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Impact of Sevoflurane Versus Propofol Anesthesia on Post-Operative Cognitive Dysfunction in Elderly Cancer Patients: A Double-Blinded Randomized Controlled Trial

Department of Anesthesiology, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, Guangxi, P.R. China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF **Liang Guo**
BCE **Fei Lin**
B **Huijun Dai**
CD **Xueke Du**
F **Meigang Yu**
F **Jinxi Zhang**
B **Huimei Huang**
F **Wanyun Ge**
BF **Guanghua Tao**
ACDE **Linghui Pan**

Corresponding Author: Linghui Pan, e-mail: plinghui@hotmail.com

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Background: Research on the clinical outcomes of surgical patients anaesthetized with sevoflurane and the association of sevoflurane with post-operative cognitive dysfunction (POCD) is scarce. We evaluated whether sevoflurane-based anesthesia increased the incidence of POCD and worsened prognosis compared to propofol-based anesthesia in elderly cancer patients.





Material/Methods: This single-center, prospective, double-blind randomized controlled trial included 234 patients aged 65 to 86 years undergoing tumor resection who received sevoflurane-based (Group S) or propofol-based (Group P) anesthesia during surgery. A series of neuropsychological tests was performed to evaluate cognitive function before surgery and at 7 days and 3 months post-operation, and the results were compared to those of healthy controls.

Results: At 7 days post-operation there were no significant differences in the incidence of POCD between patients who received sevoflurane-based or propofol-based anesthesia during surgery: Group S was at 29.1% (32 out of 110 patients) versus Group P at 27.3% (30 out of 110), $P=0.764$. At 3 months, Group S was at 11.3% (12 out of 106 patients) versus Group P at 9.2% (10 out of 109), $P=0.604$. During the first 2 days post-operation, the QoR-40 global score was significantly lower in Group S compared to Group P [POD 1: $P=0.004$; POD 2: $P=0.001$]. There were no significant differences in in-hospital post-operative complications, post-operative length of hospital stay, all-cause mortality at 30 days, and 3 months post-operation, or post-operative quality of life at 3 months between patients in Group S and Group P.

Conclusions: Sevoflurane-based anesthesia did not increase the incidence of POCD compared to propofol-based anesthesia at 7 days or 3 months post-operation or impact short-term post-operative prognosis.

MeSH Keywords: **Communication Disorders • Mild Cognitive Impairment • Prognosis • Propofol**

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Background

Post-operative cognitive dysfunction (POCD) is an important issue that is associated with substantial morbidity and increased mortality, especially in elderly patients who have undergone major surgical procedures under general anesthesia [1–4]. The symptoms of POCD can persist for weeks or months after surgery, resulting in prolonged hospitalization, decreased quality of life, increased need for social support, and heavy financial burden for patients [3].

Although the etiology and pathogenesis of POCD are uncertain and multifactorial [5], a causative link to general anesthesia is increasingly recognized [6,7]. Sevoflurane, an inhaled anesthetic for anesthesia maintenance, is considered a risk factor for cognitive impairment in ageing brains, but its use is controversial [6,8,9]. Some experiments [10,11] showed that sevoflurane inhalation caused apoptosis with pathological changes in rat brain hippocampus leading to neurocognitive decline. While another report [12] indicated that sevoflurane exposure did not impair acquisition learning and retention memory in young adult or aged rats.

In the clinical setting, a prospective study [6] found that sevoflurane general anesthesia was associated with negative cognitive effects in elderly surgical patients with pre-existing mild cognitive dysfunction; however, the incidence of POCD in the early post-operative period did not differ between sevoflurane or propofol-based general anesthesia. In a randomized controlled trial, the incidence of POCD on post-operative day 1 and day 3 were lower in elderly surgical patients receiving propofol compared to sevoflurane anesthesia, but this study was limited by the lack of delineation between post-operative delirium and POCD [13]. Taken together, these data indicate that the relationship between sevoflurane anesthesia and cognitive decline in elderly surgical patients requires further investigation.

Worldwide, there had been rapid aging of the population and an increase in cancer cases, for which treatment often involves surgical removal of a tumor [14,15]. Several recent trials [16,17] have suggested that different anesthetics have varied immunosuppressive effects and can influence the number and incidence of metastases, cancer progression, and patient prognosis in elderly cancer patients. However, the effects of sevoflurane general anesthesia on outcomes in elderly cancer patients remain to be elucidated.

