Propofol vs Sevoflurane anaesthesia on postoperative cognitive dysfunction in the elderly. A randomized controlled trial.

G. Micha (*), P. Tzimas (*), J. Zalonis (**), K. Kotsis (***) , G. Papadopoulos (*) and E. Arnaoutoglou (*)

Abstract: Background: Postoperative cognitive dysfunction is a topic of special importance in the geriatric surgical population which primarily resolves within the short term postoperative period, but it can become a long term disorder with significant impact on patient’s quality of life. This study was designed to compare the short and long term postoperative cognitive function after propofol and sevoflurane anaesthesia in the elderly and to evaluate the role of the inflammatory process.

Methods: Patients, aged 60-74, scheduled for a non-cardiac operation of more than two-hour duration were enrolled in this prospective randomized controlled trial and allocated into two groups in order to receive propofol or sevoflurane anaesthesia. Postoperative early cognitive function was assessed by means of the Mini Mental State Examination test (MMSE) 48 hours postoperatively. Late cognitive function was evaluated by means of 10 psychometric tests, 9 months postoperatively. The role of inflammation was estimated by the incidence of SIRS and the levels of the inflammatory markers.

Results: Statistical significant decrease was observed in the postoperative MMSE values in the sevoflurane group. Nine months postoperatively, there was a decline in test performance in the same group and an increase in postoperative values of inflammatory markers in both groups, which turned non-significant in their between comparison (except CRP).

Conclusion: According to the neuropsychological test evaluation of cognition, there is a negative influence of sevoflurane anaesthesia on the early and late postoperative state. As far as the inflammatory markers are concerned, they don’t relate to the patient’s cognitive status.

Key words: Cognition disorders-Propofol-Sevoflurane-Inflammation.

INTRODUCTION

In 1955 Bedford (1) first recorded that some of the elderly patients who were subjected to operations under general anaesthesia “were never the same” postoperatively. This change is termed postoperative cognitive dysfunction (POCD) and is nowadays evaluated by means of psychometric tests. The deficit differs in each patient regarding the duration and the intensity. It may involve all levels of cognition such as language comprehension, visual-spatial intelligence, process of speech, abstract thinking and social integration. (2) It can be distinguished in early and late POCD when it is observed within the first 7 days or 3 months postoperation respectively. (3) These events are associated with a higher rate of postoperative complications, increased length of hospital stay and have an impact on the patient’s wellbeing and quality of life. (4,5) Furthermore, data have shown a positive relation to mortality in elderly patients that develop POCD 3 months postoperatively. (6) POCD is common after cardiac operations. However, its incidence remains significant in non-cardiac ones (25.8% -40% in the 1st week, 9.9% at 3 months and 1% at 2 years postoperatively) with even higher rates in more than 60-year-old patients. (7) The pathophysiology of POCD still remains unclear. Several mechanisms have...
been proposed including neurotoxicity of volatile anaesthetics, inflammation, anticholinergic activity, low intraoperative cerebral oxygenation and cerebral microemboli. (3,8) Evidence from animal studies suggest that sevoflurane exposure can lead to neurodegeneration with increase in β-amyloid protein levels,(9) changes in exploratory and anxiety-like behaviour in these subjects and activation of specific kinases that lead to tau phosphorylation and spatial memory deficits.(10) Recent data in human neuroblastoma cell line indicate that sevoflurane in clinically relevant concentrations does not cause human neuron-like cell injury. It also provides preconditioning in a concentration-dependent manner when administered prior to exposure. (11) Propofol is neuroprotective in vitro through inhibition of NMDA receptor-mediated calcium increase in a dose dependent manner, (12,13) while subanaesthetic concentrations seem to have an apoptotic effect. (14) In humans there is a number of studies that compare sevoflurane and propofol anaesthetic agents when administered in the elderly under general anesthesia. These studies have contradicting results regarding the impact in POCD. (15-18)

