Journal of Anesthesia & Clinical Research
ISSN: 2155-6148

Jildenstål et al., J Anesth Clin Res 2012, 3:6
DOI: 10.4172/2155-6148.1000220

Research Article Open Access

Does Depth of Anesthesia Influence Postoperative Cognitive Dysfunction or Inflammatory Response Following Major ENT Surgery?

Pether K Jildenstål[1]*, Jan L Hallén[2], Narinder Rawal[3] and Lars Berggren[4]

[1]Department of Anesthesiology and Intensive Care, University Hospital, Örebro, Sweden
[2]Department of Anesthesiology and Intensive Care, University Hospital, Örebro, Sweden
[3]Department of Anesthesiology and Intensive Care, University Hospital, Örebro, Sweden
[4]Department of Anesthesiology and Intensive Care, University Hospital, CAMTÖ, Centre for Assessment of Medical Technology, Örebro, Sweden

Abstract

The aim of this study was to evaluate the role of depth of anesthesia on POCD after major ENT surgery and to assess changes in postoperative inflammatory markers in patients undergoing major ENT surgery. Thirty two patients aged 40 to 94 yrs, scheduled for surgery under general anesthesia were randomly assigned to one of two groups. In group A (AEP group) depth of anesthesia (DOA) was measured with auditory evoked potential (AEP). In the control group (group C) DOA was monitored according to clinical signs. Cognitive function was evaluated using Mini-Mental State Examination (MMSE), Confusion Assessment Method (CAM) and Cognitive Failure Questionnaire (CFQ). Inflammatory markers were measured before and after anesthesia. Perioperative requirements for desflurane and fentanyl were significantly lower in group A. On the first postoperative day MMSE changes indicating POCD were noted in 1 patient in group A and 7 patients in group C ($P<0.03$). One month follow up did not show any difference between the groups regarding POCD. Our study indicates that AEP-guided anesthesia allows dose reduction of anesthetic agents including opioids leading to better cardiovascular stability and less early POCD. Anesthesia depth did not influence the inflammatory response to surgery.

Keywords: Cognitive decline; General anesthesia; Auditory Evoked Potential (AEP)

Introduction

Early postoperative cognitive dysfunction (POCD) is commonly associated with major surgery and anesthesia, occurring in 7 to 71% of patients [1-3]. Advanced age, degree of surgical trauma, depth of anesthesia and inflammatory activation are some of the risk factors for POCD [1,4-7]. It has been proposed that systemic inflammation may contribute to postoperative cognitive deficits and there could be a relationship between interleukin response and impaired postoperative cognition [8-10]. Monitoring the depth of anesthesia using digital processing of the EEG makes it possible to reduce anesthetic requirements and doses of opioids perioperatively, which can also influence POCD [5,11-14]. Inflammatory response and opioids are two risk factors for development of POCD [4,15].

The aim of this study was to evaluate the role of depth of anesthesia on POCD after major ENT surgery and to assess changes in postoperative inflammatory markers in patients undergoing major surgery.

Methods

This single centre study was approved by the ethics committee (Ethics Committee Nr. 2010/143 19 May 2010) Uppsala, Sweden. Written, informed consent was obtained from 32 adult patients ASA 1-3, aged 40 through 94 years scheduled to undergo major ENT surgery under general anesthesia. The study was conducted between September 2010-February 2011. Exclusion criteria were pregnancy, patients unable to fulfil investigational procedures due to mental disabilities, hearing impairment, patients with any form of substance abuse as well as patients undergoing surgery out of hours and patients who could not complete the perioperative protocol.

A selected group of experienced anesthesiologists or nurse anesthetists, specially trained in guiding anesthesia depth using auditory evoked potential (AEP, A-line), performed the anesthesia. The postoperative personnel were blinded to group assignment, and all data were processed independently of group allocation and were blinded to the investigator until the finalisation of the study.

Randomisation procedure and baseline characteristics

An independent person not involved in the study performed the computerised randomisation procedure assigning patients a specific study number and group allocation, which was then inserted into sealed envelopes. After inclusion criteria were fulfilled the envelope was opened and the patient included in the study (Figure 1).

