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Research Article

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Anesthetic Depth Monitoring Decreased the Incidence of Postoperative Delirium Assessed in Nursing Delirium Screening Scale in Elective Non-Cardiac Surgical Patients Receiving Intravenous Patient-Controlled Analgesia

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Abstract

Background

To identify the impact of processed electroencephalogram (pEEG)-guided anesthesia on postoperative delirium (POD) assessed by NuDESC, postoperative analgesic requirements, and the incidence of postoperative nausea/vomiting (PONV) in the elective non-cardiac surgical patients with intravenous patient-controlled analgesia (IVPCA) in the wards.

Methods

In this retrospective observational study, the anesthesiologists were free to use M-Entropy™, an pEEG device, to monitor the depth of anesthesia intraoperatively during the period (September 2015 ~ February 2018). Acute pain service team assessed the analgesic/side effects of IVPCA and POD at least twice daily for 3 days postoperatively. POD was screened by Nursing Delirium Screening Scale (NuDESC) (0-10). Pain severity was measured by an 11-point verbal numerical rating scale (0–10).

Results

A total of 1178 patients (≧60 years) were enrolled and divided to Entropy (749 patients) vs. non-Entropy group (429 patients). Multivariate logistic analysis showed that age (≧70), surgical types (non-joint), intraoperative highest minimum alveolar concentration (MAC) (<0.9MAC) and the POD incidence were independent predictors for group differences (multiple odds ratio and 95% confidence interval: 5.99, 4.34-8.29; 2.01, 1.49-2.72; 6.84, 4.38-10.67; 0.09, 0.04-0.19). The POD incidence in Entropy group (2.2%, 17 patients) was significantly lower than that in non-Entropy group (6.7%, 29 patients) (p <0.001). However, pEEG-guided anesthesia did not affect the phenomenological characteristics of POD. In addition, intraoperative pEEG-guided anesthesia did not reduce total morphine dose of IVPCA, the incidence of PONV and pain severity.

Conclusions

Processed EEG-guided anesthesia decreased POD incidence assessed in NuDESC in IVPCA patients undergoing elective non-cardiac surgery returning to the common ward. In addition, it did not reduce postoperative pain severity, postoperative analgesic requirements and PONV incidence. More researches are needed to investigate the effects of pEEG-guided anesthesia on POD and other postoperative conditions.

Key Words: Anesthetic depth monitoring, processed electroencephalogram, postoperative delirium, patient-controlled analgesia.

Introduction

Postoperative delirium (POD), which is characterized by an acute change in consciousness and cognitive impairment with a fluctuating course, can be associated with serious consequences ranging from a lengthened hospital stay to an increased mortality rate although it is transient and reversible in most cases [1-3]. POD is a common postoperative complication with a wide range of reported incidence from 10% to 46%, which may be due to its variations in clinical manifestations and the heterogeneity in previous studies attributable to differences in the recruited populations, surgical procedures, anesthesia methods, and assessment tools [4, 5].

The choice of assessment tool is an important factor affecting the POD incidence. Although the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) from the American Psychiatric Association provides the diagnostic criteria for delirium, definitive delirium diagnosis based on these criteria is a time-consuming process that involves a trained and experienced physician [3, 6]. In contrast, the nursing delirium screening scale (NuDESC) is a convenient systematic delirium assessment tool with which the care providers can finish the evaluation in one minute [7]. The tool, which has recently gained popularity worldwide, was translated into several languages [8-11] for clinical use in a wide variety of settings including the postoperative care unit (PACU), common ward [12], emergency department [13], and palliative care unit [14]. Despite a high sensitivity (>95 %) but a relatively low specificity (>70 %) associated with the use of NuDESC in POD assessment as reported in a study comparing different delirium bedside screening tools [15], a recent meta-analysis revealed moderate to high sensitivity and high specificity of NuDESC in this setting [16]. Notwithstanding the discrepancy in their findings, both studies validated NuDESC as a reliable assessment tool for POD.

