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 dysfunc-

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

Alessio Valente¹*, Francesca Caliandro¹, Camillo Marra², Vincenzo Di Lazzaro⁵, Giuseppe La Torre³, Angelo Santoliquido⁴, Germano De Cosmo¹

¹Institute of Anesthesiology and Resuscitation Medicine, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168, Roma, Italy
²Institute of Neurology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168, Roma, Italy
³Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy
⁴Institute of Internal Medicine, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168, Roma Italy
⁵Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, Università Campus Bio-Medico di Roma, via Álvaro del Portillo 21, 00128 Rome, Italy

Corresponding author: Alessio Valente, Piazza Monte Torrone 13, 00141 Roma, Italy; Tel: +39 333 2018531; E-mail: neurobios@yahoo.com

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.

Received date: February 11, 2017
Accepted date: March 8, 2017
Published date: March 17, 2017

Citation: Valente, A., et al. No Difference in Early Post Operative Cognitive Dysfunction after Abdominal Surgery with Sevoflurane or Propofol Based General Anesthesia. (2017) J Anesth Surg 4(1): 27- 31.

DOI: 10.15436/2377-1364.17.067

Keywords: Anesthesia inhalatory; Anesthesia intravenous; Sevoflurane; Propofol; General Surgery; Delirium; Dementia; Amnestic; Cognitive disorders.
POCD after major non-cardiac surgery has been observed in 19.7% of patients older than 60 years\cite{13-19,33,34}. 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)\cite{18}. 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\cite{17,33,34,35}.

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\cite{13,19,33,34,35} 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\cite{36,37}. 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 hemorrhages);
7. Difficult airway management that caused deviation from usual anesthetic technique.

**Intraoperative Protocol**

Anesthetic technique was not imposed to anesthesiologists. Anyway, protocols applied in our University hospital were quite homogeneous. Patients were premedicated (Midazolam 5 mg per os). General anesthesia was induced with: Fentanyl 1 - 4.4 \( \mu \)g/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 (Diprifusor™ TCI, Marsh Protocol) 3 - 4 \( \mu \)g/ml were used for maintenance. Patients were ventilated in volume controlled mode with \( \text{EtCO}_2 \) maintenance to 30 - 35 mmHg and \( \text{FiO}_2 \) 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 \( \mu \)g/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\cite{38} and the Stroop Color Word Interference test\cite{39}, validated and used in previous multicentric studies\cite{40,41}. 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\cite{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\cite{42}.

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\cite{43}, 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
POCD after Abdominal Surgery with Sevoflurane or Propofol

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 sevoflurane had a not-significant lower odd of getting POCD with respect to patients treated with sevoflurane (\( \text{OR} = 0.78; 95\% \text{ CI}: 0.15 - 3.50 \) with \( p = 0.3945 \)). On the other hand, the lower education level and higher surgery duration, duration of anesthesia, VAS pain on the day of surgery, on 2\textsuperscript{nd} 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 (\( \text{OR} = 3.74; 95\% \text{ CI}: 0.78 – 18.04 \) with \( p > 0.05 \); \( \text{OR} = 1.33; 95\% \text{ CI}: 1.02 – 1.75 \) 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    |

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\cite{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\cite{20-23} is not confirmed by a definite consensus on this subject at the present moment\cite{24-26-27}.

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 – 1.7146)| 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   |

*(\( p < 0.05 \))
Recent experimental studies[^26,29] warn about a direct involvement of drugs used in general anesthesia-especially isoflu- rane 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[^3]. 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[^23], the post-operative cortisol trend or thyroid hormonal status[^9,10] or to Apolipoprotein E ε4 allele homozygosis[^11,20].

Age and low educational level, commonly recognized risk factors[^3], were associated to POCD development in our series, although this association did not reach significativity.

Overall POCD incidence in this study appears low if compared to some published reports[^22,33], 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[^27].

**Acknowledgements:** Special thanks to Dr. Luca Martinelli for his contribution to statistical analysis.

**References**

1. Newman, S., Jan, S., Shashivadan, H., et al. Postoperative Cognitive Dysfunction after Noncardiac Surgery. (2007) Anesthesiology 106(3): 572–590. [Pubmed][Crossref]

2. Hanning, C.D. Postoperative cognitive dysfunction. (2005) Br J Anesth 95(1): 82-87. [Crossref]

3. Gao, L., Taha, R., Gauvin, D., et al. Postoperative cognitive dysfunction after cardiac surgery. (2005) Chest 128(5): 3664-3670. [Pubmed][Crossref]

4. Johnson, T., Monk, T., Rasmussen, L.S., et al. Postoperative cognitive dysfunction in middle-aged patients. (2002) Anesthesiology 96(6): 1351-1357. [Pubmed][Crossref]