Patients were randomly assigned to one of two study groups:

AEP group (group A): Anesthesia was guided by AEP: A-line®ARX index (AAI), version 1.6. Mid-latency auditory evoked potential (MLAEP) was calculated using the A-line monitor (Danmeter A/S, Odense, Denmark) [16,17], AAI between 15 and 25 was regarded as adequate [17].

Control group (group C): Anesthesia was guided by clinical signs of depth of anesthesia including blood pressure, heart rate, pupil reaction, sweating and lacrimation at the discretion of the attending anesthesiologist or nurse anesthetist. AEP was recorded in all patients in the control group but was blinded to the attending anesthesiologist or nurse anesthetist. After surgery, the data were transferred to storage media for later analysis of AAI.

***Corresponding author:** Volkan Hancı, MD, Esenler Mahallesi, Cumhuriyet Caddesi, Yağmur Apartmanı, Apartman No:30, Daire:24, Çanakkale, Turkey, Tel: +90.530.643.32.40; E-mail: vhanci@gmail.com

Received June 05, 2012; **Accepted** June 26, 2012; **Published** July 03, 2012

Citation: Jildenstål PK, Hallén JL, Rawal N, Berggren L (2012) Does Depth of Anesthesia Influence Postoperative Cognitive Dysfunction or Inflammatory Response Following Major ENT Surgery? J Anesth Clin Res 3:220. doi:10.4172/2155-6148.1000220

Baseline characteristics and clinical data were recorded before surgery. Preoperative blood pressure and heart rate were recorded and a 12-lead ECG was obtained. All patients were anesthetized according to department routine i.e. oral paracetamol (acetaminophen) 1 gm approximately 20 minutes before surgery. Induction of general anesthesia was performed by administering fentanyl 1.5 μg/kg intravenous, a target controlled infusion (TCI) AlarisTM Pk TCI (Carefusion, Basingstoke, UK) of remifentanil (Minto model), was administered intravenously to reach a target 1.0 ng.mL^{-1}. Propofol 1.0 mg/kg intravenous and additional propofol of 0.3 mg/kg IV was given if necessary to maintain adequate anesthetic depth as guided by AEP or clinical signs in group A and C respectively. Intubation was facilitated by using atracurium 0.3 mg/kg IV. Anesthesia was maintained with oxygen in air, remifentanil 1ng/mL IV and desflurane. Before the start of surgery, all patients received bupivacaine 0.25% (2.5 mg/mL) 10 mL with adrenaline in the incision area to reduce perioperative bleeding and pain. Glucose 10% with electrolytes was administrated at a rate of 1.0 mL/kg^{-1}/h IV during surgery. At induction, Ringer's acetate solution was given at a rate of 10 mL/kg IV for the first 20 minutes to avoid hypotension. Thirty minutes before extubation, droperidol 10 μg/kg IV was given as an antiemetic. Remifentanil was stopped 20 min before the end of surgery. To treat pain after surgery titrated doses of fentanyl (1.0-2.0 μg/kg IV), were given.

Hypotension was defined as a decrease in mean arterial pressure (MAP) of 25% or more below preoperative baseline [18]. Hypertension was defined as an increase in MAP of 20% or more above preoperative baseline values [19]. Hypotension was treated primarily with volume substitution by a rapid infusion intravenous of 250 mL Hydroxyethyl Starch HES (130/0.4). Persistent hypotension (>5 minutes) was treated with ephedrine 5.0 mg/mL intravenous if hypotension persisted after an additional 2.5 minutes it was treated with 250 mL HES (130/0.4) and phenylephrine intravenous up to a maximum of 3 boluses of 0.1 mg/mL each. If hypotension persisted after 3 doses the patient was excluded from the study. In case of hypertension a titrated infusion intravenous of remifentanil up to a target of 10 ng/mL was given. Persistent hypertension (>10 minutes) was treated with an injection intravenous of 50 μg/mL fentanyl and increased desflurane concentration. If hypertension persisted after these procedures, the patient was excluded from the study.