The objective of this study was to examine the hypothesis that elderly patients receiving sevoflurane-based general anesthesia during surgical resection of solid tumors have a higher incidence of POCD and worse short-term outcomes than those receiving propofol-based general anesthesia. Endpoints included cognitive function before surgery and at 7 days and 3 months

post-operation; post-operative recovery during the first 7 days after surgery, post-operative length of hospital stay, all-cause mortality within 30 days and 3 months post-operation, and patient quality of life at 3 months post-operation.

Material and Methods

Study design

This was a single-center, prospective, double-blind controlled trial that was approved by the ethics committee of the Affiliated Tumor Hospital of Guangxi Medical University (NO. KS2016-23) and registered with the Chinese Clinical Trial Registry (NO. ChiCTR-IOR-16009851). Each study subject provided written informed consent before the first visit.

Study participants

Eligible patients were selected before surgery. The duration of the surgical procedure was expected to last more than 2 hours, and post-operative hospitalization for at least 7 days was anticipated. Inclusion criteria were: 1) aged ≥ 65 years; 2) American Society of Anesthesiologists (ASA) grade I, II, or III; 3) elective tumor resection under general anesthesia; 4) fluent in Chinese (speaking and reading); and 5) able to independently complete the neuropsychological tests. Exclusion criteria were: 1) refusal to participate in the study; 2) a score of ≤ 23 on the Mini-Mental State Examination (MMSE) at screening [18]; 3) history of neurosurgery or cardiosurgery; 4) use of tranquilizers or antidepressants; 5) severe anxiety disorder or serious hearing and visual decline; 6) severe hepatic dysfunction (Child-Pugh stage C) or renal dysfunction (requiring renal replacement therapy); 7) Parkinson disease, Alzheimer disease, or coma; 8) alcoholism or drug dependence; 9) tumor metastasis or cancer cachexia; or 10) cancelled surgery.

Control participants (Group C) were healthy volunteers recruited from the local community. Inclusion criteria were: 1) aged ≥ 65 years; 2) ASA grade I, II, or III; 3) fluent in Chinese (speaking and reading); and 4) the ability to independently complete the neuropsychological tests. Exclusion criteria were: 1) refusal to participate in the study; 2) a score of ≤ 23 on the MMSE at screening [18]; 3) history of functional neurosurgery or brain injury; and 4) undergoing an operation or anesthesia.

Randomization and blinding

Eligible patients undergoing tumor resection for thoracic, gastrointestinal, genitourinary, gynecological and hepatobiliary cancer were randomly assigned in a 1:1 ratio to receive either sevoflurane inhalational anesthesia (Group S) or propofol intravenous anesthesia (Group P) using a computer-generated

random number sequence. Numbers were enclosed in sealed envelopes and opened when patients entered the operating room. Patients, investigators, and anesthetists were blinded to the group allocation.

Perioperative interview and neurocognitive examination

Patients were provided information about anesthesia the day before surgery. Patients' demographic data, including age, sex, body mass index (BMI) and education level, and clinical characteristics including ASA, tumor status, medical history and current medication were recorded. Psychological data were collected using the MMSE, Beck Depression Inventory, and the State Trait Anxiety Inventory. The MMSE scale is an important screening tool that evaluates orientation to time and place, registration of words, calculation, attention, concentration, recall of words, language, and visual construction [18]. The Beck Depression Inventory is designed to measure mood levels. The State Trait Anxiety Inventory is a commonly used measure of trait and state anxiety [19,20].

