Curr Anesthesiol Rep (2015) 5:1–9
DOI 10.1007/s40140-014-0088-z

PERIOPERATIVE DELIRIUM (JM LEUNG, SECTION EDITOR)

Depth of Anesthesia and Postoperative Delirium

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Published online: 25 November 2014

Abstract In this article, we reviewed the association between depth of anesthesia and postoperative delirium. We also evaluated the evidence for intraoperative brain function monitoring to prevent delirium after surgery. Anesthetics produce profound neurochemical changes that may disrupt normal brain function and result in postoperative delirium. Brain function monitoring has emerged as a tool for titration of anesthetic delivery to avoid sedative drugs overdose and may prevent postoperative delirium. A meta-analysis of five existing trials showed that brain function monitoring significantly reduced the risk of delirium after surgery (odds ratio 0.56, 95 % confidence intervals: 0.40–0.77). However, the current evidence is still not definitive because of limited sample size and heterogeneity among studies. Future studies are required to evaluate different depths of anesthesia and postoperative delirium.

This article is part of the Topical Collection on *Perioperative Delirium*.

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Keywords Postoperative delirium · Brain function monitoring · Bispectral index · Depth of anesthesia

Introduction

Postoperative delirium is the state of acute confusion that occurs typically during the first few days after surgery [1, 2, 3•]. During an episode of delirium, there is fluctuation in consciousness with alternating periods of inattention and changes in cognitive function and perception [4]. It is commonly believed that delirious patients are hyperactive and are easily recognized. These patients may become violent, imposing self-injury, and producing harm to the attending healthcare workers. Other studies, however, have shown that the majority of patients are actually mute and quiet [5, 6]. These patients are only identified by careful examination using standardized instruments, such as the confusion assessment method [7]. It is the latter group of hypoactive patients, whom we often miss during routine ward assessment, that may contribute to the enormous variations in the incidence of postoperative delirium among studies [average (range) 37 % (0–74 %)] [2, 8, 9]. Postoperative delirium is also an independent risk factor for complications after surgery, leading to poor functional recovery and cognitive impairment [10–18].

Given the high incidence and significant impact on long-term outcome, a number of articles have highlighted the predisposing factors for postoperative delirium [8, 19–21]. Although age and pre-existing cognitive impairment are the most consistent risk factors, emerging data suggest that anesthetic per se may also contribute to the development of delirium after surgery. The purpose of this article was to review the association between anesthesia and delirium. We also evaluate

the evidence for processed electroencephalogram (EEG) in guiding anesthetic administration to prevent postoperative delirium.

Anesthetics and Postoperative Delirium

The pathophysiology of postoperative delirium has not been fully elucidated; however, the prevailing mechanism suggests that delirium is primarily a consequence of the loss of connectivity between the various parts of the brain network. The failure of sensory integration and the loss of connection between sensory processing and motor responses, particularly within the thalamo-cortical system, may contribute to postoperative delirium [22–27]. In this regard, elderly patients and patients with pre-existing cognitive impairment have reduced baseline brain connectivity, and would be at risk of further network disconnection following surgery. At the receptor level, large doses of anesthetic agents would cause an increase in inhibitory tone by activation of gamma-aminobutyric acid receptors, rendering the brain network more vulnerable. Anesthetics also block central cholinergic receptors, producing further inhibitory effect on brain circuitry [28]. In animal experiments, standard doses of routine anesthetics have been shown to produce long-lasting neurochemical changes in the form of an increase in tau hyperphosphorylation [29–31], caspase-3 activation [32–35], and β amyloid deposition in the brain [33, 36–38]. Each of these processes may further reduce brain connectivity. It is therefore feasible that large doses of anesthetics might predispose patients to postoperative delirium.