Measurements

The AAI from the MLAEP was calculated using the A-line monitor [16,17]. AAI values range from 0 to 60 where 60 indicates an awake patient. MLAEP was elicited with a bilateral click stimulus of 32-db intensity and 2 ms duration. Three silver/silver chloride electrodes (A-line AEP electrodes) were positioned at mid forehead (+), left or right forehead (reference electrode), and left or right mastoid (–) [16,17]. Extraction of the MLAEP was done using a short moving-time average technique together with an ARX evolution model. These calculations of the AAI have been described elsewhere in detail [16,17].

Analysis of intraoperative blood pressure variation was based on differences between the intraoperative MAP and preoperative MAP monitored by automatic blood pressure registration every 5 minutes (Draeger Infinity, Lübeck, Germany). During anesthesia, the patients were monitored with a 3-lead ECG and ST- T, segment analysis. Pulse oximetry saturation (SpO_2), end tidal CO_2, desflurane, and oxygen in air concentrations and neuromuscular transmission were monitored at 5-minute intervals during anesthesia.

In the recovery room, vital signs (BP, heart rate, oxygen saturation) were measured every 15 minutes during the first 90 to 120 minutes. Supplemental oxygen at 2 L/min was administrated via a nasal cannula in all patients during the first 30 minutes. If O_2 saturation decreased below 94% without oxygen, the patient received oxygen for another 30 minutes. Alertness was evaluated with the Aldrete score during the first 60 minutes postoperatively [20].

Aldrete score below 8 was regarded as inadequate postoperative wakefulness [20]. Postoperative nausea and vomiting (PONV) were treated with ondansetron 2 mL of 2 mg/mL IV or metoclopramide 10 mg/mL. Postoperative pain was treated by morphine intravenously on demand if VAS was ≥ 3, additionally paracetamol 1 g was administered four times during the first postoperative day.

Evaluation of cognitive dysfunction

Mini-Mental State Examination (MMSE) [21-23], the Confusion Assessment Method (CAM) [24] and Cognitive Failures Questionnaire (CFQ) [25], were used pre- and postoperatively to evaluate cognitive status.

These tests assess orientation, registration, attention and calculation, recall, language, short memory function, behaviour and activities of daily living. These cognitive tests were performed on two occasions, the day before or the day of surgery (baseline) and then on first postoperative day when the patient was fully awake. An MMSE value below 25 was regarded as POCD [22,23]. Delirium criteria were assessed by CAM [25]. At follow-up patients were contacted by telephone after 1 month and evaluated using a modified CFQ.

Evaluation of inflammatory response after surgery

Inflammatory markers TNF-alpha, IL 6, IL 8 and IL 10 and High sensitive C-reactive protein (H-CRP) were measured to assess the inflammatory response to surgical trauma and anesthesia [26-28].

Blood samples were analyzed blindly; they were obtained in all patients preoperatively, at 2 h and 20 h postoperatively.

The samples were immediately transferred to the biomedical laboratory and centrifuged for 10 min at 300 g. The serum was withdrawn and frozen at –80°C until analysed using a Milliplex Human Cytokine/Chemikine Immunoassay kit (Millipore Corporation, Billerica, MA, USA) according to the manufacturer's instructions. The measurements were performed using a Luminex 200TM reader and the results were analysed using Luminex xPONENT software (Millipore Corporation, Austin, TX, USA) [29]. Each serum sample was analysed in duplicate and the result was expressed as the mean of the two measurements.

Statistics

The number of patients that were to be recruited into the study was based on an assumed early POCD incidence of 60% [1]. An estimated reduction in POCD of 47% with an alpha error of 0.05 and beta error of 0.8 required 32 patients. Data were compared using the Mann-Whitney U test for non-parametric data and Student's t-test for parametric values. Categorical data were analysed using Fisher's exact test and confirmed by Wilcoxon rank sum test. A Pearson's Chi-squared test was performed to compare proportions. Bonferroni's correction test was performed to do multiple-comparison correction. Values are expressed as median and range or mean ± SD, when appropriate. Descriptive statistics regarding inflammatory markers are expressed median (md), 1st and 3rd quartile (q1 and q3). Mann-Whitney U test were used to compare inflammatory markers between groups. Differences (levels pre, 2 h and 20 h post operation) within groups were analyzed with

non-parametric ANOVA (Friedman's) test. If significant differences were detected, a Wilcoxon paired signed-rank test was used. P-values <0.05 were considered significant. All analyses were done in SPSS (version 17.0 SPSS Inc., Chicago, Illionois, USA).