Inflammatory alterations in the brain tissue can affect all levels of cognition. POCD after surgery and anaesthesia has been linked to an excessive release of cytokines in animal models. In humans there is no positive relation of SIRS to POCD in patients subjected to cardiopulmonary bypass. Nevertheless, evidence in non-cardiac operations are lacking. On the contrary to sevoflurane anaesthesia, a postoperative decrease of the inflammatory markers after propofol administration has been observed. (19)

**Research objective**

The clinical interpretation of all these data from animal studies in humans remains inconclusive on their role in POCD; therefore, the aim of this study was to evaluate the impact of propofol and sevoflurane anaesthetic agents on the early and late postoperative cognitive function of elderly patients and to assess the role of inflammation at the same time frame.

**Research Materials and Methods**

This prospective randomized, double blind clinical trial was approved by the Ethics Committee of our hospital (Anticancer hospital of Athens “St Savvas”-Ethical Committee No.2010/67, 27 May 2010, president V. Mertikopoulos), Athens, Greece. Written informed consent was obtained from all study patients. Patients of 60-74 years of age, native Greek speakers, of at least preliminary educational status were enrolled. They were about to be subjected to an operation for a tumor resection of more than two-hour duration (non-cardiovascular or neurosurgical). The particular age range was selected due to similar cognitive performance in different domains as assessed by the norms provided for the Greek population (20-23). Another reason was to avoid the practice effect that is mostly observed in patients over 75 years of age when the MMSE test is repeated at short intervals. This can be explained by the absence of multiple standardized versions available for the Greek population that could be of use at short intervals. (24) Exclusion criteria involved patients not competent in writing, with severe impairment of hearing or vision, with preoperative cognitive dysfunction as stated by the MMSE test (levels ≤23), central nervous system (dementia, Parkinson’s, Alzheimer disease) or psychiatric disease, antidepressant therapy or abuse of drugs or alcohol, assessment with psychometric tests in the past and patients that were re-operated during the study period.

Patients were subjected by a member of the team who was blinded to the study group, into a set of 9 neuropsychological tests in order to assess different aspects of cognition summarized in Appendix 1. (20-23,25-29) The MMSE test was performed preoperatively, 48 hours postoperatively and 9 months later, while the rest of the tests were carried out preoperatively and 9 months later according to the flow chart provided (Figure 1). When patients entered the operating room they were randomly allocated into two Groups (A and B) by means of closed sealed envelopes. The neuropsychological assessment was performed by a trained anaesthetist who undertook patient enrollment and blood tests yet he did not deliver anesthesia to the patient and, therefore, was unaware of study group allocation. A blood sample of 5ml was obtained and induction of anaesthesia followed soon afterwards. Regardless of group, all patients were administered intravenous propofol (2mg kg⁻¹) and fentanyl (2mcg kg⁻¹) for induction. Group A patients received propofol (6–10 mg kg⁻¹ h⁻¹) and Group B patients received sevoflurane (2-3%) for maintenance in order to establish a Bispectral Index (BIS) at levels of 40-60 during the operation. All patients received an O₂/Air mixture. Routine monitors were applied to all patients, including constant electrocardiogram, pulse oximeter, non-
### PROPOFOL VS SEVOFLURANE ANAESTHESIA

