BJA

British Journal of Anaesthesia, ■ (■): 1–10 (2018)

doi: 10.1016/j.bja.2018.05.059
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Propofol compared with sevoflurane general anaesthesia is associated with decreased delayed neurocognitive recovery in older adults

Y. Zhang[1], G.-J. Shan[1], Y.-X. Zhang[1], S.-J. Cao[1], S.-N. Zhu[2], H.-J. Li[3], D. Ma[4], D.-X. Wang[1,*], and The First Study of Perioperative Organ Protection (SPOP1) investigators

[1]Department of Anaesthesiology and Critical Care Medicine, Peking University First Hospital, Beijing, China, [2]Department of Biostatics, Peking University First Hospital, Beijing, China, [3]Department of Project Development and Management, Peking University Clinical Research Institute, Beijing, China and [4]Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital, London, UK

*Corresponding author. E-mail: wangdongxin@hotmail.com

Abstract

Background: The choice of general anaesthetics may affect postoperative cognitive outcomes. This study was designed to compare the potential impact of propofol-based *vs* sevoflurane-based general anaesthesia on the development of delayed neurocognitive recovery in older adults early after major cancer surgery.

Methods: Older adults (aged ≥65 and <90 yr) who were scheduled to undergo major cancer surgery (≥2 h) were randomised to receive either propofol- or sevoflurane-based general anaesthesia. Cognitive function was assessed before and 1 week after surgery with a battery of neuropsychological tests. Age- and education-matched non-surgical controls were recruited, and their cognitive functions were tested at comparable time intervals in order to adjust for learning effects from repeated tests. Delayed neurocognitive recovery was diagnosed according to the International Study of Post-operative Cognitive Dysfunction 1 definition.

Results: From April 1, 2015 to October 15, 2016, 392 patients were enrolled and randomised. Of these patients, 387 completed the intervention and 30-day follow-up, and 379 completed 1-week neuropsychological tests. Fifty-nine control subjects were enrolled and completed repeated neuropsychological tests. The incidence of delayed neurocognitive recovery at 1 week was significantly lower in the propofol group [14.8% (28/189)] than in the sevoflurane group [23.2% (44/190); odds ratio=0.577; 95% confidence interval, 0.342–0.975; P=0.038]. Safety outcomes did not differ between the two groups.

Conclusions: When compared with sevoflurane-based general anaesthesia, propofol-based general anaesthesia might decrease the incidence of delayed neurocognitive recovery in older adults after major cancer surgery.

Clinical trials registration: NCT02662257; Chinese Clinical Trial Registry (identifier: ChiCTR-IPR-15006209).

Keywords: anaesthesia; general; cognition; propofol; sevoflurane

Editorial decision: 26 May 2018; **Accepted:** 26 May 2018

Editor's key points

- It is unknown whether and to what extent anaesthetic techniques or agents impact postoperative cognitive outcomes, such as delirium and delayed neurocognitive recovery.
- Previous studies that have compared cognitive outcomes after total intravenous anaesthesia and volatile agent-based anaesthesia have yielded conflicting results.
- This current study provides suggestive evidence that, compared with sevoflurance-based anaesthesia, total intravenous anaesthesia might be associated with slightly less delayed neurocognitive recovery within a week of major surgery for cancer in adults aged ≥65 yr.
- Overall, the independent contribution of anaesthesia to postoperative cognitive outcomes is likely to be small.

Anaesthesia and surgery have been associated with cognitive disorders, including delirium and delayed neurocognitive recovery [postoperative cognitive dysfunction (POCD) occurring within the 1st month after surgery].[1–3] Unlike delirium, the diagnostic criteria for delayed neurocognitive recovery or early POCD have varied widely.[4,5] In an international multicentre study [International Study of POCD (ISPOCD1)], the incidence of POCD was 25.8% at 1 week, 9.9% at 3 months,[6] and 1% at 1–2 yrs in older adults after major non-cardiac surgery.[7] The occurrence of delayed neurocognitive recovery or POCD is associated with worse outcomes, including an increased risk of leaving labour market prematurely, dependency on social transfer payments, and mortality.[8,9]