Results

A total of 32 patients were enrolled in the study. No patient was excluded or lost to follow up. The two groups were comparable with respect to demographic variables (Table 1). Perioperative requirements for desflurane (end-tidal concentration 4.5 (0.4) vs. 5.1 (0.7), P<0.001) and fentanyl (154 µg (29.5) vs. 200 µg (38), P<0.0006) were significantly lower in group A (Table 2). There was no significant difference between the groups for remifentanil requirements (group A 803.1 (596.8) vs. 965.6(982.3) in group C, P<0.47) (Table 2). In group A, 4 patients (25%) received additional fluids and vasopressors compared to 13 patients (81%) in group C (P<0.004) (Table 2). AAI differed significantly between the groups: AAI was 18 (range 10–25) in group A vs. 12 (range 7–20) in group C, (P<0.0001) (Figure 2).

In group C, early (first 60 minutes) postoperative recovery was significantly delayed on all 4 occasions during the first hour (Table 4). On the first postoperative day changes indicating POCD were noted in 1 patient (6%) in group A and 7 patients (43%) in group C (P<0.03) (Table 3). CAM evaluation showed that 2 patients had delirium, one for 48 h and the other for 72 h, both belonged to group C (Table 3). One month follow up did not show any difference between the groups regarding POCD as evaluated by modified CFQ-test (Table 3). Within the two groups a significant increased in H-CRP and IL6 was seen at 2 h and 20 h P<0.001 (Table 5). A significant increase in IL10 was also noted in control group (P<0.001) (Table 5). However, there were no differences between the two groups in inflammatory markers or H-CRP at any time point (Table 5). Inflammatory response was not associated with POCD.

Discussion

Our study showed that of AEP-guided anesthesia allowed us to reduce anesthetic depth and doses of anesthesia drugs, this was associated with a reduced risk of POCD during the first 24 hours after major ENT surgery. However, at 1-month follow-up no difference in POCD was seen in the patients anesthetized with or without AEP-guidance. In this study we also evaluated the role of extent of tissue damage by selecting a major surgical procedure and measuring inflammatory markers. The incidence of POCD was higher in the control group i.e. 40% vs. 6%. In our previous study of 450 patients undergoing minor ophthalmic surgery the incidence was less than 1% in AEP-guided anesthesia group, which was significantly lower than controls [5]. This suggests that the extent of surgery may have a role in development of POCD. Our results also suggest that the depth of anesthesia can influence POCD, but has no effect on the inflammatory markers, in this setting.

The patients in our control group required significantly larger doses of ephedrine and fluids. Four patients (25%) in the study group required vasopressors and fluids while 13 patients (81%) required this treatment to maintain hemodynamic stability. It is possible that the higher incidence of POCD in the control group might be influenced by these interventions. This is in contrast to the findings of Yocum et

