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

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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 fulfill 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.

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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) Alaris®TM Pk TCI (Carefusion, Basingstoke, UK) of remifentanil (Minto model), was administered intravenously to reach a target 1.0 ng/mL. 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 administered at a rate of 1.0 mL/kg/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 μg/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 status. 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 (SpO₂), end tidal CO₂, 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 administered via a nasal cannula in all patients during the first 30 minutes. If O₂ 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 measured 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 with 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
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 1 patient (6%) in group A and 7 patients (43%) in group C (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 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
operative drugs. Elderly patients with decreased levels of adenosine and acetylcholine may experience a decrease in hypoxic drive leading to respiratory events particularly in the immediate postoperative period [4].

Reviewing the literature on the possible link between analgesia and POCD, Fong et al. could not draw any firm conclusions but they did find an increased number of hypoxic events in patients who received opioids [4]. It has been proposed that opioids may have an indirect effect on cognitive ability as they influence postoperative pain and sleep quality [5].

Cerebral function monitoring allows reduced drug dosage [13]. Kertai et al. have shown that duration of low anesthetic depth can possibly be associated with an increased incidence of POCD [13]. Both vasopressors and POCD. It seems likely that cerebrovascular autoregulation is maintained better in the vasopressor group [30].

The use of clinical signs to guide anesthesia may lead to both over medication and mortality [6].

In our study fentanyl requirements were significantly higher in the AEP group (Control Group: 60 minutes = 803.1 [596.8], 45 minutes = 596 [6.0], 15 minutes = 596 [6.0], 0 minutes = 596 [6.0]) compared to the Control group (AEP group: 60 minutes = 979.9 [8.5], 45 minutes = 979.9 [8.5], 15 minutes = 979.9 [8.5], 0 minutes = 979.9 [8.5]).

The tests we used (MMSE, CAM and CFQ) have been validated in several studies and are widely used to assess cognitive function in patients undergoing major surgery [22]. The CFQ test battery was reduced to 5 items for ease of use and sensitivity and is considered optimal as a screening level for 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.

**Practice limitations**

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

A recent editorial states that POCD is an emerging condition that is becoming increasingly important in the field of anesthesiology and postoperative care [31]. The prevalence of POCD in postoperative patients is estimated to be around 30% [32]. The exact incidence of POCD is difficult to determine as the criteria for its diagnosis vary widely among studies [33].

In conclusion, POCD is a complex and multifaceted condition that requires further research and clinical trials to better understand its epidemiology, pathophysiology, and treatment options. However, the current evidence suggests that POCD is a common and serious complication of anesthesia and postoperative care and should be considered in all postoperative patients.
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.

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