

No Difference in Early Post Operative Cognitive Dysfunction after Abdominal Surgery with Sevoflurane or Propofol Based General Anesthesia

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Abstract

Background: There is an increasing need to investigate the influence of anesthetics on post-operative cognitive dysfunction (POCD), probably resulting from concurring perioperative stress factors. This study aimed to seek a difference in early POCD after general anesthesia with either propofol or sevoflurane as maintenance agent in patients undergoing abdominal surgery.

Methods: Patients older than 60, undergoing general anesthesia for laparotomic abdominal surgery with Sevoflurane/air or Propofol Target Controlled Infusion were included in this observational study. Working and long term memory, attentive capacity and correct reading velocity were evaluated before and 1 week after surgery. POCD was detected from the difference between postoperative and baseline performances, subtracting the learning effect observed in a control group.

Results: Of 92 patients included, 25 received propofol and 67 sevoflurane. Overall POCD incidence was 14.14%. POCD was 12.00% in propofol group and 14.93% in sevoflurane group ($P = 0.72$). There was no significant association between age, sex, duration of surgery or anesthesia and POCD occurrence ($P > 0.05$). Lower education level (OR = 3.74; 95% CI: 0.78 – 18.04; $P > 0.05$) and overall pain as referred by patients at 7th day (OR = 1.33; 95% CI: 1.02 – 1.75; $P = 0.029$) had a high odd of POCD.

Conclusion: Our results indicate no preference between sevoflurane or propofol in order to obtain a better early neurocognitive outcome. Pain was associated to POCD generation. In order to verify or exclude anesthetic toxicity, ongoing prospective studies in humans including dosage of neuronal death markers could be useful.

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Introduction

In latest years a deal of clinical research has focused on adverse effects of surgical and anesthetic treatments^[1]. Post-operative cognitive dysfunction (POCD), according to Hanning's definition^[2], is the functional worsening in two or more cognitive functions measured by neuropsychological tests in the post-operative period, after residual effects of drugs and organic disease

have been ruled-out.

Firstly described in cardiac surgery and advanced age patients, it can occur in every kind of surgery and even in younger age^[1-5]. Cardiac surgery and elderly population are associated with higher risk probably because of cerebral perfusion abnormalities, associated to extra-corporeal circulation, pre-existing cerebrovascular diseases, frequently compromised general medical conditions or already established cognitive dysfunction.



tion^[3,7,19,33,34].

POCD after major non-cardiac surgery has been observed in 19.7% of patients older than 60 years^[1,6-8]. It can be evidenced a few days following surgery, with a maximum incidence in 7th post-operative day (early POCD), and may hold over days or weeks, persisting at 1 - 2 years in 1% of non-cardiac surgery patients (persisting POCD)^[6,7]. Persisting POCD seems to affect quality of life and survival, but early POCD is also important: it represents the peak of POCD incidence and significantly prolongs hospitalization^[7,33,36].

POCD pathogenesis is unknown, probably multifactorial. It may be due to the influence of several factors: inflammatory mediators, metabolic, neuroendocrine, physical and psychological stresses suffered by the patient in the peri-operative period^[1,9-11] and drugs. Patients are nowadays anesthetized for an increasingly greater number of invasive procedures. There is a growing need to acquire information about the influence of each single factor, including drugs and anesthetics used in surgical patients, on the genesis of POCD^[12,13]. Anyway, the study of the influence of the POCD-risk associated to single drugs appears difficult because modern general anesthesia usually employs multiple drugs to obtain various goals as hypnosis, amnesia, analgesia, muscle relaxation and preservation from stress reaction. The aim of this observational study was to investigate if early POCD has a different incidence after general anesthesia maintained with either propofol or sevoflurane in patients older than 60 undergoing abdominal surgery in common, real clinical practice.

Methods

Study Population

Our University Hospital Ethics Committee approved the study. ASA I-III patients older than 60 were enrolled in a prospective observational study of 1 year duration. A written informed consent was obtained from each patient. Patients enrolled had to undergo abdominal laparotomic surgery (mainly digestive tract resection) which programmed duration was 60-240 minutes with general anesthesia with sevoflurane or propofol as maintenance agent. Assuming $\alpha = 0.05$, $\beta = 0.2$, an expected difference in POCD generation between groups of 20% and a $\sigma = 2.8$, the minimum number of patients per group was estimated to be 25.