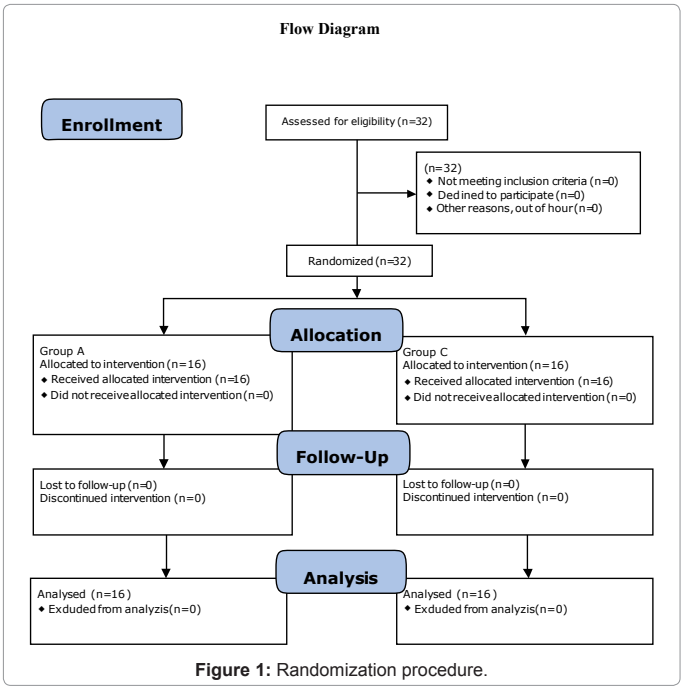

Figure 1: Randomization procedure.

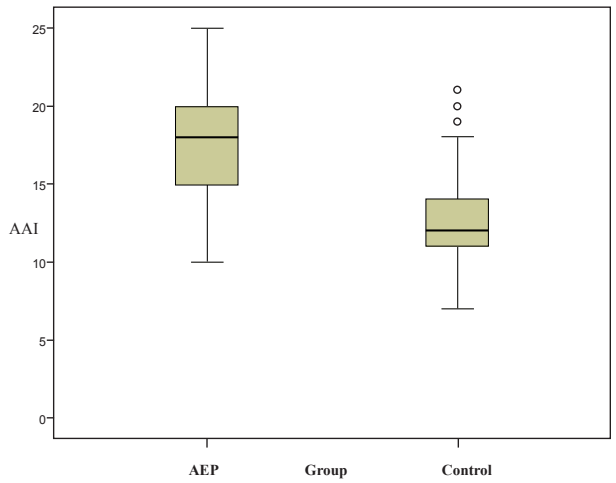

Figure 2: Median of all AAI- index (median IQR) in group A and group C. (Mann Whitney U test, two sided P-value < 0.0001) with 3 outliers as indicated.

Patient characteristics	AEP group (n =16)	Control group (n = 16)	Two sided p-value
Age (year)	59.4 (9.8)	60.9 (15.4)	< 0.98
Gender M/F (n)	5/11	5/11	
Weight (kg)	82.0 (18.2)	76.9 (19.1)	< 0.31
BMI	27.9 (7.0)	26.0 (5.6)	< 0.27
ASA class 1, 2 (n)	16	15	
ASA class 3 (n)	0	1	
Anesthesia time(min)	196.3 (77.2)	215.4 (72.3)	< 0.23
Total Thyroidectomy (n)	1	2	
Radical neck dissection (n)	12	11	
Parotidectomy (n)	3	3	

Table 1: Patient characteristics, ASA classification and type of ENT surgery.

	AEP group (n =16)	Control group (n = 16)	Two sided p-value
Systolic BP (mmHg)	101.6 (7.5)	97.9 (8.5)	<0.22
Diastolic BP (mmHg)	59.6 (6.0)	56.1 (5.4)	<0.09
MAP	76.1 (5.0)	72.9 (6.4)	<0.067
Heart rate (min)	69.6(13.3)	66.8 (10.6)	<0.72
Ringer acetate (mL)	700.0 (328.6)	925.4 (343.5)	<0.03
HES 130/0.6	100.0 (167.3)	331.3 (349.7)	<0.04
Ephedrine (mg)	2.4 (1.2)	10.0 (17.5)	<0.005
Phenylephrine (mg)	0.0 (0.0- 0.0)	0.1 (0.0- 1.0)	<0.164
Patients receiving fluids (n / %)	4 (25%)	13 (81.25%)	<0.003
Patients receiving vasopressors (n / %)	1 (6.25%)	13 (81.25%)	<0.001
A-lineAutoregressiveIndex (AAI)	18.0 (2.0)	12.3 (1.3)	<0.0001
Desflurane ET conc. (%)	4.5 (0.4)	5.2 (0.7)	< 0.001
Propofol (mg)	130 (37.8)	140 (34.5)	< 0.40
Fentanyl (µg)	154.4 (29.5)	199.7 (38.3)	< 0.0006
Remifentanil (ng)	803.1 (596.8)	965.6 (982.3)	<0.47
Morphine (mg)	1.7 (1.0)	1.9 (1.1)	<0.70

Table 2: Hemodynamic data, perioperative fluids, ephedrine, anesthetic and post-operative drugs.