#### Appendix 1

Neuropsychological tests

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Description</th>
<th>Scoring/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination (MMSE)</td>
<td>Consists of questions to detect: orientation to time and place, registration of 3 words and recall, calculation, language and visual construction</td>
<td>Orientation, registration, attention, calculation, recall</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning</td>
<td>Five trial presentation of a 15-word list followed by a single presentation of an interference list and 2 post-interference recall trials (one immediate, one delayed)</td>
<td>Verbal learning (Trail I &amp; Trial 2I-V) recall, recognition</td>
</tr>
<tr>
<td>Trail Making Test A, B</td>
<td>Part A: Patient draws lines to connect subsequent numbers. Part B: Patient connects the same number of consecutively numbered and lettered circles by alternating between the two sequences</td>
<td>Orientation, attention, scanning, visuomotor tracking, divided attention, cognitive flexibility</td>
</tr>
<tr>
<td>Stroop Neuropsychological Screening</td>
<td>A list of color names printed in colors different than the name written. Patient is required to read through the list as quickly as possible, reading out the printed color.</td>
<td>Attention, concentration, executive function</td>
</tr>
<tr>
<td>Controlled Oral Word Association (CDWA)</td>
<td>Consists of 3 word-naming trials: patient is asked to say how many words as he can think of in one minute that begin with the given letter of the alphabet, excluding proper nouns, numbers or the same word with different suffix.</td>
<td>Verbal function, language skills</td>
</tr>
<tr>
<td>Three Words-Three Shapes</td>
<td>Patient is given a set of 3 different shapes matched with 3 different irrelevant words to memorize for 30 sec. Then he is asked to draw the shapes and write down the matching words.</td>
<td>Learning, memory, recall, recognition</td>
</tr>
<tr>
<td>Babcock Story Recall</td>
<td>Patient listens to a 21-item story and is asked immediately afterwards to repeat it. Then he listens to it again and 10 minutes later a recall is requested.</td>
<td>Memory</td>
</tr>
<tr>
<td>Clock Test</td>
<td>Patient is given a sheet of paper and he is instructed to draw a circle, to make the circle look like the face of a clock and then to draw the hands of the clock to read “10 past 11.”</td>
<td>Construction, memory</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>A 21-item scale where each item contains 4 statements of graded severity ranging from 0-3 according to severity.</td>
<td>Depression</td>
</tr>
<tr>
<td>Instrumental Activities Daily Living (IADLS)</td>
<td>Consists of 8 self-care tasks each one contains statements of graded severity.</td>
<td>Functional status</td>
</tr>
</tbody>
</table>

Invasive blood pressure measurement, respiratory gas analyzer (end-tidal CO$_2$ and sevoflurane, inspiratory O$_2$) and BIS recordings (BIS Covidien Medronic Systems). Episodes of hypotension (mean arterial pressure $\leq$60mmHg for more than 30 minutes) or oxygen saturation $\leq$ 80% for more than 30 minutes were recorded.

Patients of both groups were subjected to MMSE 48 hours postoperatively by the same member of the medical team in order to achieve
estimate the presence of depression which is known to influence cognitive functions.(28)

Statistical analysis

All data analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 20 for Windows (SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Shapiro Wilk test. Continuous data that were not normally distributed were compared using the Mann-Whitney U-test. Differences between categorical data were analyzed with the chi-square test. A p value of <0.05 was considered statistical significant.

RESULTS

Patient’s characteristics

A total of 80 patients were enrolled in the study (June 2010-July 2013), 40 of which in Group A and 40 in Group B. Four patients from Group A were excluded (in 2 cases the operation was cancelled and 2 patients were hemodynamically unstable) and 3 from Group B (no availability in optimal testing consistency. A decrease ≥2 units in the postoperative MMSE values was considered significant according to a previous study.(30, 31)

At the same time, in order to assess the early postoperative cognitive status, a blood sample for the measurement of the inflammatory markers (CRP, IL6, IL10, TNF-a) was obtained once again. The presence of SIRS was established by recording the levels of heart rate, of white blood cells count and of body temperature 24 hours pre- and 48 hours postoperatively. Biometric parameters (age, body mass index-BMI), educational status, duration of operation, number of previous operations, perioperative blood transfusion and Charlson Comorbidity index (32) were recorded in all patients. Confusion Assessment Method (33) was also performed, so as to assess the presence of delirium. Postoperative analgesia involved morphine administration in order to achieve a Visual Analogue Scale ≤3. MMSE was evaluated only when their performance in the Confusion Assessment Method proved absence of delirium. Late postoperative cognitive function was assessed 9 months postoperatively by administering the same set of neuropsychological tests. The Beck Depression Inventory (BDI) was administered pre- and 9 months postoperatively in order to detect and
9 months follow up). Finally, 36 patients in Group A and 37 in Group B were analyzed. All of the participants were subjected to surgical operations of more than two hours duration with the indication of a cancer tumor and all of them had a positive biopsy postoperatively. The two groups were similar with regard to patient’s characteristics (Table 1). None of the patients presented postoperative delirium as stated by the Confusion Assessment Method and no episodes of hypotension or drop in oxygen saturation were recorded.