There is another putative mechanism where anesthetics may disrupt brain connectivity. Large doses of anesthetic impair cerebral autoregulation [39, 40]. In this scenario, cerebral vasodilatation cannot compensate for any decrease in perfusion pressure below the lower limit of autoregulation. Progressive hypoperfusion beyond this point may therefore result in cerebral ischemia [41]. Among those who presented to the emergency room with acute stroke between 13 and 48 % of patients had an episode of delirium during the first week of hospitalization [42, 43]. Post-stroke delirium is associated with longer hospital stay and higher morbidity and mortality [odds ratio (95 %confidence intervals, CI): 3.83 (1.70–8.62)] [43–45]. Currently, there is no study demonstrating the association between delirium and stroke after surgery, owing to the fact that the incidence of postoperative stroke is low (0.1 %) [46, 47]. However, a recent observational study showed that new ischemic brain lesions on magnetic resonance imaging could be identified in 11.4 % (8/70 patients, 95 % CI 5.9–21.0 %) of patients following noncardiac surgery [48]. These lesions (covert stroke) may represent the underlying basis for postoperative delirium. Interestingly, delirium has been reported as the only manifestation of stroke in the non-operative setting [49]. The ongoing Neurological Impact of Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (NeuroVISION) study evaluates the epidemiology and clinical consequences of covert stroke in a representative sample of 1,500 patients undergoing noncardiac surgery (clinicaltrials.gov identifier NCT01980511). NeuroVISION has included postoperative delirium as a secondary endpoint and may help to clarify the missing link between postoperative covert stroke and delirium.

Currently, the literature suggests that postoperative delirium could be due to a direct inhibitory effect of anesthetics on the brain network. Alternatively, this may be the consequences of perioperative cerebral hypoxia and ischemia. Although there is no direct evidence to support these hypotheses, both mechanisms are likely to be dose-dependent, and therefore a technique that minimizes anesthetic exposure could be useful to prevent delirium after surgery.

Brain Function Monitoring and Anesthetic Administration

In order to tailor anesthetic delivery to the needs of individual patient, an accurate measure of anesthetic effect is required. For many years, anesthesiologists have routinely used clinical signs, such as blood pressure, heart rate, lacrimation, and sweating to indicate the depth of anesthesia. This is however unreliable. In patients with confirmed awareness during anesthesia, hypertension and tachycardia occurred in <15 % of cases [50]. In another study, intraoperative hemodynamic changes in patients with confirmed awareness during anesthesia were indistinguishable from the matched controls [51]. In order to prevent awareness, anesthetists have learned to give “a little extra” to ensure hypnosis during surgery, and this often results in deeper level of anesthesia.

Since anesthetic works primarily on the brain to produce loss of consciousness, it seems logical to monitor brain activity as a surrogate measure of anesthetic depth. In the past decade, a number of manufacturers have produced devices to measure depth of anesthesia. Table 1 summarizes the features of commercially available brain function monitors [52–62]. These devices are designed to collect (spontaneous or evoked) EEG signals from a specific (typically frontal) electrode montage. EEG data are extracted using specific algorithms. These are then correlated with clinical status (e.g., response to verbal command) in a reference population using a statistical model to generate a dimensionless linear index of anesthetic depth. Therefore, these indices are statistical functions that

Table 1 Characteristics of the currently available monitors of anesthetic depth

Parameters	Machine/manufacturer	Consumable	Physiologic signals	Recommended range of values for anesthesia	Principles of measurement
Bispectral index (BIS) [52, 69•]	BIS Complete 2-channel (or 4-channel) monitor (Coviden, Boulder, CO)	BIS (4-electrode, bilateral, pediatric, and extend) sensor	1–2 channel EEG	40–60	BIS is derived from the weighted sum of three EEG parameters: (1) relative α/ß ratio (2) biocherence of the EEG waves (SyncFastSlow) and (3) burst suppression The relative contribution of these parameters has been tuned to correlate with the degree of sedation produced by various sedative agents. BIS ranges from 0 (asleep) to 100 (awake)
Patient state index (PSI) [53]	SedLine brain function monitor (Masimo, Irvine, CA)	PSArray^2 sensor	4 Channels EEG	25–50	PSI is derived from progressive discriminant analysis of several quantitative EEG variables that are sensitive to changes in the level of anesthesia, but insensitive to the specific agents producing such changes. It includes changes in: (1) power spectrum in various EEG frequency bands (2) hemispheric symmetry, and synchronization between brain regions and the inhibition of regions of the frontal cortex PSI ranges from 0 (asleep) to 100 (awake)
Narcotrend stage Narcotrend index [54]	Nacrotrend monitor (MonitorTechnik, Bad Bramstedt, Germany)	Ordinary ECG electrode	1–2 channels EEG	35–65 (corresponds to stage D_{0-2} to C_1)	The Narcotrend monitor classifies EEG signals into 15 stages of anesthesia (A = awake; B_{0-2} = sedated; C_{0-2} = light anesthesia; D_{0-2} = general anesthesia; $E_{0,1}$ = general anesthesia with deep hypnosis; $F_{0,1}$ = burst suppression). The classification algorithm is based on a discriminant analysis of entropy measures and EEG spectral variables. More recently the monitor converts the Narcotrend stages into a dimensionless number from 0 (asleep) to 100 (awake) by nonlinear regression
State and response entropy [55]	GE Datex-Ohmeda entropy module (GE Healthcare, Milwaukee, WI)	Entropy sensor	Single channel EEG	40–60	Entropy described the "irregularity" of EEG signal. Entropy module calculates spectral entropy of the EEG spectrum. Two spectral parameters are calculated: (1) State entropy (SE, frequency band 0–32 Hz) and (2) Response entropy (RE, 0–47 Hz) also includes muscle activity SE has been re-scaled, so that 0 is asleep and 91 is awake, while the range for RE is 0–100
AEP_{Index} [56]	aepEX PLUS (Medical Device Management, Braintree, Essex, UK)	Ordinary ECG electrode	AEP	40–60	aepEX PLUS measures middle latency AEP (0–144 ms). The waveform is updated by moving average technique. AEP_{Index} has been scaled and ranges from 0-100