Exclusion criteria were:

- (1) Diseases of the central nervous system including pre-existing cognitive dysfunction severe enough to impede patient cooperation;
- (2) Significant carotid disease, investigated with ultrasonography;
- (3) Consumption of drugs with activity on central nervous system including alcoholism or addictive drug dependence;
- (4) Poor comprehension of the language used in processing the study tests (Italian);
- (5) Hypoxic, severe hypo/hypercapnic or hypo/hypertensive episodes during surgery or in the post-operative period;
- (6) Occurrence of vascular disease during surgery or in the post-operative period (in particular including thrombosis or haemorrhages);
- (7) Difficult airway management that caused deviation from usual anesthetic technique.

(8) The surgical group study performances were compared to an age-matched control group of 14 healthy people.

Intraoperative Protocol

Anesthetic technique was not imposed to anesthesiologists. Anyway, protocols applied in our University hospital were quite homogeneous. Patients were premedicated (Diazepam 5 mg per os). General anesthesia was induced with: Fentanyl 1 - 4.4 $\mu\text{g}/\text{Kg}$, Propofol 2 - 3 mg/Kg and Vecuronium Bromide 0.08 mg/kg . Sevoflurane 2 - 2.5% in O_2/Air or Propofol Target Controlled Infusion (DiprifusorTM TCI, Marsh Protocol) 3 - 4 $\mu\text{g}/\text{ml}$ were used for maintenance. Patients were ventilated in volume controlled mode with EtCO_2 maintenance to 30 - 35 mmHg and FiO_2 40 - 50%.

Muscular relaxation was antagonized at end of intervention with Atropine 0.02 mg/Kg and Neostigmine 0.07 mg/Kg . Analgesia was offered through Fentanyl 5 - 9 $\mu\text{g}/\text{kg}$ according to clinical needs and Ketorolac 30 mg i.v. during surgery, and with post-operative continuous infusion of Morphine 0.625 mg/h and Ketorolac 2.5 mg/h for 48 hours. If necessary, Tramadol supplementation was offered. An observer different from the anesthesiologist in charge collected the following data: anesthetic and surgery duration, opioid and neuromuscular blocking agent consumption, pain Visual Analog Scale (VAS, 1 to 10) at 3 and 48 hours and a global evaluation of pain suffered in the postoperative period, expressed through Numeric Rating Scale (NRS, 1 to 10), at the moment of final neuropsychological test.

Neuropsychometric Evaluation

On the day before surgery and the day before discharge (usually the seventh post-operative day) patients underwent neuropsychological testing: the 15 words memorization Rey test^[14] and the Stroop Color Word Interference test^[15], validated and used in previous multicentric studies^[4,7]. Four neuropsychological functions were investigated with such tests: working memory, long term memory, attentive capacity and correct reading velocity. Results were collected and analyzed by observers blinded to anesthesia regimen. The same tests were performed twice on the control group of healthy age-matched people at 1 week distance. The definition of cognitive dysfunction was based on agreed protocols from the literature^[2,16].

The mean and standard deviation (SD) of changes in performance (the difference between the first and second result) in each test were calculated in the control group. The mean difference in performance among controls was taken as a learning effect of the control group. For each patient, the difference between postoperative and baseline values was calculated, and the learning effect subtracted from these changes. The result was divided by the control group SD, to obtain the "Z-score" for each test^[2].

A composite Z-score was calculated from the mean of all Z-scores of each patient. Large positive Z-scores indicate deterioration in cognitive dysfunction compared with controls. According to definition^[2], patients had POCD when two or more Z-scores in the individual tests or the composite Z-score were equal or greater than 1.96.

Statistical Analysis

Differences in POCD incidence between the two anesthetic regimens were assessed using non parametric tests (chi

square and Mann-Whitney for qualitative and quantitative variables, respectively).

A multivariate approach was used in order to adjust the analysis for possible confounders. Two different regression models were developed, a logistic and a survival analysis (Cox model). The results are respectively presented as Odds Ratios, and Hazard Ratios with their own and 95% Confidence Intervals (95% CIs). With the latter model, time between intervention and discharge was taken into account in the analysis. The statistical significance was set at $p < 0.05$. The statistical analysis was conducted using the package SPSS™, release 12.0 for Windows™.