A battery of neuropsychological tests, including the Visual Verbal Learning Test, the Concept Shifting Test, the Stroop Color Word Interference Test, and the Letter-digit Coding Test were administered before surgery, and 7 days and 3 months post-operation and at the corresponding time points in Group C (Baseline [day 1], 7 days and 3 months later) by 2 investigators trained to perform standard neuropsychological tests by psychologists. The neuropsychological tests were translated into Chinese and administered in a quiet room with only the study participant and an investigator present. All participants who could not complete the neuropsychological tests independently were excluded. The Visual Verbal Learning Test is based on Rey's auditive recall of words and evaluates learning and memory [21]. A list of 15 words was read aloud at 1 second intervals in fixed order and each word was presented visually for 2 seconds on a computer screen over 3 learning trials. Participants were required to recall as many words as possible immediately after each trial to evaluate short-term memory. Investigators recorded and calculated the total number of correct words over the three trials. After 30 minutes, participants were asked to recall as many words as possible to evaluate long-term memory. The Concept Shifting Test is based on Halstead and Reitan's neuropsychological test battery and measures concept shifting and executive functioning [22]. Participants were asked to cross out digits in numerical order as quickly as possible. The Stroop Color Word Interference Test (Part C) assesses the ability to process a stimulus and resist cognitive interference [23]. Participants were required to name different color patches as quickly as possible. The Letter-digit Coding Test evaluates mental processing speed and concentration [24]. Participants were asked to match as many symbols and digits as possible in 60 seconds according to a

printed key. Evaluations were conducted as specified by the International Study of Post-operative Cognitive Dysfunction 1 (ISPOCD 1) and Steinmetz et al. [1,3]. Duration of assessment was no longer than 120 minutes so that the daily routine of patients was not disturbed.

Anesthesia and post-operative analgesia

Three senior anesthetists were designated to administer the anesthesia protocol. None of the surgical patients received premedication. After 5 minutes of pre-oxygenation, anesthesia induction with etomidate (20160407, Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China), sufentanil (1161003, Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) and rocuronium (160401.2, Zhejiang Xianju Pharmaceutical Co., Ltd., Xianju, China) and intubation were performed. Anesthesia was maintained with either sevoflurane (74081, Maruishi Pharmaceutical Co., Ltd., Japan) in Group S or propofol (MX116, Corden Pharma S.P.A. Viale dell' Industria 3, 20867, Caponago, Italy) in Group P; sufentanil was used for analgesia, and rocuronium was administered to maintain muscle relaxation. During anesthesia, the bispectral (BIS) index (BIS VISTA™, 185-0151-USA, 15 Hampshire Street, Mansfield, MA, USA) was maintained between 40 and 60, the mean arterial pressure (MAP) was maintained within 20% of baseline (the day before surgery), and heart rate (HR) was maintained in the range of 50 to 90 bpm. Hypotension was defined as a MAP reduction >20% of baseline, and sinus bradycardia was defined as a HR <50 bpm. If hemodynamic parameters were outside the target ranges, MAP was increased with noradrenaline or decreased with nitroglycerin, and HR was increased with atropine or decreased with esmolol. MAP and HR were recorded at 5 time points: the day before surgery (baseline), skin incision, maximum trauma, end of surgery, and extubation. At the end of treatment, the patients were transferred to the post-anesthesia care unit (PACU) for recovery.

After revival and extubation, analgesia was provided with patient-controlled intravenous analgesia (PICA) (100 mL of normal saline containing 2 µg/kg sufentanil and 10 mg of tropisetron, with an infusion rate of 2 mL/hour, a lockout time of 15 minutes, and a duration of 2 days).

Dexmedetomidine [25], midazolam [1], or scopolamine [26] were not administered, as there is no consensus on their effects (beneficial or detrimental) on cognition.

Evaluation of post-operative recovery profiles

The Quality of Recovery-40 (QoR-40) questionnaire was administered to assess the extent of functional recovery in the first 7 days after treatment. The QoR-40 is a widely reported measure of patient-assessed quality of recovery after surgery.

The QoR-40 includes 5 dimensions: physical comfort (12 items); emotional status (9 items); psychological support (7 items); physical independence (5 items); and pain (7 items) [27]. Each item is graded on a 5-point Likert scale (between 1 and 5), and the global score ranges from 40 to 200, with a higher score indicating better recovery.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was administered to assess quality of life at 3 months post-operation. The EORTC QLQ-C30 is an important tool for measuring quality of life in a wide range of cancer patients. The EORTC QLQ-C30 incorporates nine multi-item scales and six single-item scales. The multi-item scales include 5 functional scales (physical, role, emotional, cognitive and social functioning), 3 symptom scales (fatigue, nausea/vomiting and pain) and a Global Health/Quality of Life scale. The single item scales are dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulty [28]. Each item is graded on a 4-point Likert scale, and the Global Health/Quality of Life scale is evaluated with a 7-point Likert scale. Scale scores ranging from 0 to 100 are calculated according to the EORTC scoring manual. A high functional scale score represents a better quality of life; conversely, a high symptom scale score indicates a worse quality of life.