Due to a lack of effective treatment, primary prevention of POD through minimizing perioperative risks is crucial [1]. Previous studies have demonstrated a positive correlation between the intraoperative monitoring depth of anesthesia and the incidence of POD [17-19]. Processed electroencephalogram (pEEG), which is a widely accepted tool for monitoring the depth of anaesthesia, has been reported to serve as a reliable guidance for anaesthetic dosage adjustment. Nevertheless, whether the use of pEEG plays a beneficial role in decreasing the risk of POD remains controversial. Although some studies reported its effectiveness for reducing the incidence of POD, a recent large-scale randomized controlled trial recruiting over 1200 participants failed to reproduce the result [20]. In addition, postoperative pain has been identified as a perioperative risk factor for POD [21]. Although intravenous patient-controlled analgesia (IVPCA) has been widely used for postoperative control in different clinical settings, the relationship between IVPCA and the development of POD remains unclear. Therefore, the current study aimed at investigating the effectiveness of intraoperative pEEG monitoring for preventing POD in surgical patients receiving postoperative IVPCA.

Materials and Methods

Study design and protocol

The current investigation was a retrospective observational study recruiting all adult patients who received elective non-cardiac surgery under general anaesthesia between September 2015 and February 2018 at a single tertiary referral hospital. During the period, pEEG was introduced to our department and allowed to use freely by anesthesiologists' decision. All patients were divided into Entropy (i.e., with intraoperative pEEG) and non-Entropy (i.e., without intraoperative pEEG) groups. Information about demographic characteristics (e.g., age, gender, body mass index) as well as a history of alcohol drinking, dementia, and use of psychiatric medication were collected and recorded. The surgeries that the participants underwent were divided into two categories, namely, joint (including knee, hip, spine) surgery and non-joint (all surgical sites excluded knee, hip, spine) surgery. In addition, the predictors were divided into two categories according to their mean. Minimum alveolar concentration, MAC, measure the end-tidal anesthetic. It presented the level of anesthetic within the alveoli and, in turn, at the level of central nervous sy stem [22]. 1 MAC was defined as that 50% of people did not move in response to a surgical stimulus. The highest minimum alveolar concentration (MAC) during operation were recorded.

Participants

Patient recruitment criteria for the current study were the same as those described in our previous report [23]. The inclusion criteria were adult patients (i.e., age 60 or over) regardless of gender who received postoperative IVPCA for at least three consecutive days within the study period. The exclusion criteria were (1) patients still under sedation after surgery (e.g., those to be transferred to the ICU), (2) non-Chinese speakers, (3) those with preoperative cognitive impairment and/or dementia. The protocol and procedures of the present study were reviewed and approved by the Institutional Review Board (IRB) of Chi Mei Medical Center, Tainan, Taiwan (Approval number: IRB10009-012) and registered in a publicly accessible database [University Hospital Medical Information Network (UMIN), Japan; http://www.umin.ac.jp/ctr/index.htm; Trial ID: UMIN000022711]. Taking the routine nature of the procedures of the current study into consideration, the IRB waived the requirement for a written consent from the participants.

Outcomes (primary and secondary)

The primary aim of this study was to investigate whether pEEG-guided anesthesia could decrease the incidence rate of POD in elective non-cardiac surgical patients aged 60 or older who received postoperative IVPCA. In addition, we compared the phenomenological characteristics of NuDESC in POD from postoperative day one to day three between patients with and those without p-EEG guided anesthesia.

Although pEEG monitoring was originally designed for the adjustment of the hypnotic dosage of anaesthetics, pEEG-guided anesthesia was found to be associated with decreased analgesic requirements, less postoperative nausea/vomiting (PONV) and reduced postoperative pain in patients undergoing non-cardiac

surgery [24-26]. Accordingly, the secondary outcomes of the present study were the differences in analgesic dosage, pain score, and the incidence of PONV between patients with and without pEEG-guided anesthesia.

Equipment and procedures

Processed electroencephalogram (pEEG) was acquired with a standard equipment (M-Entropy™, GE Healthcare, Helsinki, Finland) that was designed for the computation of two parameters: State Entropy (SE) and Response Entropy (RE). SE (range 0–91) reflects the cortical state of the patient with a range of 40-60 suggesting adequate anaesthesia depth during surgery, while RE (range 0-100) measures the activity of facial muscle which is an early indication of emergency when quickly rising [27]. Three electrodes were placed on the forehead of the participants according to the manufacturer's instructions.

Intravenous patient controlled analgesia (IVPCA) was achieved by the use of a standard intravenous pump (CADD®-Solis Ambulatory Infusion Pump, Smith Medical ASD. Inc., Oakdale , USA) that delivered intravenous morphine at an initial loading dose of 5mg, followed by a bolus dose of 1 mg without a continuous background infusion. Repeated dosage was set at an interval of at least 10 minutes.