Results

We enrolled 109 patients. 17 patients were excluded, 10 because of refusal to repeat tests, 7 because of post-operative complications that clearly impaired patient cooperation ability at the time of second evaluation: fever in 4 cases, confusion associated to poor glycaemic control in 2 cases and to hyponatremia in 1 case. Those who withdrew did not differ significantly in any characteristics from those who continued in the study. 92 patients could be included in the study, 25 (27.17%) of them received propofol as maintenance agent and 67 (72.82%) sevoflurane.

POCD definition was satisfied in 13/92 patients (14.14%). This happened in 3/25 (12.00%) in propofol group and 10/67 (14.93%) in sevoflurane group ($P = 0.72$). 26/92 (28.26%) of all patients showed a significant decrease (Z-score equal or greater than 1.96) in only one cognitive function analyzed, 10/25 (40.00%) of propofol patients and 16/67 (23.88%) of sevoflurane patients respectively ($P = 0.126$) (Table 1). The logistic regression model revealed that patients treated with propofol had a not-significant lower odd of getting POCD with respect to patients treated with sevoflurane (OR = 0.78 ; 95% CI: 0.19 – 3.09). The same happened in females with respect to males (OR = 0.87; 95% CI: 0.26 – 2.90), respectively ($P >$

0.05). Age, sex distribution, and education level of patients and controls were also similar between groups ($P > 0.05$) (Table 2).

Table 1: Incidence of Postoperative cognitive dysfunction (POCD) ($P = 0.73$).

	POCD
All Patients (n = 92)	13 (14.14%)
Propofol (n = 25)	3 (12.00 %)
Sevoflurane (n = 67)	10 (14.93%)

Table 2: Demographic data (Mean +/- SD) ($P > 0.05$).

	Age (years)	Sex (male %)	Education
Controls (n = 14)	72 +/- 10	36	2 +/- 1
All Propofol (n = 25)	71 +/- 6	52	2 +/- 1
All Sevoflurane (n = 67)	70 +/- 7	61	2 +/- 1
POCD Propofol (n = 3)	75 +/- 7	66	2 +/- 1
POCD Sevoflurane (n = 10)	69 +/- 7	60	2 +/- 1

(Education numerically expressed as: 1: No School; 2: Primary school completion; 3: Secondary school; 4: University)

Duration of anesthesia, duration of surgery, VAS on the day of surgery, on 2nd postoperative day and pain NRS at the moment of final evaluation are shown in (Table 3). There was no association between age or sex and POCD occurrence ($P > 0.05$). On the other hand, the lower education level and higher values of 7th day NRS of pain have a highest odd of getting POCD (OR = 3.74; 95% CI: 0.78 – 18.04 with $P > 0.05$; OR = 1.33; 95% CI: 1.02 – 1.75 with $P = 0.029$, respectively). Results are shown in (Table 4).

Table 3: Main surgical variables: Mean +/- SD ($P > 0.05$).

	Anaesthesia duration (min)	Surgery duration (min)	VAS pain Day 1	VAS pain Day 2	NRS pain Day 1 - 7
Propofol (n = 25)	212 +/- 78	150 +/- 63	3.89 +/- 3.27	3 +/- 2.96	1.22 +/- 2.19
Sevoflurane (n = 67)	220 +/- 81	171 +/- 81	2.38 +/- 3.43	4.79 +/- 2.48	1.29 +/- 1.93
POCD Propofol (n = 3)	160 +/- 10	120 +/- 10	3 +/- 3	7.33 +/- 3.79	3 +/- 3
POCD Sevoflurane (n = 10)	208 +/- 77	166 +/- 67	4.1 +/- 3.25	4.35 +/- 1.94	2.2 +/- 2.74

Table 4: Odds Ratios of variables for POCD.