5. Monk, T.G., Weldon, B.C., Garvan, C.W., et al. Predictors of Cognitive Dysfunction after Major Noncardiac Surgery. (2008) Anesthesiology 108(1): 18–30. [Pubmed][Crossref]

6. Abildstrom, H., Rasmussen, L.S., Rentowl, P., et al. Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. (2000) Acta Anaesthesiol Scand 44(10): 1246-1251. [Pubmed][Crossref]

7. Moller, J.T., Cluitmans, P., Rasmussen, L.S., et al. Long-term postoperative cognitive dysfunction in the elderly: ISPSOCD1 study. (1998) Lancet 351: 857–861. [Pubmed][Crossref]

8. Rasmussen, L.S., Johnson, T., Kuipers, H.M., et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. (2003) Acta Anaesthesiol Scand 47(3): 260-266. [Pubmed][Crossref]

9. Rasmussen, L.S., O’Brien, J.T., Silverstein, J.H., et al. Is peri-operative cortisol secretion related to post-operative cognitive dysfunction? (2005) Acta Anaesthesiol Scand 49(9): 1225-1231. [Pubmed][Crossref]

10. Mafricula, F., Fodale, V. Thyroid function, Alzheimer’s disease and postoperative cognitive dysfunction: a tale of dangerous liaisons? (2008) J Alzheimers Dis 14(1): 95-105. [Pubmed][Crossref]

11. Abildstrom, H., Christiansen, M., Siersma, V.D., et al. Apolipoprotein E genotype and cognitive dysfunction after noncardiac surgery. (2004) Anesthesiology 101(4): 855-861. [Pubmed][Crossref]

12. Pratico, C., Quattrocchi, D., Lucanto, T., et al. Drugs of anesthesia acting on central cholinergic system may cause post-operative cognitive dysfunction and delirium. (2005) Med Hypotheses 65(5): 972-982. [Pubmed][Crossref]

13. Seymour, D.G., Severn, A.M. Cognitive Dysfunction after Surgery and anesthesia: what can we tell the grandparents? (2009) Age and ageing 38: 147–150. [Pubmed][Crossref]

14. Brand, N., Jolles, J. Learning and retrieval rate of words presented auditorily and visually: (1985) J Gen Psychol 112(2): 201–210. [Pubmed][Crossref]
15. Bohnen, N., Twijnstra, A., Jolles, J. Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. (1992) Acta Neurol Scand 85(2): 116–121.

16. Rasmussen, L.S., Larsen, K., Houx, P., et al. The assessment of postoperative cognitive function. (2001) Acta Anaesthesiol Scand 45(3): 275–289.

17. Enlund, M., Mentell, O., Flenninger, A., et al. Evidence of cerebral dysfunction associated with isoflurane-or propofol based anaesthesia for orthognathic surgery, as assessed by biochemical and neurophysiological methods. (1998) Ups J Med Sci 103(1): 43–59.

18. Schoen, J., Husemann, L., Tiemeyer, C., et al. Cognitive function after sevoflurane vs propofol based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. (2011) Br J Anaesth 106(6): 840-850.

19. Tang, N., Ou, C., Liu, Y., et al. Effect of inhalational anesthetic on postoperative cognitive dysfunction following radical rectal resection in elderly patients with mild cognitive impairment. (2014) J Int Med Res 42(6): 1252-1261.

20. Cai, Y., Hu, H., Liu, P., et al. Association between the apolipoprotein E4 and postoperative cognitive dysfunction in elderly patients undergoing intravenous anesthesia and inhalation anesthesia. (2012) Anesthesiology 116(1): 84-93.

21. Larsen, B., Seitz, A., Larsen, R. Recovery of Cognitive Function after Remifentanil-Propofol Anesthesia: A Comparison with Desflurane and Sevoflurane Anesthesia. (2000) Anesth Analg 90: 168–174.

22. Grundmann, U., Uth, M., Eichner, A., et al. Total intravenous anaesthesia with propofol and remifentanil in paediatric patients: a comparison with a desflurane-nitrous oxide inhalation anaesthesia. (1998) Acta Anaesthesiol Scand 42(7): 845-850.

23. Ledowski, T., Bein, B., Hanss, R., et al. Neuroendocrine stress response and heart rate variability: a comparison of total intravenous versus balanced anesthesia. (2005) Anesth Analg 101(6): 1700-1705.

24. Magni, G., La Rosa, I., Gimignani, S., et al. Early postoperative complications after intracranial surgery: comparison between total intravenous and balanced anesthesia. (2007) J Neurosurg Anesthesiol 19(4): 229-234.

25. Tonner, P.H., Scholz, J. Total intravenous or balanced anaesthesia in ambulatory surgery? (2000) Curr Opin Anaesthesiol 13(6): 631-636.

26. Rodgers, A., Walker, N., Schug, S., et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomized trials. (2000) BMJ 321(7275): 1493-1497.