Postoperative Monitoring and Evaluation Parameters

For patients receiving IVPCA, assessments of delirium, effectiveness of analgesia, and side effects (e.g., postoperative nausea/vomiting) were performed twice a day by the nursing staff of the acute pain service team (APS) that comprised 38 attending anesthesiologists, eight residents, pain nurses, and pharmacists [23, 28]. Attending anesthesiologists provided additional evaluations for problematic patients [23].

Evaluation of delirium was conducted with NuDESC, which is a five-item rating scale that assesses disorientation, inappropriate behaviour, inappropriate communication, illusion/hallucinations, and psychomotor retardation. The severity of postoperative rest/movement-evoked pain was assessed and recorded using 11-points VNRS (0: no pain; 10: the worst imaginable pain) with a score of ≦3 being considered adequate pain control. In addition, the side effects of IVPCA including nausea, vomiting were examined and recorded during each visit [23, 28].

Statistical Analysis

Data were analyzed using the STATA 12.0 (Stata Corp, College station, TX, USA) statistical software. Univariate logistic analysis was used to identify predictors for the differences between Entropy and non-Entropy groups. The significance of difference was presented as odds ratio (OR) and 95% confidence intervals (CI). An entry criterion for multivariate selection was set as $p < 0.1$. Multivariate logistic regression with backward elimination procedure was used to achieve the final model, and $p < 0.05$ was set as the exit criterion. Categorical variables were measured by chi-square test or Fisher's exact test. A p value of <0.05 was considered significant.

Results

Demographic and clinical characteristics of participants

In total, 1178 IVPCA patients undergoing elective non-cardiac surgery were enrolled and divided into Entropy (749 people, 63.5%) and non-Entropy (429 people, 36.5%) groups (Figure 1, Table 1).