Early postoperative cognitive function

MMSE score preoperative values were 29 (28-30) and 29 (28-30) in the propofol and sevoflurane group respectively. Postoperative decline of cognitive function (reduction of baseline MMSE values more than 2 units) was observed in one patient of Group A (2.8%) and in 10 of Group B (27%) (p=0.004). This difference is regardless of age, gender, ASA classification, BMI, number of previous operations, educational status, perioperative blood transfusions and Charlson Comorbidity score values.

The role of inflammation

Our results showed a significant prevalence of SIRS in the sevoflurane group, (p=0.001) with no relevance to cognitive decline as stated by the MMSE postoperative values (Table 2). On the matter of the inflammatory markers, we observed that there was an increase of the median values of all markers in both groups, but there was no statistical significant difference in the postoperative, IL6, IL10 and TNF-a values between the two study groups (Table 2). Only CRP values showed a significant increase in Group B compared to Group A postoperatively (p= 0.013).

Late postoperative cognitive function

According to the neuropsychological tests analysis (Table 3), there is a statistically significant decline in Group B values in time in a number of tests performed. This decline is present in the MMSE test, in Controlled Oral Word Association test, in Stroop Neuropsychological Screening, in Clock test, in Three Words-Three Shapes test, in Babcock Story Recall test I and II and in the functional status of patients receiving sevoflurane as stated by the Instrumental Activities of Daily Living test. In Rey Auditory Verbal Learning test there is a progressive decrease in the performance status in trials VI and ΣI-V which implies a decreased rate of learning ability in sevoflurane group. Moreover, in Trail Making test B time to complete the tasks performed increases significantly in Group B 9 months postoperatively, which shows a decline in the process of attention, scanning, visuomotor tracking and cognitive flexibility. Depression as stated by the BDI test is not statistically significant in between groups at any time during the study period.

| Table 1 |
| Patient’s characteristics |
| Age (years) | 64(62-67) | 65.62(62-68) | 0.360 |
| Gender (M/F) | 19/17 | 20/17 | 0.913 |
| ASA class1 * | 3(8.3%) | 3(8.1%) | 0.972 |
| ASA class 2,3 | 33(91.7%) | 34(91.9) | 0.991 |
| BMI † | 26.8(25.03-28.68) | 26.8(25.6-28.9) | 0.616 |
| Duration of operation(minutes) | 140.8(130-148.8) | 147.7(125-152.5) | 0.949 |
| Previous operations(Number) | 2(1-4) | 1(1-3) | 0.246 |
| Education ** | 1(0-2) | 1(1-2) | 0.218 |
| Perioperative blood transfusion (Number of units) | 5(13.9%) | 4(10.8%) | 0.689 |
| Charlson comorbidity score | 5(5-5) | 5(5-6) | 0.145 |
| Confusion Assessment Method | 1(2.8%) | 0(0%) | 0.49 |

* ASA: American Society of Anesthesiologist, † BMI: Body Mass Index. ** Education: (0=First grade, 1=Second grade, 2=Third grade. Group A: propofol group, Group B: sevoflurane group Data are presented as median and IQR (Interquartile Range).
function is affected by the sevoflurane anaesthesia as stated by the neuropsychological tests administered nine months postoperatively. On the other hand, the patients who received propofol have an intact cognitive status. Schoen et al (15) investigated the effects of total intravenous anaesthesia with propofol compared with sevoflurane anesthesia.