Table 1 continued

Parameters	Machine/manufacturer	Consumable	Physiologic signals	Recommended range of values for anesthesia	Principles of measurement
Aline autoregressive index (AAI version 4.1) [57]	AAI monitor (Danmeter A/S, Odense, Demark)	Ordinary ECG electrode	AEP	15–25	AAI is derived from the middle latency AEP (20–80 ms). AAI is extracted from an autoregressive model with exogenous input (ARX model) so that only 18 sweeps are required to reproduce the AEP waveform in 2–6 s. The resultant waveform is then transformed into a numeric index (0–100) that describes the shape of the AEP. AAI >60 is awake, AAI of 0 is deep anesthesia
(AAI version 4.2) [58]	AEP/2 monitor (Danmeter A/S, Odense, Demark)	Ordinary ECG electrode	AEP	40–60	Incorporating EEG data (β ratio) when signal-to-noise ratio for AEP measurement is <1.3
Cerebral state index (CSI) [59]	Cerebral state monitor (CSM), Danmeter A/S, Odense, Demark	Ordinary ECG electrode	Single channel EEG	40–60	CSI is a weighted sum of (1) α ratio, (2) β ratio, (3) difference between the two and (4) burst suppression. It correlates with the degree of sedation by adaptive neuro-fuzzy inference system. CSI ranges from 0 (asleep) to 100 (awake)
Index of consciousness (IoC) [60]	IoC-View monitor (Morpheus Medical, C/Llacuna, Spain)	Ordinary ECG electrode	Single channel EEG	40–60	Symbolic dynamic method is used to encode EEG signals. Other components include β ratio and burst suppression to indicate light and deep anesthesia. The IoC value is obtained by correlating these EEG parameters with clinical level of consciousness using a discriminatory function. IoC ranges from 0 (asleep) to 99 (awake)
qCON [61]	qCON 2000 monitor (Quantium Medical, Mataró, Barcelona, Spain)	Ordinary ECG electrode	Single channel EEG	40–60	qCON calculates the spectral ratios at 4–8 Hz, 8–13 Hz, 11–22 Hz and 33–44 Hz with the total spectrum and correlates with the clinical states in 1,110 subjects using adaptive neuro-fuzzy inference system. qCON ranges from 0 (asleep) to 99 (awake)
SNAP index [62]	SNAP II monitor (Stryker Instruments, Kalamazoo, MI)	Ordinary ECG electrode	Single channel EEG	40–60	SNAP index compares spectral parameters at 80–120 Hz with that in 0.1–18 Hz. SNAP index ranges from 0 to 100

From [73], with permission from Wolters Kluwer Health

EEG Electroencephalogram, *AEP* Auditory evoked potential

represent the likelihood of present depth of anesthesia [63]. Obviously, the accuracy of these indices will depend on the quality of the calibration dataset. It should be noted that measurements of entropy and auditory evoked potential have not undergone probability modeling, but the scales have been readjusted so that the values are comparable to other indices.