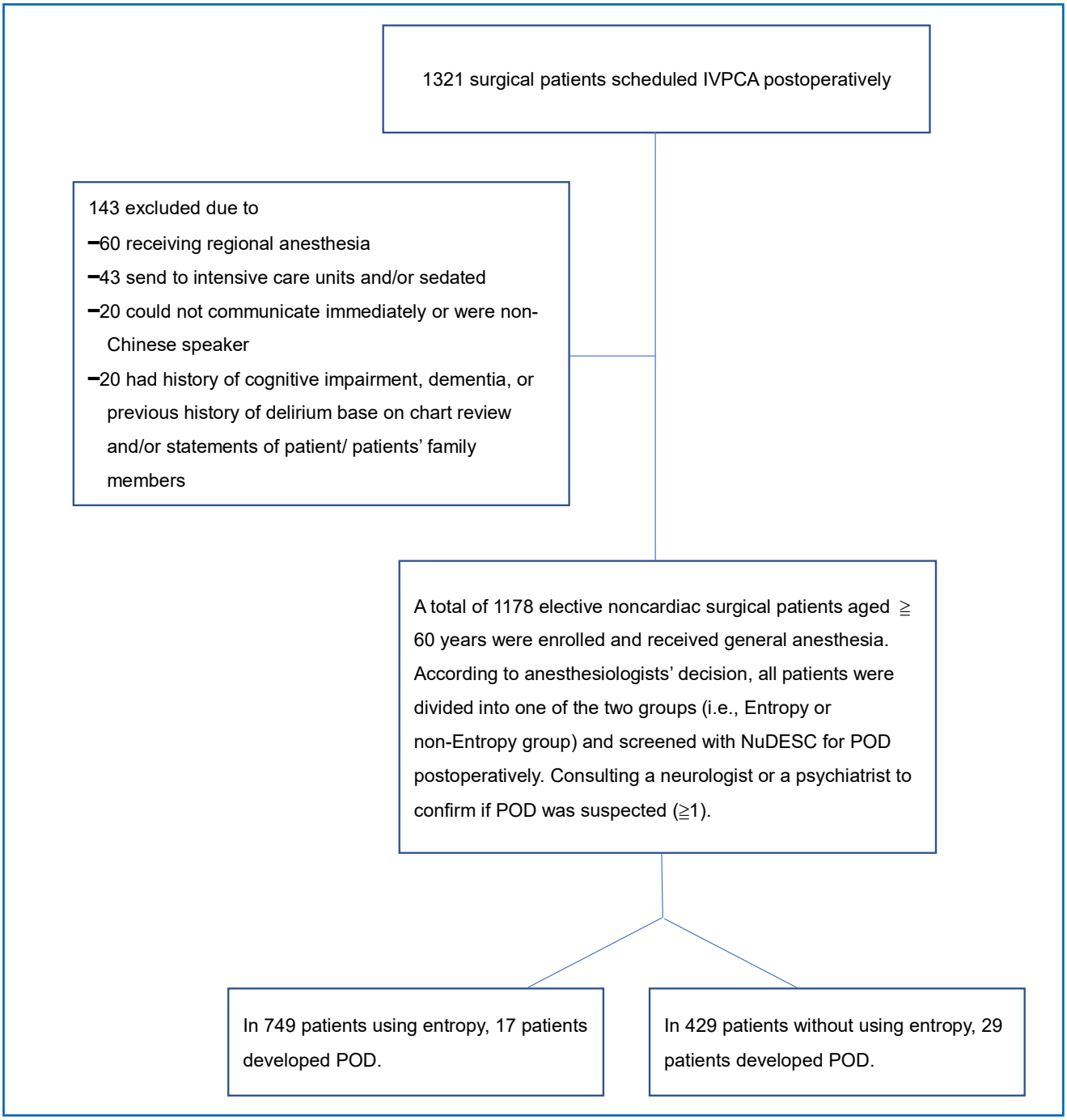

Figure 1: Flowchart of the population. IVPCA: intravenous patient controlled analgesia. **POD:** postoperative delirium. NuDESC: Nursing Delirium Screening Scale.

Table 1: Comparison of baseline characteristics and perioperative parameters of IVPCA patients between Entropy group and non-Entropy group.

Variables	Entropy, n (%) N=749 (63.5)	non-Entropy, n (%) N=429 (36.5)	Crude odds ratio (95% CI)	*P*
Preoperative baseline characteristics				
Age group				
60-69	256 (34.2)	333 (77.7)		
≧70	493 (65.8)	96 (22.3)	6.68 (5.08-8.77)	<0.001
Gender				
Female	398 (53.2)	220 (51.3)		
Male	351 (46.8)	209 (48.7)	0.92 (0.73-1.17)	0.58
BMI				
≦30	638 (85.2)	374 (87.2)		
>30	111 (14.8)	55 (12.8)	1.18 (0.83-1.67)	0.74
ASA physical status				
I,II,III	728 (97.2)	411 (95.8)		
IV	21 (2.8)	18 (4.2)	0.65 (0.34-1.25)	0.26
Hypertension				
No	342 (45.7)	200 (46.7)		
Yes	407 (54.3)	229 (53.3)	1.03 (0.81-1.31)	0.79
Diabetes mellitus				
No	425 (56.8)	264 (61.6)		
Yes	324 (43.2)	165 (38.4)	1.21 (0.95-1.55)	0.12
Intraoperative parameters				
Type of surgery				
Joint	243 (32.4)	176 (41.0)		0.003
Non-Joint	506 (67.6)	253 (59.0)	1.45 (1.13-1.85)	0.003
Duration of surgery				
<185 min	333 (44.5)	210 (49.0)		
≧185 min	416 (55.5)	219 (51.0)	1.19 (0.94-1.51)	0.15
Duration of anesthesia				
<220 min	379 (50.7)	200 (46.7)		
≧220 min	370 (49.3)	229 (53.3)	0.85 (0.67-1.08)	0.20
Inhalation MAC				
<0.9	336 (44.8)	29 (6.7)		
≧0.9	413 (55.2)	400 (93.3)	0.06 (0.09-0.13)	<0.001
Intraoperative opioid use (fentanyl: >1ug/kg/hr)				
No	508 (67.8)	306 (71.3)		
Yes	241 (32.2)	123 (28.7)	1.18 (0.91-1.52)	0.21
Intraoperative hypnotics use (midazolam)				
No	701 (93.5)	395 (92.1)		
Yes	48 (6.5)	34 (7.9)	0.79 (0.50-1.25)	0.32
Postoperative parameters and complications				
Delirium				
No	732 (97.8)	400 (93.3)		
Yes	17 (2.2)	29 (6.7)	0.32 (0.17-0.59)	<0.001
Total morphine dose/day of IVPCA				
<18 mg/day	328 (46.5)	175 (40.6)		