### Discussion

Our data analysis reveals that there is a decrease in early postoperative cognitive function in 27% of Group B (sevoflurane) patients. This decrease is not correlated to SIRS or to the other inflammatory markers measured. Late postoperative cognitive function is affected by the sevoflurane anaesthesia as stated by the neuropsychological tests administered nine months postoperatively. On the other hand, the patients who received propofol have an intact cognitive status. Schoen et al (15) investigated the effects of total intravenous anaesthesia with propofol compared with sevoflurane anesthesia.

### Table 2

Comparisons of inflammatory markers, SIRS and MMSE between the two groups in the early postoperative period

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS postoperative</td>
<td>5 (13.9%)</td>
<td>19 (51.4%)</td>
<td>0.001</td>
<td>0 (0%)</td>
<td>3 (8.1%)</td>
<td>0.081</td>
</tr>
<tr>
<td>SIRS-MMSE *</td>
<td>0 (0%)</td>
<td>3 (8.1%)</td>
<td></td>
<td>0 (0%)</td>
<td>3 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>CRP preoperative</td>
<td>0.35 (0.0-2.4)</td>
<td>1.4 (0.85-4.85)</td>
<td>0.004</td>
<td>0.35 (0.0-2.4)</td>
<td>1.4 (0.85-4.85)</td>
<td>0.004</td>
</tr>
<tr>
<td>CRP postoperative</td>
<td>14.75 (1.85-63.6)</td>
<td>40.8 (13.05-114.6)</td>
<td>0.013</td>
<td>14.75 (1.85-63.6)</td>
<td>40.8 (13.05-114.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>IL6 preoperative</td>
<td>1.5 (1.33-2.63)</td>
<td>2.54 (1.55-3.97)</td>
<td>0.016</td>
<td>1.5 (1.33-2.63)</td>
<td>2.54 (1.55-3.97)</td>
<td>0.016</td>
</tr>
<tr>
<td>IL6 postoperative</td>
<td>17.26 (7.08-31.17)</td>
<td>22.3 (12.55-46.72)</td>
<td>0.186</td>
<td>17.26 (7.08-31.17)</td>
<td>22.3 (12.55-46.72)</td>
<td>0.186</td>
</tr>
<tr>
<td>IL10 preoperative</td>
<td>95.3 (26.85-120.6)</td>
<td>73.9 (7.88-136.75)</td>
<td>0.931</td>
<td>95.3 (26.85-120.6)</td>
<td>73.9 (7.88-136.75)</td>
<td>0.931</td>
</tr>
<tr>
<td>IL10 postoperative</td>
<td>106.2 (21.3-129.72)</td>
<td>117 (7-148.2)</td>
<td>0.786</td>
<td>106.2 (21.3-129.72)</td>
<td>117 (7-148.2)</td>
<td>0.786</td>
</tr>
<tr>
<td>TNF-a preoperative</td>
<td>56.6 (8.35-216.3)</td>
<td>11.9 (5.4-65.4)</td>
<td>0.266</td>
<td>56.6 (8.35-216.3)</td>
<td>11.9 (5.4-65.4)</td>
<td>0.266</td>
</tr>
<tr>
<td>TNF-a postoperative</td>
<td>49.5 (29-199.3)</td>
<td>19.5 (2.7-77.8)</td>
<td>0.119</td>
<td>49.5 (29-199.3)</td>
<td>19.5 (2.7-77.8)</td>
<td>0.119</td>
</tr>
</tbody>
</table>

* Comparison of SIRS (Systemic inflammatory response syndrome) and postoperative decline of MMSE (Mini-Mental-State-Examination) values ≥2 units. Group A: propofol group, Group B: sevoflurane group. Data are presented as median and IQR (Interquartile Range). P values are between Group A and B preoperatively and 9 months postoperatively.

