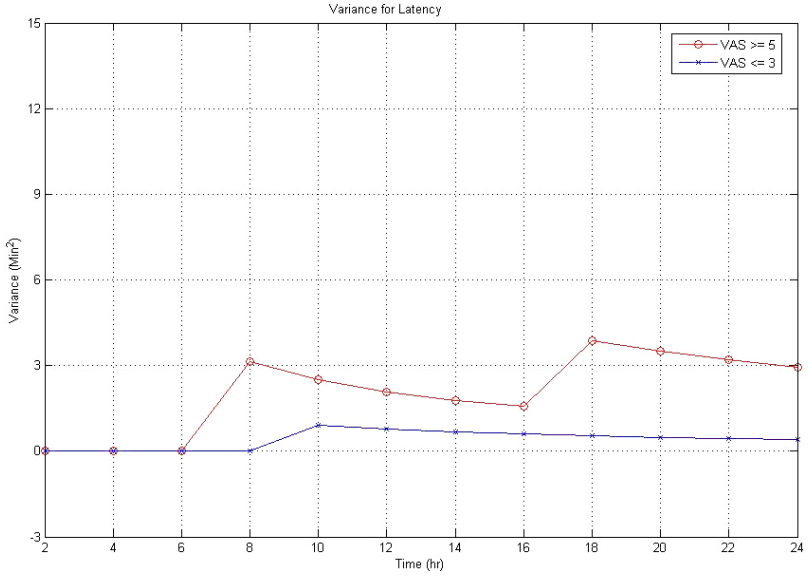
(B)

Fig. 7 Area parameter extracted from the evoked pain pattern using cumulative method for adding 2 h each time from finishing the operation until 24 h: **(A)** VAS group, **(B)** SE group.

parameter is a good indicator for higher VAS patients and the variance of latency parameter is a better outcome for interpreting the patients with side effects. However, the amplitude parameter had no significant differences in both VAS and SE groups.

DISCUSSION

In this paper, we use the *i*-pain system developed from our previous research[19] to collect the patients' daily medical information into a major server. A total of 741 cases from 1519 patients were screened to analyze the EPP in terms of two different ranges of VAS and side effects. Based on the evoked potentials concept, we have applied this novel technique for discrimination of pain intensity level and side effects using time-domain parameters extracted from EPP in postoperative pain via PCA. With the large scale of clinical data input, we have successfully constructed a comprehensive platform to encompass the high-throughput data acquisition and systemic analysis to yield a series of evidence-based medical evaluation for modern acute



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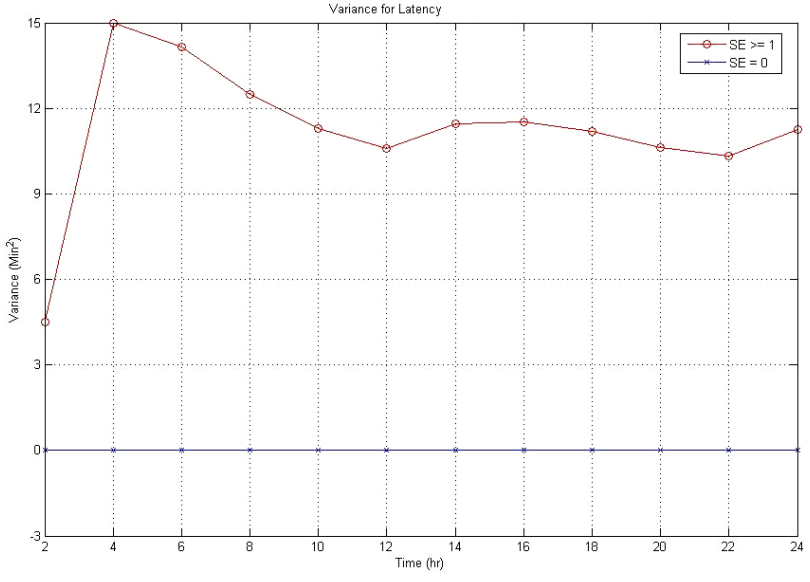
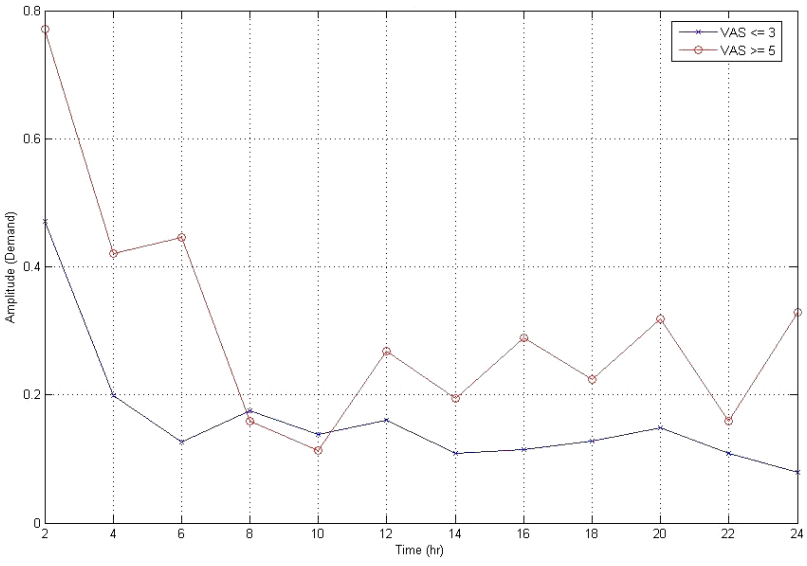