	AEP group (n =16)	Control group (n = 16)	p-value
MMSE Day 1 after anesthesia	1 (6%)	7 (43%)	< 0.03
CAM Day 1 after anesthesia	0	2(12.5%)	0.48
CFQ 1 month after anesthesia	0	0	

(Fischer exact chi-square test)

Table 3: MMSE below 25 points. (0-30 points.), CAM, CFQ (modified).

	AEP group (n =16)	Control group (n = 16)	p-value
0 minutes	0 (0%)	5 (31.25%)	< 0.01
15 minutes	2 (12.5%)	12 (75%)	< 0.001
30 minutes	1 (6.25)	12 (75%)	< 0.001
45 minutes	0 (0%)	8 (50%)	< 0.001
60 minutes	0 (0%)	4 (25%)	< 0.03

(chi-square test)

Table 4: Postoperative alertness score. (Aldrete score, 0-10).

Median (Q1,Q3)	AEP Group (n=16)	Control Group (n=16)	Two sided (p-value*)
IL-6 (Pre)	0.50 (0.09-1.10)	0.36 (0.10-1.32)	0.850
IL-6 (2h post)	8.06 (3.95-13.69)	7.54 (4.85-16.28)	0.546
IL-6 (20 h post)	7.89 (5.74-13.70)	7.65 (3.06-15.88)	0.970
Within group			
Pre - 2 h post	<0.001	0.001	
Pre - 20 h post	0.001	0.001	*
H-CRP (Pre)	2.32 (0.75-4.59)	1.55 (0.63-3.31)	0.366
H-CRP (2h post)	1.59 (0.62-4.22)	1.25 (0.55-1.87)	0.407
H-CRP (20 h post)	11.75 (7.18-23.58)	12.43 (3.47-22.74)	0.624
Within group			
Pre - 2 h post	0.023	0.026	
Pre - 20 h post	0.001	0.001	*
IL-10 (Pre)	2.56 (1.60-3.28)	1.81 (1.37-3.17)	0.571
IL-10 (2h post)	2.75 (2.01-8.02)	5.25 (2.29-6.48)	0.366
IL-10 (20 h post)	3.60 (2.24-4.57)	3.42 (1.95-5.52)	0.985
Within group			
Pre - 2 h post	0.950	0.003	
Pre - 20 h post	0.430	0.005	*
IL-8 (Pre)	6.45 (5.20-9.04)	5.83 (4.93-10.90)	0.792
IL-8 (2h post)	11.28 (6.77-19.14)	9.36 (7.05-11.36)	0.291
IL-8 (20 h post)	9.53 (6.76-11.23)	7.21 (5.12-13.40)	0.346
TNF-Alfa(Pre)	5.6 (4.44-6.88)	5.94 (4.91-9.20)	0.291
TNF-Alfa (2h post)	5.04 (4.29-5.78)	5.42 (4.10-8.57)	0.366
TNF-Alfa (20 h post)	5.28 (4.03-6.80)	6.29 (3.32-9.84)	0.851

Mann Whitney U-test between groups. * Wilcoxon test within groups

Table 5: Cytokine, TNF-alfa and H-CRP.

al. who did not find any association between the use of perioperative vasopressors and POCD. It seems likely that cerebrovascular auto regulatory mechanisms are more important than the influence of vasopressors [30].

The use of clinical signs to guide anesthesia may lead to both over and under dosage of anesthetic drugs. Clinical signs are not a reliable guide of anesthetic depth [11,12]. Several studies have shown that cerebral function monitoring allows reduced drug dosage [13]. Kertai et al. have shown that duration of low anesthetic depth can possibly contribute to worsening of postoperative outcomes such as morbidity and mortality [6].