### Table 3

Neuropsychological test results for the patients at baseline and 9 months after surgery

<table>
<thead>
<tr>
<th>Test</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State</td>
<td>29 (28-30)</td>
<td>29 (28-30)</td>
<td>0.443</td>
<td>29 (29-30)</td>
<td>28 (26-30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning</td>
<td>4 (4-6)</td>
<td>4 (3-5)</td>
<td>0.503</td>
<td>5 (4-6)</td>
<td>4 (3-5)</td>
<td>0.155</td>
</tr>
<tr>
<td>Trial I</td>
<td>7 (7-11)</td>
<td>8 (7-10)</td>
<td>0.585</td>
<td>9.5 (7-11.8)</td>
<td>8 (6-10.5)</td>
<td>0.056</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning</td>
<td>40 (34-48)</td>
<td>39 (33.5-44)</td>
<td>0.357</td>
<td>42.5 (38-51)</td>
<td>37 (31.5-45.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Trial VI</td>
<td>60 (47-71.8)</td>
<td>53 (42-75.5)</td>
<td>0.431</td>
<td>54 (43.3-64)</td>
<td>57 (46.5-74)</td>
<td>0.366</td>
</tr>
<tr>
<td>Trail Making A</td>
<td>108 (85.8-161.5)</td>
<td>120 (93-179.5)</td>
<td>0.223</td>
<td>109.5 (81.3-147.8)</td>
<td>142 (98-182)</td>
<td>0.024</td>
</tr>
<tr>
<td>Trail Making B</td>
<td>78 (64-93)</td>
<td>73 (58-99.5)</td>
<td>0.728</td>
<td>87 (72-99.5)</td>
<td>73 (55-86.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stroop Neuropsychological Screening</td>
<td>40 (31.3-47)</td>
<td>40 (31.5-48)</td>
<td>0.828</td>
<td>43 (37-52.8)</td>
<td>40 (34-43.5)</td>
<td>0.043</td>
</tr>
<tr>
<td>Controlled Oral Word Association</td>
<td>3 (3-4)</td>
<td>4 (3-4)</td>
<td>0.417</td>
<td>4 (3-3-4)</td>
<td>3 (3-4)</td>
<td>0.044</td>
</tr>
<tr>
<td>Three Words-Three Shapes</td>
<td>10.5 (9-13)</td>
<td>11 (9-14)</td>
<td>0.845</td>
<td>11 (9-12)</td>
<td>10 (8-12)</td>
<td>0.045</td>
</tr>
<tr>
<td>Babcock Story Recall Part 1</td>
<td>10.5 (9-13)</td>
<td>11 (9-13)</td>
<td>0.919</td>
<td>11 (10-14)</td>
<td>10 (9-11.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Babcock Story Recall Part 2</td>
<td>4 (3-4)</td>
<td>4 (3-4)</td>
<td>0.731</td>
<td>4 (3-3-4)</td>
<td>3 (3-4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Clock Test</td>
<td>4 (3-4)</td>
<td>4 (3-4)</td>
<td>0.696</td>
<td>9 (8-15)</td>
<td>9 (9-14.5)</td>
<td>0.931</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>7 (5.8)</td>
<td>7 (5.8)</td>
<td>0.913</td>
<td>7 (6.7)</td>
<td>6 (5.5-7)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Group A: propofol group, Group B: sevoflurane group. Data are presented as median and IQR (Interquartile Range). P values are between Group A and B preoperatively and 9 months postoperatively.
on POCD in 128 patients undergoing coronary artery bypass (CABG) surgery. Contrary to our study findings, the primary result of their study showed that patients in the sevoflurane group had a significantly better cognitive postoperative function than those in the propofol group. Those patients were subjected to neurocognitive tests on the 2nd, 4th, and 6th postoperative day and there was no difference in the levels of CRP between the two groups. The difference in Schoen et al study is primarily patients’ age (< 60 years and >75) which were excluded from our study. Evidence on animal studies suggest that age is of importance regarding postoperative cognitive dysfunction.(34) Moreover, patients were subjected to more complex surgical operations and presented with a higher degree of cerebral desaturation that could be the sole factor of POCD. Finally, there was a substantial period of time where patients in the sevoflurane group received propofol as anaesthetic agent (during cardiopulmonary bypass and ICU).