≧18 mg/day	401 (53.5)	255 (59.4)	0.83 (0.65-1.06)	0.17
PONV				
No	624 (83.4)	350 (81.6)		
Yes	125 (16.6)	79 (18.4)	0.88 (0.65-1.06)	0.45
VNRS score				
Pain at rest				
PD 1				
≤3	659 (88.0)	366 (85.3)		
>3	90 (12.0)	63 (14.7)	0.79 (0.56-1.12)	0.19
PD 2				
≤3	714 (95.3)	404 (94.2)		
>3	35 (4.7)	25 (5.8)	0.79 (0.46-1.34)	0.38
PD 3				
≤3	729 (97.3)	419 (97.7)		
>3	20 (2.7)	10 (2.3)	1.14 (0.53-2.47)	0.72
Movement-evoked pain				
PD 1				
≤3	284 (37.9)	152 (35.4)		
>3	465 (62.1)	277 (64.6)	0.89 (0.70-1.15)	0.39
PD 2				
≤3	446 (59.5)	278 (64.8)		
>3	303 (40.5)	151 (35.2)	1.25 (0.97-1.59)	0.07
PD 3				
≤3	678 (90.5)	392 (91.4)		
>3	71 (9.5)	37 (8.6)	1.10 (0.73-1.68)	0.62

Notes: Duration of surgery/anesthesia is divided by the mean (185 in surgery, 220 in anesthesia). P <0.05, statistical significance. * Equianalgesic opioids dosing

Abbreviations: IVPCA: intravenous patient controlled analgesia; CI: confidence interval; BMI: body mass index; ASA: American Society of Anesthesiologists classification; MAC: minimum alveolar concentration; PD: postoperative day; PONV: postoperative nausea and vomiting; VNRS: verbal numerical rating score.

Primary outcome: Difference in incidence rate of POD between the two groups

The patient characteristics of the two groups are shown in Table 1. The proportion of patients aged ≧70 in the Entropy group was significantly higher than that in the non-Entropy group (65.8% vs 22.3%, p <0.001). Regarding surgical types and intraoperative highest MAC, the Entropy group had a higher proportion of non-joint surgery and MAC<0.9 compared to those in the non-Entropy group (67.6% vs 59.0%, p =0.003; 44.8% vs 6.7%, p <0.001). The incidence of POD in the Entropy group was significantly lower than that in the non-Entropy group (2.2% vs 6.7%, p <0.001). There were no significant differences in other baseline characteristics and perioperative parameters between the two groups.

Multivariate logistic analysis (Table 2) revealed that age ≧70 and the intraoperative highest MAC <0.9 were significant predictors of intraoperative pEEG use (multiple OR, 95% CI: 5.99, 4.34-8.29; 6.84, 4.38-10.67). The incidence of POD was significantly lower in patients with intraoperative pEEG compared to those without (multiple OR 0.09, 95% CI: 0.04-0.19). The proportion of Entropy monitoring was higher in patients receiving non-joint surgery compared to those undergoing joint procedures (multiple OR: 2.01, 95% CI: 1.49-2.72).

Table 2: Multivariate logistic analysis in IVPCA patients with or without intraoperative Entropy

Predictors	Entropy, n (%) N=749	non-Entropy, n (%) N=429	Multiple odds ratio (95% CI)	*P*
Age group				
60-69	256 (34.2)	333 (77.7)	1.0	
≧70	493 (65.8)	96 (22.3)	5.99 (4.34-8.29)	<0.001
Type of surgery				
Joint	243 (32.4)	176 (41.0)	1.0	
Non-Joint	506 (67.6)	253 (59.0)	2.01 (1.49-2.72)	<0.001
MAC				
<0.9	336 (44.8)	29 (6.7)	6.84 (4.38-10.67)	<0.001
≧0.9	413 (55.2)	400 (93.3)	1.0	
Delirium				
No	732 (97.8)	400 (93.3)	1.0	
Yes	17 (2.2)	29 (6.7)	0.09 (0.04-0.19)	<0.001

Abbreviations: IVPCA: intravenous patient-controlled analgesia; CI: confidence interval; MAC: minimum alveolar concentration.