The advantage of brain function monitor is that it facilitates EEG interpretation by transforming the complex EEG signals into a single accessible number. When alarm settings are appropriately adjusted, it allows anesthesiologists to concentrate on the overall patient care without being distracted by the constantly changing raw EEG waveforms [64]. Based on the depth indices, anesthesiologist aims to titrate anesthetic administration so as to prevent periods of under-dosing and to avoid autonomic stimulation and unintentional awareness. Similarly, brain function monitoring facilitates anesthetic delivery to avoid periods of overdose and minimizes anesthetic exposure. In a meta-analysis of 20 studies involving a total of 2,557 patients, anesthesia guided by bispectral index (BIS) monitoring reduced propofol infusion rate by 17.8 % (95 % CI 9.9–25.8 %) and decreased volatile administration by 18.4 % (95 % CI 3.3–30.7 %), compared with standard patient care [65, 66]. This was associated with a decrease in time to tracheal extubation and recovery room discharge by 2.6 (95 % CI 1.8–3.5) min and 6.8 (95 % CI 2.3–11.2) min, respectively [65]. Although similar results were shown for other devices (entropy: 6 trials, 695 patients) and (narcotrend: 2 trials, 124 patients), study designs were different,

Table 2 Characteristics of studies evaluating the impact of brain function monitoring and postoperative delirium

Study (period of study)	Patient population and anesthetic type	Intervention group	Control group	Outcome measures; duration of follow-up	Major results
Sieber (2005–2008) [68]	114 patients, ≥ 65 years; fixation of hip fracture; spinal anesthesia with propofol sedation	Light sedation ($n = 57$): BIS 85.7 ± 11.3 Propofol 2.5 ± 2.7 mg/kg	Deep sedation ($n = 57$): BIS 49.9 ± 13.5 Propofol 10.2 ± 5.6 mg/kg	Confusion assessment method from day 2 to hospital discharge	Lower rate of delirium with light (19.3 %) than deep (40.4 %) sedation, $p = 0.02$ Light sedation group required less propofol usage ($p < 0.001$), higher average BIS ($p < 0.001$) and shorter duration of BIS < 50 ($p < 0.001$)
Jidenstål (2005–2008) [67]	451 patients, 18–92 years; anterior or posterior segment ophthalmic surgery; general anesthesia	AAI-guided ($n = 224$): AAI 18 (11–21) Propofol 92.5 ± 26.5 mg Desflurane 2.5 ± 0.6 %	Clinical signs ($n = 226$): AAI 12 (10–19) Propofol 103.8 ± 39.5 mg Desflurane 3.3 ± 0.8 %	Mini-mental test on day 1 after surgery	Lower rate of cognitive impairment in AAI group (0.9 %) compared with controls (7.1 %, $p < 0.001$) Others: AAI-guided anesthesia resulted in higher AAI values ($p < 0.001$), lower propofol and desflurane consumption ($p = 0.001$), fewer episodes of hypotension and less fluid and vasopressor requirement compared with controls ($p < 0.001$)
Chan (2007–2009) [70•]	921 patients, ≥60 years, elective major noncardiac surgery; general anesthesia	BIS-guided ($n = 462$): BIS 53.2 ± 8.9 Propofol 2.7 ± 0.9 μg/ml Volatile 0.57 ± 0.29 MAC	Routine care ($n = 459$): BIS 38.6 ± 6.5 Propofol 3.3 ± 1.1 μg/ml Volatile 0.93 ± 0.34 MAC	Confusion assessment method twice daily until hospital discharge	Lower rate of delirium with light (15.6 %) than deep (24.1 %) sedation, $p = 0.01$ BIS monitoring was associated with higher average BIS ($p < 0.001$), shorter duration of BIS < 40, lower propofol ($p < 0.001$) and volatile anesthetic use ($p < 0.001$) POCD at 3 months after surgery was lower with BIS-guided anesthesia (10.2 %) compared with routine care (14.7 %), $p = 0.02$
Radtke (2009–2010) [71•]	1,155 patients, ≥60 years, elective major noncardiac surgery; general anesthesia	BIS-guided ($n = 575$): BIS 39.0 ± 7.2 No. with BIS < 20–10.8 %	Routine care ($n = 580$): BIS 38.7 ± 7.4 No. with BIS < 20–19.5 %	DSM IV criteria twice daily until day 7 after surgery	Lower incidence of delirium in BIS group (16.7 %) compared with controls (21.4 %), $p = 0.04$ Average BIS value did not differ between groups ($p = 0.472$), but the number of patients with BIS <20 was fewer in the BIS-guided group compared with controls, $p = 0.04$ No difference in POCD at 1 week and 3 months after surgery (0.372)