Likewise, Magni et al(17) also compared these two anaesthetic agents and concluded that there is no statistically significant difference on the matter of the short term neurocognitive function. This study refers to patients that were subjected to neurosurgical operations of the brain. It should be mentioned that there are, in this kind of operations, multiple factors affecting the brain function and secondarily the cognitive state that are not fully clarified.

In the prospective randomized trial of Tang N et al (35) patients of more than 60 years of age with mild cognitive dysfunction prior to the operation, were subjected to a radical rectal resection under propofol or sevoflurane anaesthesia.

In accordance with the previous study they didn’t find any statistically important difference between the two anaesthetic agents regarding the incidence of short term POCD. However, they revealed a more severe impact on the cognitive status of patients administered with sevoflurane. The mild cognitive impairment prior to the operation has already compromised the cognitive reserves. This fact in addition to the low BIS values (<30 at induction) can be the key factors to these findings.

On the other hand, Xu et al(18) in a recent meta-analysis regarding the effect of propofol and inhalation anaesthesia on the incidence of POCD concluded that, in accordance to our results, propofol anaesthesia is associated with a lower incidence of POCD in elderly patients undergoing non-cardiac surgery. This meta-analysis involved 753 patients enrolled in 13 RCTs while 7 of these studies compared propofol with sevoflurane anaesthesia.

Moreover, the systemic inflammatory response can affect all cognitive functions (36) by increasing levels of inflammatory markers which lead to neuroinflammation, subsequent microglia activation and damage to normal functioning neurons. This is advocated by studies where administration of an anti-TNF-α antibody(37) or the anti-inflammatory drugs minocycline (38) and meloxicam (39) can attenuate postoperative cognitive decline. These events are related to an increased risk of dementia and Alzheimer’s disease. In a study of an elderly population (n=41) that were subjected to arthroplasty it was also associated with short-term POCD although these results are not related to the type of anaesthetic technique or agent.(40) Propofol can induce suppression of inflammatory markers in a dose-related manner as it was demonstrated in a study that was performed on mice at administrated doses of 5, 10 and 20 mg kg⁻¹h⁻¹. Those mice that were administered with higher than 10 mg kg⁻¹h⁻¹ doses of propofol had lower concentrations of TNF-α and IL-6.(41)

In the study of Schneemilch et al,(42) the inhaled anaesthetic agent sevoflurane increased the levels of these markers postoperatively in patients that were subjected to elective spinal cord disectomy but not in those that received total intravenous anaesthesia. On the contrary, in the study of Kvarnström et al(43) involving the sevoflurane versus propofol anaesthesia in colorectal surgical procedures for tumor resection, there was no difference between the two agents on the matter of inflammation. In our study, there was a significant increase of the inflammatory markers postoperatively in both groups, but there was no statistical significant difference between them apart from CRP values. Moreover, there was a statistical significant difference between the two groups regarding SIRS but it was not correlated to early POCD according to MMSE test evaluation. These results could be explained by the nature of the underlying cause of the operations which was cancer in all of our patients and it can be solely a cause of increase in these markers.(44)

**Limitations of the study**

Our study should be considered in the light of certain limitations. It should be mentioned that the induction of anaesthesia in the sevoflurane group was with propofol but the total amount of the drug was too low to be considered enough to compromise...
the results of the study. Additionally, the tool of assessing the early POCD was only the MMSE test in order to limit the practice effect that occurs with repeated administration of neuropsychological tests. It is documented that practice effects are minimal in MMSE (group means change less than a single point) and these changes occur mostly in patients >75 years of age who were not included in our study.(24) The major limitation of this study is that we arbitrarily selected this number of 80 patients which constitutes a drawback of our study.

CONCLUSION

POCD in the elderly appears to be correlated with the administration of the volatile agent sevoflurane and not with the intravenous agent propofol. A safe conclusion though cannot be provided but we can propose some considerations and point out the need for further research.

References