Features of POD patients between groups

There were no significant differences in baseline characteristics, perioperative parameters, and PONV among patients with POD between the Entropy and non-Entropy groups (Table 3). There were no significant differences in NuDESC scores, phenomenological characteristics between the Entropy and non-Entropy groups. Regarding the occurrence and duration of POD patients (Table 4), there were some significant difference. The most incidence and prevalence day were all postoperative day 1 in Entropy group while those in non-Entropy group was day 2. Most duration lasting was 1 day in two group and there was no significant difference between two group.

Table 3: Comparison of baseline characteristics and perioperative parameters of POD patients with or without intraoperative Entropy.

Variables	POD, N=46		Crude odds ratio (95% CI)	*P*
	Entropy, N=17	non-Entropy, N=29		
Preoperative baseline characteristics				
Age group				
60-69	1 (5.8)	6 (20.6)		
≧70	16 (94.2)	23 (79.4)	4.17 (0.45-38.09)	0.23
Gender				
Female	10 (58.9)	13 (44.9)		
Male	7 (41.1)	16 (55.1)	0.56 (0.16-1.91)	0.35
BMI				
≦30	4 (23.6)	1 (3.5)		
>30	13 (76.4)	28 (96.5)	0.11 (0.01-1.14)	0.054
ASA physical status				
I, II, III	16 (94.2)	23 (79.4)		
IV	1 (5.8)	6 (20.6)	0.23 (0.02-2.18)	0.23
Hypertension				
No	7 (41.1)	9 (31.1)		
Yes	10 (58.9)	20 (68.9)	0.64 (0.18-2.23)	0.48
Diabetes mellitus				
No	9 (53.0)	20 (68.9)		
Yes	8 (47.0)	9 (31.1)	1.97 (0.57-6.79)	0.27
Intraoperative parameters				
Type of surgery				
Non-Joint	12 (70.6)	19 (65.6)		
Joint	5 (29.4)	10 (34.4)	0.79 (0.21-2.88)	0.72
Duration of surgery				

<185 min	6 (35.3)	12 (41.4)		
≧185 min	11 (64.7)	17 (58.6)	1.29 (0.37-4.46)	0.68
Duration of anesthesia				
<220 min	6 (35.3)	14 (48.3)		
≧220 min	11 (64.7)	15 (51.7)	1.71 (0.49-5.87)	0.39
Inhalation MAC				
<0.9	8 (47.0)	9 (31.0)		
≧0.9	9 (53.0)	20 (69.0)	0.50 (0.14-1.74)	0.27
Intraoperative opioid use (fentanyl: >1ug/kg/hr)				
No	9 (53.0)	19 (65.6)		
Yes	8 (47.0)	10 (34.4)	1.68 (0.49-5.73)	0.39
Intraoperative hypnotics use				
No	13 (76.4)	27 (93.2)		
Yes	4 (23.6)	2 (6.8)	4.15 (0.67-25.68)	0.17
Postoperative phenomenological characteristics of POD detected in NuDESC				
NuDESC scores (1–10)				
1	5 (29.4)	8 (27.5)		1.00
2-5	10 (58.8)	18 (62.1)		0.91
6-10	2 (11.8)	3 (10.4)		1.0
Features				
Disorientation	10 (58.8)	17 (58.6)		0.99
Inappropriate behavior	8 (47.0)	14 (48.2)		0.96
Inappropriate communication	11 (64.7)	16 (55.1)		0.74
Illusions/ hallucinations	5 (29.4)	16 (55.1)		0.40
Psychomotor retardation	3 (17.6)	5 (17.2)		1.00

Abbreviations: POD: postoperative delirium; CI: confidence interval; BMI: body mass index; ASA: American Society of Anesthesiologists classification; PONV: postoperative nausea and vomiting;
VNRS score: verbal numeric rating scale; PD: postoperative day; NuDESC: nursing delirium screening scale; MAC: minimum alveolar concentration.

Table 4: Occurrence and duration of POD during postoperative day 1-3 in IVPCA patients between groups

	Entropy (N=17)	**non-Entropy (N=29)**	***P***
Incidence of POD, n (%)			
PD 1	9 (1.2%)	11 (2.5%)	0.14
PD 2	6 (0.8%)	14 (3.2%)	0.004
PD 3	2 (0.2%)	4 (0.9%)	0.19
Prevalence of POD, n (%)			
PD 1	9 (1.2%)	11 (2.5%)	0.131
PD 2	7 (0.9%)	18 (4.1%)	<0.001
PD 3	5 (0.6%)	9 (2.0%)	0.046
Duration of POD, n (%)			
1 day	13 (76.4)	19 (65.5)	0.92
>1 day	4 (23.6)	10 (34.5)	0.75

Abbreviations: POD: postoperative delirium; IVPCA: intravenous patient controlled analgesia; PD: postoperative day.