Statistical analyses

Statistical analyses were performed using SPSS version 22.0® (SPSS Inc., Chicago, IL, USA) for Windows.

Sample size calculation

The sample size was calculated based on a clinical trial that showed a POCD incidence of approximately 40% at 7 days after major noncardiac surgery [2]. The incidence of POCD was expected to decrease from 40% in Group S to 20% in Group P. For an α -error of 0.05 (2-sided) and a power of 90%, at least 110 patients were assigned to each group. Considering approximately 6% of patients would be lost to follow-up at 7 days post-operation [2], 117 patients were recruited in each group. The ratio of surgical patients enrolled to healthy volunteers in Group C was 4: 1.

Outcomes

Primary outcomes were the incidence of POCD at 7 days and 3 months post-operation. Secondary outcomes were quality of recovery (QoR-40) from post-operative day 1 (POD1) to POD7, incidence of in-hospital post-operative complications, length of hospital stay, all-cause mortality within 30 days and 3 months of surgery, and quality of life (QLQ-C30) at 3 months post-operation.

Outcomes analyses

POCD was assessed with an established formula. A Z score for each individual neurophysiological test was calculated according to the formula: $Z = (X - X_{\text{reference}}) / (SD_{\text{control}})$, where X is the difference between the baseline and post-operative neuropsychological tests score (at 7 days or 3 months post-operation) in Group S or Group P; $X_{\text{reference}}$ is the difference between baseline and neuropsychological tests score at the corresponding time point in Group C; and SD_{control} is the SD of those changes in the Group C. A patient was classified as exhibiting cognitive decline or POCD if the Z score on two individual tests was ≥ 1.96 [1,4].

Continuous variables with normal distributions were analyzed using an unpaired *t*-test or one-way analysis of variance (ANOVA). Continuous variables with abnormal distributions were analyzed with the Mann-Whitney U test or Kruskal-Wallis H test. Proportions were compared with Fisher's exact, correction for continuity or chi-square tests, with odds ratios (ORs) calculated by logistic analysis. *P* values were 2-sided, and a *P* value < 0.05 was considered significant.

Results

Participant characteristics

From December 1, 2016 to December 31, 2017 there were 575 patients screened for eligibility, of which 341 patients met the exclusion criteria, and 234 patients signed consent to participate in this clinical trial. After randomization, 117 patients received sevoflurane-based anesthesia (Group S) and 117 patients received propofol-based anesthesia (Group P). At 7 days post-operation, 5 patients refused assessment to protect their privacy (3 patients in Group S and 2 patients in Group P), and 9 patients in very poor condition could not complete the neuropsychological tests independently (4 patients in Group S and 5 patients in Group P). At 30 days post-operation, 1 patient in Group S died. Within the 3-month follow-up, 5 patients died (4 patients in Group S and 1 patient in Group P) (Figure 1).

There were no significant differences in demographic and clinical characteristics before surgery between patients in Group S, Group P, and Group C (Table 1). There were no significant differences in the clinical characteristics during anesthesia between patients in Group S and Group P (Table 2). There were no significant differences in perioperative hemodynamic parameters between patients in Group S and Group P (Table 3).

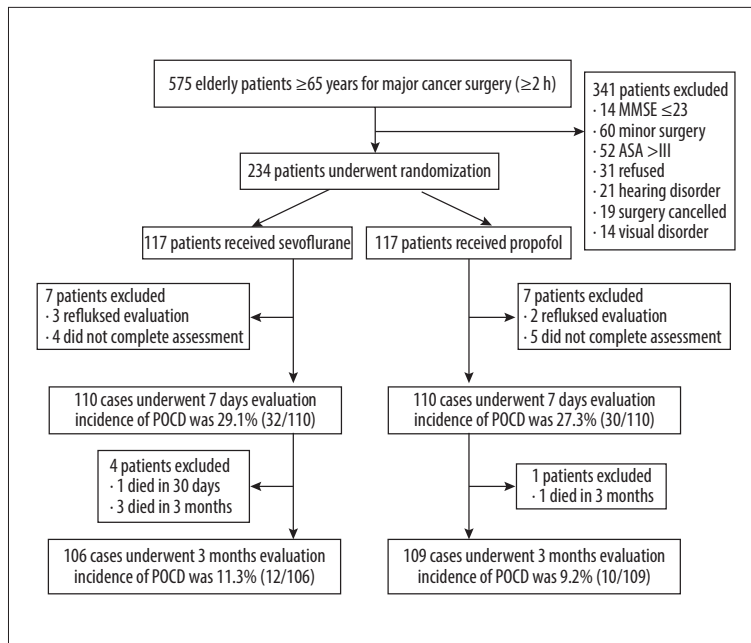


Figure 1. Flowchart of the study.