	OR (95% CI) for POCD	P-value
Propofol vs. Sevoflurane	0.78 (0.15 - 3.50)	0.3945
Age	0.998 (0.917 – 1.087)	> 0.5
Female vs male gender	0.87 (0.26 – 2.90)	0.4004
VAS day 1	1.102 (0.929 – 1.306)	0.3490
VAS day 2	1.188 (0.951 – 1.485)	0.4207
NRS day 7*	1.331 (1.015 – 1.746)*	0.0290
Anaesthesia Duration	0.996 (0.987 – 1.004)	> 0.5
Surgery Duration	0.997 (0.988 – 1.006)	> 0.5
Low education level	3.74 (0.78 – 18.04)	> 0.5

*($P < 0.05$)

Discussion

This observational study has not showed a different risk of POCD after one week from abdominal surgery with general anesthesia between patients who received sevoflurane or propofol as a maintenance agent in real clinical practice, according to published papers involving a comparison in neurocognitive outcome between halogenated agents and propofol in general or cardiac surgery^[17-19]. In other words, these results do not indicate any preference between sevoflurane or propofol in order to obtain a better early neuro-cognitive outcome after abdominal surgery in patients older than 60 years. A better anesthetic recovery found by some authors with intra-venous agents compared with inhalatory agents^[20-23] is not conformed by a definite consensus on this subject at the present moment^[24,25-27].

Recent experimental studies^[28,29] warn about a direct involvement of drugs used in general anesthesia-especially isoflurane in the genesis of a persistent damage of the central nervous system through induction of neuronal apoptosis or changes in the activity of central nicotinic receptors^[12,20,30]. This hypothesis is not supported by other authors^[27]. A higher incidence of early POCD with general vs regional anesthesia does not persist at 30 days and 1 year^[8]. All these observations are not consistent with the hypothesis of a causal role of a single drug of anesthetic agents^[12] in POCD development. Our results also are not in favour of this view. Possible anesthetic influence on POCD generation may depend on its complex and multi-faceted influence on patient perioperative condition. Anesthetics may offer different abilities to protect the brain from adverse effects of surgical stress. Drug combinations may differ in their efficacy in assuring hypnosis^[31] or satisfactory analgesia, leaving susceptible patients prone to worsening of cerebral function and eventually to POCD.

A global NRS-based evaluation of pain suffered during the 7 days postoperative period was associated to early POCD. As pain is a very important element of surgical stress, this association may be reasonable, and has not been observed in the past. Postoperative pain has been associated to delirium^[35] but not with POCD. Reported pain could have a causal relationship or a simple association with cognitive deterioration, but optimal postoperative analgesia could be useful in preventing POCD, which affects hospitalization^[36]. Patient susceptibility is considered very important in POCD pathophysiology. Emergence of POCD appeared to be correlated to inflammation^[32], the post-operative cortisol trend or thyroid hormonal status^[9,10] or to Apolipoprotein E ϵ 4 allele homozygosity^[11,20].

Age and low educational level, commonly recognized risk factors^[5], were associated to POCD development in our series, although this association did not reach significance.

Overall POCD incidence in this study appears low if compared to some published reports^[2,7,33], even though similar to that reported in a classical review^[1]. We used a low number of tests to examine patients, which could have reduced study power. We choose to limit neuropsychological testing to the present ones because their performance, lasting about 20 minutes, was fairly tolerated by patients on the day before surgery or discharge and in pilot observations we found that a greater test number heavily worsened patient compliance. Anyway, test choice was based on previous recommendations^[1,2,7,33]. According to these, tests were characterized by sensitivity, reproducibility and absence of influence by cultural factors, and we used Z score calculation to exclude learning effect^[2].

The observational nature of our study raises some issues.

First, anesthetic technique was not imposed to the anesthesiologist, but the practice in our operating rooms permitted to differentiate two groups of patients on the basis of the maintenance agent used for hypnosis, as induction agents, muscle-relaxing and analgesic regimens were very similar or identical between groups. Secondly, the disparity in group sizes, due to preference of inhalatory anesthesia in our institution, is not ideal to check possible difference of POCD incidence, that in our series is slight: nearly 3% (12.00% vs 14.93%). A randomized controlled trial should confirm these results, but a difference of 3% in POCD risk between drugs, even if statistically significant, would not be the main reason to guide their choice in a clinical

environment, probably. In order to verify or exclude the anesthetic toxicity hypothesis, further studies concerning dosage of markers of neuronal death or apoptosis could be useful and are progressing^[37].

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