Secondary outcomes: Analgesic amount, pain score, and the incidence of PONV

A comparison of postoperative parameters and complications between the Entropy and non-Entropy groups demonstrated no differences in analgesic requirement and the incidence of PONV as well as the pain score at rest and with movement from postoperative Day 1 to Day 3.

Discussion

The current study was the first to investigate the association between pEEG-guided anesthesia and POD in the surgical population with postoperative IVPCA. We demonstrated that pEEG-guided anesthesia reduced the incidence rate but did not influence the phenomenological characteristics of POD assessed in NuDESC in patients receiving elective non-cardiac surgery with postoperative IVPCA. Although the significantly older patients in the Entropy group, their incidence of delirium was notably lower than that in the non-Entropy group. Taking into consideration that age is the most important risk factor of POD, our results highlighted a potential beneficial impact of pEEG on reducing the incidence of POD.

As to significantly higher prevalence of older patients (≧70 years) in the Entropy group than that in the non-Entropy group may reflex anesthesiologists' concern over a potential danger of an excessive depth of anesthesia in this population.

Our finding regarding an association between pEEG-guided anesthesia and a reduced incidence of POD was consistent with that of previous studies [17-19]. One of the possible mechanisms would be that the pEEG-guided anaesthesia decreased the anesthetics (both hypnotics and analgesics) requirement [25, 29] and the duration of burst suppression. Burst suppression, an electroencephalography pattern consisting of a continuous alternation between high-voltage slow waves and isoelectric activity, is a characteristic of inactive or pathologic brain. Some studies have reported that the risk factors of burst suppression include hypothermia [30], coma [31], drug intoxication [32, 33] and older age [34, 35]. Burst suppression is also an indicator of excessively deep anaesthesia during surgery [31] and has been reported to be an independent risk factor for POD [36]. In addition, decreased anesthetics requirement under pEEG-guided titrating prevent excessively deep anesthesia leading to less burst suppression duration and may reduce the incidence of POD. In our investigation, though we did not calculate the precise amount of anesthetics during the whole operation, the proportion of the intraoperative highest MAC <0.9 were significant higher in Entropy group, it may reveal that under pEEG titrating, less anesthetics could be necessary. Although a recent large-scale randomized clinical trial demonstrated significant associations of pEEG with reductions in anesthetics requirement and the duration of burst suppression in older adults undergoing major surgery, it failed to show a difference in the incidence of POD between the pEEG and non-pEEG groups [20]. The discrepancies in effectiveness of intraoperative pEEG-guided anesthesia for the prevention of POD reported in previous studies may be attributed to their high heterogeneity including preoperative patient comorbidity, preoperative brain vulnerability and surgery type and duration as well as the use of different pEEG processors, pEEG parameter, anaesthetic technique to maintain an acceptable pEEG range, and POD assessment tool. Future studies are warranted to investigate the impacts of these factors on the association between the pEEG-guided anesthesia and POD.

The duration and phenomenological characteristics of POD assessed in NuDESC were not different between the two groups. The results were not consistent with those reported in a previous study in which management of the risk-factors for POD (i.e., cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration) significantly decreased the duration but not the severity of delirium [1]. Because POD is associated with structural abnormalities of the brain including impaired white matter integrity, ischemic lesions, brain atrophy, edema, and inflammation [37], failing to demonstrate its association with pEEG could be partly explained by the inability of pEEG to assess subcortical activities. Taken together, whether anesthetic depth monitoring has an impact on the onset, duration, severity, and phenomenological characteristics of POD remains to be elucidated.