Table 1. Demographic and clinical characteristics of the study subjects.

	Group S (n=117)	Group P (n=117)	Group C (n=60)	P value
Age (years)	69.0 (66.0, 74.0)	69.0 (66.0, 72.5)	69.0 (66.3, 72.0)	0.589
Gender (Male)	76.0 (65.0%)	71.0 (60.7%)	37.0 (61.7%)	0.785
BMI (kg/m ²)	22.9 (22.4, 23.6)	22.8 (22.1, 23.5)	22.9 (22.2, 23.8)	0.596
Education (years)	11.0 (9.0, 12.0)	9.0 (9.0, 12.0)	12.0 (9.0, 12.0)	0.304
ASA status				
II	99.0 (84.6%)	101.0 (86.3%)	51.0 (85.0%)	0.930
III	18.0 (15.4%)	16.0 (13.7%)	9.0 (15.0%)	
NYHA classification				
I	96.0 (82.1%)	98.0 (83.8%)	50.0 (83.3%)	0.938
II	21.0 (17.9%)	19.0 (16.2%)	10.0 (16.7%)	
LVEF	66.0 (63.0, 68.0)	66.0 (64.0, 68.0)	/	0.827
MMSE (score)	26.0 (25.0, 27.0)	26.0 (25.0, 27.0)	26.0 (25.0, 27.0)	0.394
Hypertension	37.0 (31.6%)	43.0 (36.8%)	19.0 (31.7%)	0.662
Diabetes	15.0 (12.8%)	14.0 (12.0%)	7.0 (11.7%)	0.969
Coronary heart disease	5.0 (4.5%)	5.0 (4.5%)	2.0 (3.3%)	0.948
History of surgery	15.0 (13.6%)	13.0 (11.8%)	6.0 (10.0%)	0.840

The results are presented as the number (%) or median (interquartile range). BMI – body mass index; ASA – American Society of Anaesthesiologists; NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; MMSE – Mini-Mental State Examination.

Table 2. Characteristics of included patients during surgery and in the PACU.

	Group S (n=117)		Group P (n=117)		P value
Duration of surgery (min)	223.0	(184.0, 278.0)	225.0	(182.5, 279.5)	0.903
Duration of anaesthesia (min)	262.0	(226.5, 319.0)	267.0	(223.5, 308.5)	0.866
Estimated blood loss (ml)	150.0	(100.0, 300.0)	200.0	(100.0, 375.0)	0.591
Infusion volume (ml)	2100.0	(1700.0, 2600.0)	2100.0	(1600.0, 2400.0)	0.659
Urine volume (ml)	280.0	(220.0, 380.0)	290.0	(225.0, 370.0)	0.931
Sufentanil (µg)	88.0	(79.0, 108.5)	90.0	(80.5, 108.5)	0.716
Mean BIS values	48.0	(46.0, 51.0)	49.0	(46.5, 51.0)	0.349
Hypotension	18.0	(15.4%)	27.0	(23.1%)	0.135
Arrhythmia					
Sinus bradycardia	23.0	(19.7%)	31.0	(26.5%)	0.215
Atrial fibrillation	2.0	(1.7%)	2.0	(1.7%)	>0.999
Atrial premature	7.0	(6.0%)	4.0	(3.4%)	0.537
Premature ventricular contraction	12.0	(10.3%)	10.0	(8.5%)	0.654
Supraventricular arrhythmia	3.0	(2.6%)	3.0	(2.6%)	>0.999
Surgical site					
Abdominal	104.0	(88.9%)	97.0	(82.9%)	0.198
Orthopaedic	13.0	(11.1%)	20.0	(17.1%)	
Surgical technique					
Conventional	47.0	(40.2%)	54.0	(46.2%)	0.356
Laparoscopic	70.0	(59.8%)	63.0	(53.8%)	
Eye opening time (min)	20.0	(15.0, 25.0)	20.0	(15.0, 25.0)	0.745
Extubation time (min)	25.0	(21.5, 29.0)	26.0	(22.0, 31.5)	0.067
Postoperative agitation	14.0	(12.0%)	8.0	(6.8%)	0.179
Duration of PACU stay (min)	90.0	(80.0, 110.0)	100.0	(90.0, 110.0)	0.230

The results are presented as the number (%) or median (interquartile range). PACU – post-anaesthetic care unit; BIS – bispectral index.