Table 2 continued

Study (period of study)	Patient population and anesthetic type	Intervention group	Control group	Outcome measures; duration of follow-up	Major results
Whitlock (2009–2010) [69•]	Subgroup of BAG-RECALL Trial; 310 patients; elective cardiothoracic surgery; general anesthesia	BIS-guided ($n = 149$): No. with BIS < 20–43.0 %	ETAC-guided ($n = 161$): No. with BIS < 20–42.9 %	Confusion assessment method for the intensive care unit (ICU); during ICU stay	Rate of delirium in the BIS-guided group (18.8 %) was not different from ETAC group (28.0 %) $p = 0.058$ Average BIS value and volatile consumption were not reported, but higher volatile concentration is associated with lower risk of postoperative delirium (odds ratio 0.70 (0.53–0.92) per 0.1 MAC increase)

Values are mean ± SD or median (range)

BIS bispectral index, *AAI* autoregressive auditory evoked potential index, *MAC* minimum alveolar concentration, *DSM* diagnostic and statistical manual of mental disorders

and the sample size of the latter trials was relatively small [66].

Anesthetic Depth and Postoperative Delirium

Could monitoring of anesthetic depth prevent postoperative delirium? Currently, no study has evaluated the impact of varying anesthetic depth on postoperative delirium. Since brain function monitoring has been shown to reduce anesthetic exposure, studies that employ these monitors to target different ranges of anesthetic depths may be useful to highlight any effect of anesthetic depth on postoperative delirium.

Table 2 summarizes the findings of five existing trials that evaluate brain function monitoring and postoperative delirium [67, 68, 69•, 70•,71•]. The average age of patients in these trials was between 60 and 81.7 years. Jildenstål and colleagues studied the utility of auditory evoked potential (AEP) in patients undergoing eye surgery [67]. AEP-guided anesthesia reduced consumption of propofol and desflurane by 10.5 and 24.2 %, respectively. The decrease in anesthetic requirement was associated with a reduction in the risk of postoperative delirium by 88 %. All other trials used BIS monitoring to adjust anesthetic administration [68, 69•, 70•, 71•].

Sieber and coworkers randomized patients having hip fracture fixation to receive deep or light sedation using propofol infusion [68]. All patients received spinal anesthesia as the primary anesthetic. This trial actually tested two levels of sedation (BIS ≥ 80 vs. BIS 50), and reported that light sedation reduced the risk of postoperative delirium by 65 %. However, it should be noted that patients allocated in the deep sedation group (BIS 50) actually received less anesthetics than the other trials.

Two trials compared brain function monitoring with routine practice based on clinical signs [70•, 71•]. In the cognitive dysfunction after anesthesia (CoDA) trial, 902 patients, ≥60 years, undergoing noncardiac surgery were randomly assigned to receive BIS-guided anesthesia (keeping BIS between 40 and 60) or routine care [70•]. BIS monitoring decreased anesthetic exposure by 21–30 % and reduced duration of deep anesthesia (BIS <40) during the course of surgery and thus producing two levels of anesthetic depth, i.e., light anesthesia in the BIS group and deep anesthesia in the routine care group. BIS monitoring was associated with a lower risk of postoperative delirium (relative reduction 42 %). Similarly, Radtke and coworkers found that BIS monitoring reduced delirium after surgery compared with controls [odds ratio (95 % CI): 0.73 (0.54–0.98)]. Although the average BIS values were similar between groups, the trial showed that BIS monitoring was effective to reduce episodes of very deep anesthesia with BIS <20. It remains plausible that the very deep level of anesthesia is the trigger of postoperative delirium.

Using a subgroup of patients undergoing cardiothoracic surgery in the BIS or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) trial [69•], Whitlock and coworkers compared the incidence of delirium between the patients who were randomize to BIS-guided anesthetic administration (targeted to a BIS value between 40 and 60) or maintenance of anesthesia at end-tidal volatile concentration of 0.7–1.3 minimum alveolar concentration (MAC). It was found that the rate of delirium tended to be lower in the BIS-monitoring group although the difference was not