Our investigation into the secondary outcomes revealed no significant associations of intraoperative pEEG-guided anesthesia with postoperative daily morphine dose, severity of postoperative pain, and the incidence rate of PONV in the study population. Anesthetic depth monitoring devices including BIS monitor, M-Entropy, and middle latency auditory evoked potentials have been introduced clinically based on the concept that optimization of the anaesthetic depth with adequate anesthetics (e.g., hypnotics and analgesics) may be beneficial to postoperative outcomes such as recovery time, postoperative pain and postoperative nausea and vomiting. Our results were similar to those reported in a previous study in which the authors reported no difference in the incidences of common postoperative complications such as PONV and severe postoperative pain between BIS-guided anaesthesia and anesthetic concentration-guided protocols in patients at high risk for intraoperative awareness [38]. However, some studies showed that the maintenance of adequate intraoperative depth of anaesthesia through monitoring the middle latency auditory evoked potentials or BIS index were associated with reductions in postoperative pain and analgesic requirements in the PACU and during postoperative 24 hours [24, 25]. Moreover, a double-blind clinical trial in which 60 patients undergoing laparoscopic cholecystectomy were randomly divided into low and high BIS (35-44 vs. 45-55) groups demonstrated that general anaesthesia in those with a low BIS was associated with less PONV and less postoperative pain compared to those with a high index [26]. Therefore, the efficacy of pEEG-guided anaesthesia for reducing postoperative pain severity and the incidence of PONV is still a controversial issue that needs to be further explored.

In addition to the influence of pEEG on the incidence of POD, its impact on the characteristics and features of POD were also investigated in this study. Our results revealed that most patients of POD in the Entropy group developed POD on postoperative day 1, whereas those in the non-Entropy group experienced that condition on postoperative day 2. The reported onset time of POD varied in previous studies; while one study without de-

tailed descriptions of anesthetic monitoring showed that more than half of their patients developed delirium on postoperative day 1 [3], other studies identified postoperative day 2 as the most common onset time of POD [21, 39]. Regarding the prevalence of POD, it was significantly higher in the non-Entropy group on the second and third postoperative days compared to that in the Entropy group despite a lack of difference between the two groups on postoperative day 1. There were no significant differences in other characteristics of POD between the two groups including the severity and duration. The effect of anesthetic depth monitoring on the onset time, duration, severity, and phenomenological characteristics of POD remains to be investigated.

Limitations

There were some limitations in this study. First, the patients amount of two groups were not balance. Processed EEG was not available in our hospital till September 2015. Since it did not be included in our Health Insurance Payment, the charge would be at patient's own expense. The patient's own expense process was allowed in February 2018. During the period, anesthesiologists were allowed to use it by their own decisions, and the number of patients included in two group were demonstrated as above. Second, the lack of a standard protocol for the induction and maintenance of anaesthesia due to the observational nature may introduce heterogeneity that could potentially bias our findings. Third, despite the goal of maintaining an SE index between 40 and 60 in accordance with the recommendation of GE Healthcare within the study period (i.e., September 2015 and February 2018) to ensure adequate hypnotic effect during general anaesthesia, other parameters such as Entropy index value and burst suppression ratio could not be recorded until March, 2018. Therefore, the impacts of these reference parameters on the anesthetists' adjustment of the depth of anesthesia that may affect the study outcomes remain unclear. Fourth, despite our routine twice-a-day assessment as well as extra visits by the APS team, the incidence of POD may be missed due to its fluctuating characteristic. Nevertheless, an education program for nursing staff focusing on the detection of POD using NuDESC was implemented before the current study to minimize a missed incidence. Fifth, our APS team visited the patients for three consecutive postoperative days because most POD developed in the first three days after surgery. Therefore, the incidence of POD after postoperative day 3 may be underestimated. Sixth, our results from a single hospital may not be extrapolated to other medical care settings, further multi-centered studies are required to validate our findings.

Conclusion

Our results supported the effectiveness of intraoperative anesthetic depth monitoring with pEEG for reducing the incidence of POD assessed in NuDESC in older patients who received intravenous patient-control analgesia. It was associated with a reduction in the overall incidence rate but not the duration and characteristics of postoperative delirium. Nevertheless, intraoperative pEEG-guided anaesthesia did not reduce postoperative pain, postoperative analgesic requirements, and postoperative nausea/vomiting in this patient population. More large-scale clinical studies are warranted to support our findings.

Figure legends

Figure 1: Flowchart of the population. IVPCA: intravenous patient controlled analgesia. POD: postoperative delirium. Nu-DESC: Nursing Delirium Screening Scale.

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Disclosure

The authors report no conflicts of interest in this work.

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