Table 3. Perioperative haemodynamic parameters.

		Group S (N=117)		Group P (N=117)		P values
Baseline	MAP (mmHg)	93.0	(88.5, 98.0)	92.0	(88.0, 97.0)	0.667
	HR (bpm)	81.0	(77.0, 84.0)	81.0	(75.5, 84.0)	0.892
Skin incision	MAP (mmHg)	96.0	(92.0, 99.0)	96.0	(93.0, 100.0)	0.774
	HR (bpm)	84.0	(81.0, 88.0)	84.0	(81.0, 87.0)	0.510
Maximum trauma	MAP (mmHg)	97.0	(93.0, 103.0)	98.0	(94.5, 105.0)	0.105
	HR (bpm)	88.0	(84.0, 93.0)	88.0	(84.0, 89.5)	0.330
End of surgery	MAP (mmHg)	97.0	(94.0, 100.5)	97.0	(94.0, 104.0)	0.332
	HR (bpm)	83.0	(79.0, 87.0)	83.0	(80.0, 87.0)	0.428
Extubation	MAP (mmHg)	97.0	(94.0, 103.0)	98.0	(95.0, 106.0)	0.208
	HR (bpm)	84.0	(80.0, 88.0)	83.0	(80.0, 88.0)	0.422

The results are presented as the median (interquartile range). MAP – mean arterial pressure; HR – heart rate

Table 4. Results of the neuropsychological tests (baseline, 7 days and 3 months).

	Group S	Group P	Group C	P value Group S vs. Group C	P value Group P vs. Group C	P value Group S vs. Group P
Neuropsychological tests (baseline)	N=117	N=117	N=60			
Verbal learning test, learning trial (correct no.)	26.0 (24.0, 28.0)	26.0 (24.0, 28.0)	26.5 (25.0, 29.0)	0.183	0.151	0.857
Verbal learning test, delay (correct no.)	6.0 (5.0, 8.0)	7.0 (5.0, 8.0)	6.0 (5.0, 8.0)	0.776	0.521	0.629
Concept shifting task, part C (s)	41.0 (37.0, 44.0)	41.0 (37.0, 44.0)	40.0 (37.0, 43.0)	0.580	0.826	0.677
Stroop color word test, part 3 (s)	53.0 (48.5, 56.5)	53.0 (50.0, 56.5)	53.5 (50.0, 57.0)	0.159	0.557	0.313
Letter-digit coding (correct no.)	13.0 (12.0, 15.0)	13.0 (12.0, 15.0)	13.0 (12.0, 15.0)	0.441	0.751	0.613
Neuropsychological tests (7 days)	N=110	N=110	N=60			
Verbal learning test, learning trial (correct no.)	24.0 (19.0, 26.0)	24.0 (21.0, 27.0)	26.5 (25.0, 29.0)	<0.001	<0.001	0.384
Verbal learning test, delay (correct no.)	5.0 (3.0, 7.0)	5.0 (4.0, 7.0)	6.0 (5.3, 8.0)	0.002	<0.001	0.594
Concept shifting task, part C (s)	44.5 (41.0, 50.0)	44.0 (40.8, 49.0)	40.0 (37.3, 43.0)	<0.001	<0.001	0.774
Stroop color word test, part 3 (s)	55.0 (52.0, 59.3)	56.0 (53.0, 60.0)	53.0 (50.3, 56.0)	0.039	<0.001	0.089
Letter-digit coding (correct no.)	12.0 (9.0, 14.0)	13.0 (11.0, 14.3)	13.5 (12.3, 15.0)	<0.001	0.002	0.158
Neuropsychological tests (3 months)	N=106	N=109	N=60			
Verbal learning test, learning trial (correct no.)	26.0 (24.0, 27.0)	26.0 (23.5, 27.0)	26.0 (25.0, 27.8)	0.226	0.205	0.864
Verbal learning test, delay (correct no.)	6.5 (5.0, 7.3)	7.0 (5.0, 8.0)	7.0 (5.3, 8.0)	0.585	0.680	0.855
Concept shifting task, part C (s)	41.5 (38.0, 45.0)	42.0 (39.0, 45.0)	41.0 (38.0, 44.0)	0.374	0.148	0.631
Stroop color word test, part 3 (s)	53.0 (49.0, 57.0)	53.0 (50.5, 56.0)	52.0 (49.0, 55.0)	0.616	0.375	0.795
Letter-digit coding (correct no.)	13.0 (11.8, 14.3)	13.0 (12.0, 15.0)	13.5 (12.0, 15.8)	0.065	0.080	0.936