Propofol and sevoflurane are commonly used general anaesthetics in clinical practice. It has been suggested that under certain circumstances, anaesthetic agents might have neuroprotective effects against various neural injuries.[10] In contrast, preclinical studies have demonstrated that inhalational anaesthetics may be neurotoxic by, for example causing amyloid-beta deposition,[11] whilst propofol may produce neuronal cell death in the developing rat brain.[12] Depending on the circumstances, it is possible that anaesthetic agents could be neuroprotective, neuroprotoxic, or have neither beneficial nor deleterious effects on the brain.[11–15] The effects of different general anaesthetics on the brain and its function in different patient populations and clinical contexts remain uncertain.

Choice of anaesthetics may affect cognitive outcome after surgery, but results from clinical studies have been conflicting. Some studies have reported worse cognitive outcomes after inhalational than after intravenous anaesthesia.[16–19] Other studies have found no significant differences with respect to cognitive outcomes between propofol and sevoflurane anaesthesia.[20,21] In contrast, yet another study found better cognitive outcome after sevoflurane than after propofol anaesthesia in patients with impaired cerebral oxygenation.[22] The reasons behind these conflicting findings are unknown. Differences in methods for assessing cognitive outcomes could play a role. For example, the Mini-Mental State Examination and the Montreal Cognitive Assessment have been used in some studies,[16,20,22] whereas more rigorous neuropsychological test batteries have been conducted in other studies.[17,19–21,23] Inclusion in research studies of a non-surgical control group is recommended to enable adjustment for learning effects from repeated neurocognitive tests.[19,24] Lack of a control group has been a limitation in many previous studies. Another important limitation has been that the 'depth of anaesthesia' was not necessarily controlled or reported.[16–23] Hence, it was unclear whether and to what extent the different cognitive outcomes represented an effect of different anaesthetics or simply different anaesthetic depths between groups.[25,26] Taking together all the disparate findings in previous research, there is currently insufficient evidence to inform the choice of general anaesthetic agent with respect to effect on neurocognitive recovery.

The aim of the current study was to compare the effect of propofol *vs* sevoflurane on the incidence of delayed neurocognitive recovery in older adults undergoing major cancer surgery, with age- and education-matched non-surgical controls included to factor in learning effects from repeated neurocognitive tests.

Methods

Study design and ethics

This was a pre-specified analysis of one centre data from a randomised controlled trial performed in 17 centres. The protocol of the trial was approval by the Clinical Research Ethics Committee of Peking University First Hospital [Beijing, China 2015 (869)] and was designed to compare the impact of sevoflurane-based *vs* propofol-based general anaesthesia on early and long-term outcomes in elderly patients after cancer surgery.[27] All patients who were recruited and underwent surgery in one centre (Peking University First Hospital) during the study period were included in the present study. Written informed consents were obtained from patients or their legal representatives in the ward the day before surgery (or on Friday for patients who would undergo surgery the following Monday). The study was registered with Chinese Clinical Trial Registry (www.chictr.org.cn; ChiCTR-IPR-15006209) and ClinicalTrials.gov (NCT02662257). Neurocognitive recovery on the 7th postoperative day, one of the pre-specified outcome measures, was assessed and analysed in the current study.

Participants

Potential participants were screened the day before surgery. Patients were included if they met all the following criteria: (1) age ≥65 and <90 yr; (2) primary cancer without any radio- or chemotherapy before surgery; and (3) scheduled to undergo surgery for cancer with an expected duration ≥2 h, under general anaesthesia. Patients were excluded if they met any of the following criteria: (1) preoperative history of schizophrenia, epilepsy, Parkinsonism, or myasthenia gravis; (2) inability to communicate in the preoperative period because of coma, profound dementia, language barrier, or incapacity from severe disease; (3) critical illness (preoperative ASA physical status classification > 3), severe hepatic dysfunction (Child–Pugh class C), or severe renal dysfunction (undergoing dialysis before surgery); or (4) neurosurgery.

To correct for the practice effect of repeatedly administered neuropsychological tests, a group of non-surgical control subjects was enrolled from family members or friends of patients. The inclusion and exclusion criteria were the same as