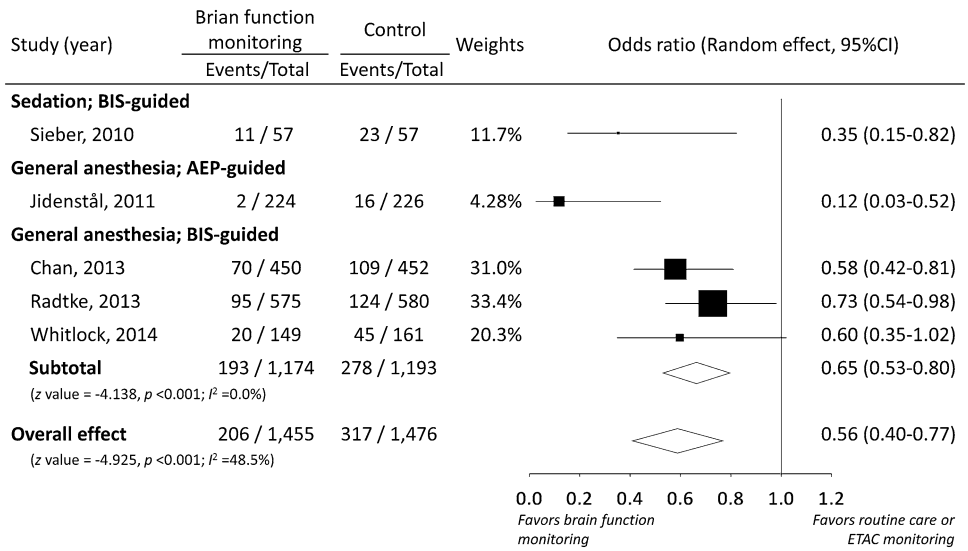

Fig. 1 Meta-analysis of randomized controlled trials evaluating brain function monitoring and postoperative delirium. (*BIS* bispectral index, *AAI* autoregressive auditory evoked potential index, *ETAC* end-tidal anesthetic concentration)

statistically significant. Surprisingly, low average anesthetic dose was identified as an independent predictor of delirium. In addition, the trial showed that larger volatile concentration appeared to reduce the risk of delirium [odds ratio (95 % CI): 0.70 (0.53–0.92)]. These findings may indicate that the delirious patients were more sensitive to anesthetics [72]. However, issues regarding post hoc study design, missing follow-up (3.8 % did not receive delirium assessment), and incomplete record (3.6 %) may have influenced these study results. Nevertheless, a pooled estimate for the 3 trials comparing the use of BIS monitoring and routine care or BIS monitoring and end-tidal anesthetic concentration demonstrated a significant risk reduction for postoperative delirium by 35 % (95 % CI 20–47 %), favoring BIS monitoring.

Overall, brain function monitoring reduced the risk of postoperative delirium and the treatment effect appeared to be substantial [odds ratio (95 % CI): 0.56 (0.40–0.77), $p < 0.001$)] (Fig. 1). However, these results warrant cautious interpretation. There are significant heterogeneity in the design and conduct of the various trials ($I^2 = 48.5$ %). It should be emphasized that these trials did not randomize patients into light or deep level of anesthesia, instead patients were allocated to have brain function monitoring or not. Although patients receiving brain function monitoring are likely to have less anesthetic exposure, we cannot exclude periods of deep anesthesia that may lead to postoperative delirium in these patients. Similarly, patients in the routine care group might not always result in deep anesthesia. These confounding factors would therefore obscure the association between anesthetic depth and postoperative delirium.

The ideal study should therefore randomize patients to two levels of anesthetic depth and measure postoperative delirium using a valid and standardized instrument at regular intervals. The Balanced Anesthesia Trial (Australian New Zealand Clinical Trials Registry No: ACTRN12612000632897) was recently initiated to recruit 6,500 high-risk patients of American Society of Anesthesiology physical status class 3 or 4, age ≥60 years, undergoing major surgery. Patients are randomly assigned to receive deep or light anesthesia with BIS target of 35 or 50, respectively. The primary outcome is all-cause mortality at one year after index surgery. A substudy has been planned to measure postoperative delirium using the confusion assessment method during the initial hospital stay. This substudy will provide clear evidence to establish the link between depth of anesthesia and postoperative delirium.

Conclusions

Postoperative delirium is common among elderly patients undergoing major surgery. Current studies have suggested that deep level of anesthesia may predispose patients to delirium after surgery. However, a definitive prospective trial is needed to establish the role of anesthetics in causing postoperative delirium.

Acknowledgments The authors are site investigators for the Balanced Anesthesia Trial. Dr. Chan is a member of the steering committee of the NeuroVISION Study. The Balanced Anesthesia Trial is supported by a General Research Fund (461513), Research Grant Council, and the NeuroVISION Study is supported by a Health and Medical Research Fund (11120321), Food and Health Bureau, Hong Kong Special Administrative region.

Compliance with Ethics Guidelines

Conflict of Interest Terence T.H. Luk, Bo Jia, Etonia Y.T. Pang, Vivian N.M. Lau, Carmen K.M. Lam, Mandy H.M. Chu, Ruquan

Han, and Matthew Chan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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