The results are presented as the median (interquartile range).

Table 5. Primary outcomes in Group S and Group P.

Primary outcomes	Group S	Group P	OR (95% CI)	P value
Incidence of POCD at 7 days	32 (29.1%) (N=110)	30 (27.3%) (N=110)	1.094 (0.608, 1.969)	0.764
Incidence of POCD at 3 months	12 (11.3%) (N=106)	10 (9.2%) (N=109)	1.264 (0.521, 3.064)	0.604

The results are presented as the number (%). POCD – postoperative cognitive dysfunction.

Primary outcomes

Evaluation of cognitive function at 7 days post-operation

At 7 days post-operation, 220 patients (110 patients in each surgical group) independently completed the neuropsychological tests (4 patients in Group P were evaluated at 6 days post-operation because they were discharged). Patients in the surgical groups showed a worse performance on the neuropsychological tests at 7 days post-operation than in the control group at the corresponding time point ($P < 0.05$) (Table 4). 32 patients in Group S and 30 patients in Group P were classified as exhibiting POCD: 29.1% (32 out of 110 patients) versus 27.3% (30 out of 110 patients), odds ratio (OR) 1.091, 95% confidence interval (CI) 0.612 to 1.945, $P = 0.764$. There were no significant differences in performance on the neuropsychological tests between patients in Group S and Group P ($P > 0.05$) (Table 5).

Evaluation of cognitive function at 3 months post-operation

At 3 months post-operation, 215 patients (106 patients in Group S and 109 patients in Group P) were assessed for cognitive function. There were no significant differences in performance on the neuropsychological tests between patients in Group S and Group P ($P > 0.05$) (Table 4). 12 patients in Group S and 10 patients in Group P were classified as exhibiting POCD (12 out of 106 patients versus 10 out of 109, OR 1.264, 95% CI 0.521 to 3.063, $P = 0.604$) (Table 5). Patients in both surgical groups showed improvements in cognitive function in terms of learning, memory, concentration, and speed of thought.

Secondary outcomes

Post-operative quality of recovery at 7 days post-operation

At 7 days post-operation, 220 patients (110 patients in Group S and 110 patients in Group P) were evaluated with the QoR-40 to assess the extent of functional recovery (4 patients in Group P were evaluated at 6 days post-operation because they were discharged). During the first 2 days post-operation, the QoR-40 global score was significantly lower in patients in Group S compared to Group P [POD 1: 150.0 (146.0, 153.0) versus 151.0 (148.0, 154.0), median difference -2.0 ($-3.0, -1.0$), $P = 0.004$; POD 2: 155.0 (152.0, 159.0) versus 157.0 (154.0, 160.0), median difference -2.0 ($-4.0, -1.0$), $P = 0.001$]. During the subsequent 5 days, there was no significant difference in the QoR-40 global score between patients in Group S and Group P (Table 6).

Incidence of complications at discharge and post-operative length of hospitalization

There was no significant difference in the incidence of in-hospital post-operative complications or post-operative length of hospital stay between patients in Group S and Group P ($P > 0.05$) (Table 6).

All-cause mortality within 30 days and 3 months post-operation

At 30 days post-operation, a telephone follow-up to confirm survival showed that 1 patient in Group S had died and no patients in Group P had died [0.9% (1 out of 110 patients) versus 0.0% (0 out of 110 patients), OR 1.009, 95% CI 0.991 to 1.027, $P = 1.000$] (Table 6). At 3 months post-operation, the telephone follow-up showed 4 patients in Group S and 1 patient in Group P had died [3.6% (4 out of 110 patients) versus 0.9% (1 out of 110 patients), OR 4.113, 95% CI 0.452 to 37.403, $P = 0.366$] (Table 6).