In our study fentanyl requirements were significantly higher in the control group. It has been proposed that opioids may have an indirect effect on cognitive ability as they influence postoperative pain and sleep [4]. Reviewing the literature on the possible link between analgesia and POCD, Fong et al. could not draw any firm conclusions but they recommended avoiding pethidine [15]. Opioids are well known to cause a decrease in hypoxic drive leading to respiratory events particularly in elderly patients with decreased levels of adenosine and acetylcholine that may have a role in mediating alertness and wakefulness [4].

POCD is a subtle impairment of brain function, for routine clinical practice the tools for making a formal diagnosis of POCD are rather cumbersome [31]. A large number of test batteries have been described. Mini-Mental State Examination (MMSE) is a well-accepted bedside instrument for grading the cognitive state and screening cognitive impairment [22,23]. A cut-off level of <25 points has a high specificity and sensitivity and is considered optimal as a screening level for cognitive impairment [22,23].

In our study we used the Mini-Mental State Examination (MMSE), Confusion Assessment Method (CAM) and Cognitive Failure Questionnaire (CFQ). The CFQ test battery was reduced to 5 items for practical reasons because it was not clinically feasible to make more extensive evaluation at one month by telephone.

Study limitations

It may be argued that our test battery was not sensitive enough for diagnosis of POCD [1].

A recent editorial states "Currently, there is no gold standard and researchers apply different batteries of tasks and different statistical tests; one review listed 14 different approaches" [31]. As reported in a review on POCD, the neuropsychological batteries chosen are often a compromise, balancing of the time constraints imposed by clinical environment with the selection of sensitive and reliable tests [1]. Neuropsychological tests are time consuming both for the patient and personnel and can take about 30 min to complete [31]. Our test took about 10 min. The tests we used (MMSE, CAM and CFQ) have been extensively used for years to detect cognitive impairment. We concur with Newman et al. that it is timely to establish a consensus that specifies a limited number of tests to be used in all studies and pool data to increase power in secondary analyses. Another limitation is that, inflammatory response after tissue trauma is dependent on many factors including activities of daily living, food intake, physical activity, menstrual cycle, age and concomitant diseases [32]. This would have required the recruitment of a larger number of patients. Despite this, we had significant changes in inflammatory markers within the groups.

Finally it is not possible to eliminate bias completely in a study of this nature.

In conclusion, our randomized controlled study indicates that AEP-guided anesthesia allows dose reduction of anesthetic agents including opioids, leading to better cardiovascular stability and less early POCD. Anesthesia depth did not influence the inflammatory response to surgery. Cognitive decline following major ENT surgery appears be short lived.

Further studies are necessary to evaluate the role of anesthesia depth and inflammatory response in POCD.

Acknowledgments

The authors would like to thank the nurses at the postoperative ward and the anesthesiologists and nurse anesthetists at the Department of Anesthesiology for their dedicated support of this project.

The study was sponsored by the scientific committee of Örebro County Council.

Conflicts of interest related to this study: None.