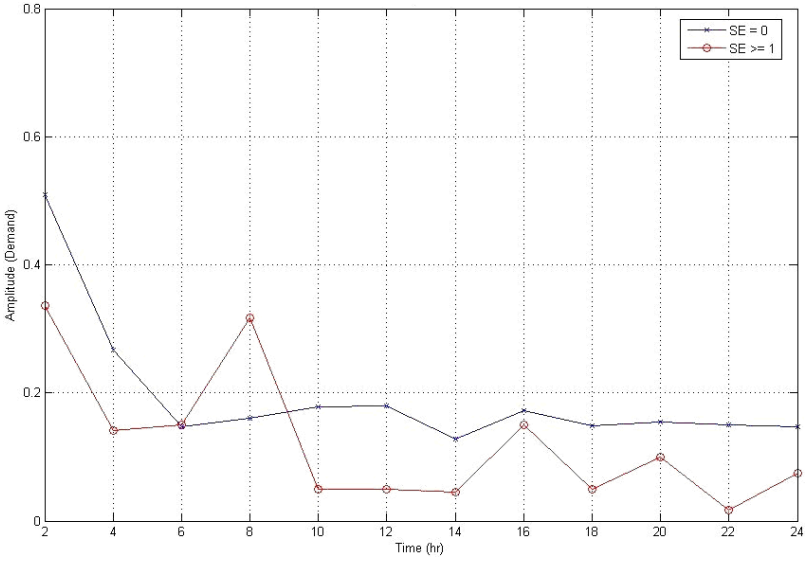
(B)

Fig. 8 Variance of latency parameter extracted from the evoked pain pattern using cumulative method for adding 2 h each time from finishing the operation until 24 h: **(A)** VAS group, **(B)** SE group.

pain service. However, the VAS and side effects are currently recorded once or twice a day via paper and then manually keyed into our *i*-pain system. However, this is still time consuming and involves too much paper work, for both doctors and nurses. That is why we record VAS and side effects only once or twice a day. It would be still too rough if we want to analyze the relationship of EPP with either VAS or SE. Recently, we have begun using an electronic diary[21–23] based on a personal digital assistant (PDA) as the data collection platform for recording the VAS and SE when medical doctors or nurses interview patients, and this may be able to record five or six times a day. This PDA is like a messenger that not only records VAS scores and side effects more frequently but also collects the PCA data via the RS232 port at time of medical staff visit. All data files are merged off-line and uploaded to a web-server PC using standard web-based TCP/IP. Then, further data mining by a web-server using intelligent analysis can be achieved in order to determine the relationship between data from the PDA (i.e. VAS and SE) and from the PCA (i.e. evoked parameters).



(A)



(B)

Fig. 9 Amplitude parameter extracted from the evoked pain pattern using cumulative method for adding 2 h each time from finishing the operation until 24 h: **(A)** VAS group, **(B)** SE group.

Although the AEPs have been used for on-line monitoring depth of anaesthesia for a decade,[24–27] no previous study has applied this technique to postoperative pain via PCA for on-line monitoring of pain quality. Evoked parameters (i.e. area, latency, and amplitude) are derived from the evoked potential pattern that was calculated from each demand after each bolus injection, i.e. the demand for pain relief, but not from subjective rating of pain. By continuous computing the preceding demands, evoked parameters are automatically generated without interviewing the patients. While the patient's grading of pain intensity requires a reliable self-appraisal and consciousness through verbal or visual contact, the output of evoked parameters is an objective parameter on the patient's demand for pain relief. Neither self-appraisal nor cognitive judgment is required for the parameters. The trigger of PCA is driven by both sensory-discriminative and emotional-cognitive components of the patient's pain. Thus, these evoked parameters are a more objective and comprehensive approach to assess the need for pain relief or intent to treat (ITT). Hence, this evoked approach to model

pain may provide an alternative method for the recent advocacy that a patient's pain rating scores should be treated as the fifth vital sign.

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