Journal of Anesthesia & Clinical Research
ISSN: 2155-6148

Czernicki et al., J Anesthe Clinic Res 2013, 4:8
DOI: 10.4172/2155-6148.1000e115

Editorial Open Access

How Deep is Deep Enough?

Michal Czernicki, Maren Gregersen, Jasleen Kukreja and Marek Brzezinski*

Department of Anesthesia and Perioperative Care, University of California, Veterans Affairs Medical Center, San Francisco, CA, USA

Postoperative Cognitive Dysfunction (POCD), defined as a deterioration of short or long-term cognitive function in the postoperative period, has been reported to affect between 30-80% of patients undergoing surgery [1]. POCD can be classified into categories based on when the cognitive decline occurs: acute, intermediate, and chronic. Its severity usually decreases over time, but it may persist for months to years [2-4]. POCD is significant as it has been shown to increase morbidity, length of hospitalization, and mortality [5].The underlying etiology for the development of POCD remains poorly defined. The commonly reported factors associated with POCD include patient factors (e.g. increasing age and poor education), surgery related factors (systemic and neuroinflammatory changes, type of surgery) and anesthesia related factors (depth and duration of exposure to anesthetics) [6-8].

The effect of anesthesia, particularly the use of volatile anesthetics, has been increasingly the center of interest [9-11]. Volatile anesthetics have been found not only to promote neuroinflammation and neurodegeneration but also to promote POCD [12]. The link between volatile anesthetic agents and POCD remains controversial in the anesthesia community [13, 14]. In this context, two recent clinical studies that examined the relationship between depth of anesthesia and the incidence of POCD deserve closer attention.

In the first study, Xu et al. investigated the effect of different doses of inhaled sevoflurane administered prior to the cardiopulmonary bypass on cerebral oxygen supply and demand, and the incidence of early POCD [15]. The authors randomized 120 patients undergoing cardiac surgery into four treatment groups and administered a high [1.5 MAC), moderate (1 MAC), low (0.5 MAC) or no sevoflurane dose prior initiation of the Cardiopulmonary Bypass (CPB). The anesthesia was maintained by intravenous injection of propofol and sulfentanil. The bispectral index value was kept between 40 and 60. Cognitive function was assessed by the Mini-Mental State Examination (MMSE) 1day before surgery and reassessed 24 and 72 h after surgery. The serum level of S-100 protein and Neuron-Specific Enolase (NSE) markers of neuronal damage were measured.

The main finding of the study was that administration of higher concentrations of sevoflurane was associated with better postoperative cognitive function and less neuronal damage. The 24 hours postoperative MMSE scores of the moderate and high dose groups (26.59 ± 3.74 and 26.69 ± 2.98 respectively) were significantly higher than those of low dose (25.78 ± 2.06) and control groups (25.24 ± 2.58; p=0.036). This difference in MMSE scores disappeared, however, 72 hours after the operation (p=0.125). Consistent with these results, the serum S-100 protein concentration of the moderate (0.2286 ± 0.027 ug/L) and high dose (0.230 ± 0.032 ug/L) showed significantly lower values than that of the control group (0.442 ± 0.099 ug/L; p=0.043 and p=0.039 respectively) 6 hours post cessation of CPB. The NSE concentrations of the moderate (7.911 ± 0.738 ug/L) and high (6.950 ± 1.353 ug/L) groups were also significantly lower than that of that of the control group (10.009 ± 1.307 ug/L; p=0.025 and p=0.015 respectively) 6 h after the cessation of CPB. In addition, the jugular bulb venous oxygen saturation in the moderate and high-dose groups was significantly higher compared with the controlled group, while the arteriovenous oxygen content difference and cerebral extraction of oxygen were significantly reduced. The main limitation of this study is that it did not look at the long-term outcome.

In the second study conducted by Chan et al. 921 patients scheduled for major non-cardiac surgery were randomly assigned to receive either bispectral index (BIS)-guided anesthesia or routine care anesthesia [16]. In the BIS group, the depth of anesthesia was adjusted to BIS values between 40 and 60. The control group measured BIS level but the results were unknown to the anesthesiologist. Neurophysiology battery tests including the cognitive failure questionnaire, the verbal fluency test, the auditory verbal learning test, and the color trail making test were performed prior to surgery, one week after surgery, and three months after surgery. The Z-score was calculated to indicate the standardized change in each of the neurophysiology tests. POCD was defined if 2 or more Z scores were 1.96 or greater. BIS values were found to be significantly lower in the control group: 36 (31-49) compared with the BIS guided group 53 (48-57). BIS guided anesthesia reduced propofol delivery by 21% and volatile anesthetic agents by 30%.

The main finding of Chan et al. was a significantly lower rate of POCD in the BIS group at the 3-month follow up (10.2% vs. 14.7%, p=0.025). There was no difference between the two groups in the early postoperative cognitive function at 1week [16].

Both studies are relevant to clinical practice as they focus on whether the incidence of POCD can be modified by the anesthetic technique. Both suggest a concentration dependent effect of volatile agents but in opposite directions. While the findings of Xu et al. suggest a concentration-dependent *neuroprotective* character of volatile agents that *prevented early* POCD, the study by Chen et al. points toward a negative effect of inhalation agents on neurocognition, with higher concentrations associated with *higher rates* of *late POCD* [15,16]. The contradictory findings of these two and other studies that looked at the relationship between depth of anesthesia and POCD highlight the complex effect of volatile anesthetic agents on neuronal tissue [15-19]. It is difficult to explain the conflicting results, and even more challenging to make clinical recommendations. On one hand, volatile anesthetics have been found to be neurotoxic as they promote neuroinflammation and neurodegradation [20-21]. On the other hand, there is evidence of neuroprotective role of volatile anesthetics that minimizes effects of neuronal ischemia and reperfusion injury [22-23]. The net effect of these two mechanisms is further influenced by other factors such as the inflammatory response, surgical trauma, genetic

***Corresponding author:** Marek Brzezinski, Associate Professor, Anesthesiology Service, Veterans Affairs Medical Center, San Francisco, CA, USA, Tel: (415) 750-2069; Fax: (415) 750-6653; E-mail: brzezinm@anesthesia.ucsf.edu

Received August 18, 2013; **Accepted** August 20, 2013; **Published** August 22, 2013

Citation: Czernicki M, Gregersen M, Kukreja J, Brzezinski M (2013) How Deep is Deep Enough? J Anesthe Clinic Res 4: e115. doi:10.4172/2155-6148.1000e115

factors, comorbidities, and cerebral metabolism. As cardiac surgery is associated with significant reperfusion injury, the neuroprotective role of volatile anesthetic agents may potentially outweigh the risk of neurotoxicity of volatile agents and explain the findings in the study by Xu et al. In fact, inhalational anesthesia was found to be associated with better cognitive outcome in patients undergoing cardiac surgery, but with worse cognitive outcome in patients undergoing non-cardiac surgery [22-24].

So, what should a clinician do these days when thinking about administering general anesthesia? It is safe to say that while the current evidence is not convincing enough to suggest changes in anesthetic management, the findings of these two studies are intriguing as post operative cognitive decline in the elderly can potentially be prevented by the titration of anesthetic agents to an optimal depth of anesthesia: maximizing neuroprotection while limiting the neurotoxicity induced by anesthetic agents. The use of brain function monitoring in elderly patients undergoing major surgery should be encouraged. Considering the high number of patients concerned about the influence of anesthesia on postoperative thinking and memory, more research is required into this field [25].

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