References

1. Newman S, Stygall J, Hirani S, Shaefi S, Maze M (2007) Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. Anesthesiology 106: 572-590.
2. Deiner S, Silverstein JH (2009) Postoperative delirium and cognitive dysfunction. Br J Anaesth 103: i41-46.
3. Mason SE, Noel-Storr A, Ritchie CW (2010) The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. J Alzheimers Dis 22: 67-79.
4. Krenk L, Rasmussen LS, Kehlet H (2010) New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiol Scand 54: 951-956.
5. Jildenstal PK, Hallen JL, Rawal N, Gupta A, Berggren L (2011) Effect of auditory evoked potential-guided anaesthesia on consumption of anaesthetics and early postoperative cognitive dysfunction: a randomised controlled trial. Eur J Anaesthesiol 28: 213-219.
6. Kertai MD, Pal N, Palanca BJ, Lin N, Searleman SA, et al. (2010) Association of perioperative risk factors and cumulative duration of low bispectral index with intermediate-term mortality after cardiac surgery in the B-Unaware Trial. Anesthesiology 112: 1116-1127.
7. Evered L, Scott DA, Silbert B, Maruff P (2011) Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesth Analg 112: 1179-1185.
8. Plaschke K, Fichtenkamm P, Schramm C, Hauth S, Martin E, et al. (2010) Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. Intensive Care Med 36: 2081-2089.
9. de Rooij SE, van Munster BC, Korevaar JC, Levi M (2007) Cytokines and acute phase response in delirium. J Psychosom Res 62: 521-525.
10. Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Pagel PS (2011) Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. J Anesth 25: 1-9.
11. Recart A, White PF, Wang A, Gasanova I, Byerly S, et al. (2003) Effect of auditory evoked potential index monitoring on anesthetic drug requirements and recovery profile after laparoscopic surgery: a clinical utility study. Anesthesiology 99: 813-818.
12. Kissin I (1997) A concept for assessing interactions of general anesthetics. Anesth Analg 85: 204-210.
13. Punjasawadwong Y, Boonjeungmonkol N, Phongchiewboon A (2007) Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev 17: CD003843.
14. Recart A, Gasanova I, White PF, Thomas T, Ogunnaike B, et al. (2003) The effect of cerebral monitoring on recovery after general anesthesia: a comparison of the auditory evoked potential and bispectral index devices with standard clinical practice. Anesth Analg 97: 1667-1674.
15. Fong HK, Sands LP, Leung JM (2006) The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg 102: 1255-1266.
16. Bell SL, Smith DC, Allen R, Lutman ME (2004) Recording the middle latency response of the auditory evoked potential as a measure of depth of anaesthesia. A technical note. Br J Anaesth 92: 442-445.
17. Plourde G (2006) Auditory evoked potentials. Best Pract Res Clin Anaesthesiol 20: 129-139.
18. Berger JJ, Donchin M, Morgan LS, van der Aa J, Gravenstein JS (1984) Perioperative changes in blood pressure and heart rate. Anesth Analg 63: 647-652.
19. Howel SJ (2003) Anaesthesia and hypertension. Curr Anaesth Crit Care 14: 100-107.
20. Aldrete JA (1995) The post-anesthesia recovery score revisited. J Clin Anesth 7: 89-91.
21. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189-198.
22. Grut M, Fratiglioni L, Viitanen M, Winblad B (1993) Accuracy of the Mini-Mental Status Examination as a screening test for dementia in a Swedish elderly population. Acta Neurol Scand 87: 312-317.
23. Rakusa M, Granda G, Kogoj A, Mlakar J, Vodusek DB (2006) Mini-Mental State Examination: standardization and validation for the elderly Slovenian population. Eur J Neurol 13: 141-145.
24. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, et al. (1990) Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 113: 941-948.
25. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR (1982) The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol 21: 1-16.
26. Bolke E, Jehle PM, Graf M, Baier A, Wiedeck H, et al. (2001) Inflammatory response during abdominal and thyroid surgery: a prospective clinical trial on mediator release. Shock 16: 334-339.
27. Kugisaki H, Sonohata M, Komine M, Tsunoda K, Someya S, et al. (2009) Serum concentrations of interleukin-6 in patients following unilateral versus bilateral total knee arthroplasty. J Orthop Sci 14: 437-442.
28. Sun T, Wang X, Liu Z, Chen X, Zhang J (2011) Plasma concentrations of pro- and anti-inflammatory cytokines and outcome prediction in elderly hip fracture patients. Injury 42: 707-713.
29. duPont NC, Wang K, Wadhwa PD, Culhane JF, Nelson EL (2005) Validation and comparison of luminex multiplex cytokine analysis kits with ELISA: determinations of a panel of nine cytokines in clinical sample culture supernatants. J Reprod Immunol 66: 175-191.
30. Yocum GT, Gaudet JG, Teverbaugh LA, Quest DO, McCormick PC, et al. (2009) Neurocognitive performance in hypertensive patients after spine surgery. Anesthesiology 110: 254-261.
31. Cann C, Wilkes AR, Hall JE, Kumar RA (2010) Are we using our brains? Diagnosis of postoperative cognitive dysfunction. Anaesthesia 65: 1166-1169.
32. Picotte M, Campbell CG, Thorland WG (2009) Day-to-day variation in plasma interleukin-6 concentrationsin older adults. Cytokine 47: 162-165.