EORTC QLQ-C30 assessment at 3 months post-operation

At 3 months post-operation, 215 patients (106 patients in Group S and 109 patients in Group P) were evaluated with the EORTC QLQ-C30 to examine post-operative quality of life. There was no significant difference in any item on the EORTC QLQ-C30 between patients in Group S and Group P ($P > 0.05$) (Table 6).

Discussion

In the current study, there was no significant difference in the incidence of POCD in elderly patients receiving sevoflurane-based or propofol-based general anesthesia during surgical resection of solid tumors. At 7 days post-operation, 28.3% of patients (62 out of 220 patients) exhibited cognitive dysfunction (32 patients in Group S versus 30 patients in Group P). At 3 months post-operation, 10.2% of patients (22 out of 215 patients) exhibited cognitive dysfunction (12 patients in Group S versus 10 patients in Group P). The results revealed that sevoflurane-based anesthesia did not contribute to the development of POCD at 7 days or 3 months post-operation. Cognitive dysfunction was more prevalent at 7 days after surgery than at 3 months post-operation, but the administration of sevoflurane- or propofol-based anesthesia did not have an impact on the prognosis of elderly cancer patients at 3 months. Anesthetic maintenance with sevoflurane did negatively affect quality of recovery in the early post-operative period in this patient population.

Deterioration of cognitive function following major surgery and general anesthesia is a controversial diagnosis that is

Table 6. Secondary outcomes in Group S and Group P.

	Group S (N=110)	Group P (N=110)	Median difference or OR (95% CI)	P value
QoR-40 in 7 days (score)				
POD 1	150.0 (146.0, 153.0)	151.0 (148.0, 154.0)	-2.0 (-3.0, -1.0)	0.004
POD 2	155.0 (152.0, 159.0)	157.0 (154.0, 160.0)	-2.0 (-4.0, -1.0)	0.001
POD 3	160.0 (155.0, 164.0)	162.0 (158.0, 165.0)	-1.0 (-2.0, 0.0)	0.110
POD 4	164.0 (160.0, 167.0)	164.0 (160.0, 168.0)	0.0 (-2.0, 1.0)	0.530
POD 5	167.0 (164.0, 171.0)	167.0 (165.0, 170.0)	0.0 (-1.0, 1.0)	0.824
POD 6	170.0 (168.0, 173.3)	170.0 (168.0, 172.3)	0.0 (-1.0, 1.0)	0.511
POD 7	173.0 (170.0, 176.0) (N=110)	173.0 (171.0, 175.0) (N=106)	0.0 (-1.0, 1.0)	0.796
In-hospital postoperative complications				
Wound infection or dehiscence	6 (5.5%)	5 (4.5%)	1.212 (0.359, 4.093)	0.757
Pulmonary complications	17 (17.5%)	12 (10.9%)	1.493 (0.676, 3.294)	0.319
Hydrothorax	6 (5.5%)	5 (4.5%)	1.212 (0.359, 4.093)	0.757
Electrolyte disturbance	5 (4.5%)	5 (4.5%)	1.000 (0.281, 3.556)	>0.999
New onset arrhythmia	6 (5.5%)	5 (4.5%)	1.212 (0.359, 4.093)	0.757
Deep venous disturbance	3 (2.7%)	2 (1.8%)	1.514 (0.248, 9.243)	>0.999
Secondary operation in hospital	6 (5.5%)	3 (2.7%)	2.058 (0.501, 8.447)	0.496
Postoperative length of hospital stay (days)	12.0 (9.0, 14.0)	12.0 (9.0, 14.0)	0.0 (-1.0, 1.0)	0.768
All-cause 30-day mortality	1 (0.9%)	0 (0.0%)	1.009 (0.991, 1.027)	>0.999
All-cause 3-month mortality	4 (3.6%)	1 (0.9%)	4.113 (0.452, 37.403)	0.336
Quality of life (EORTC QLQ-C30) at 3 months after surgery				
	(N=106)	(N=109)		
Functional scales				
Global health status	83.0 (83.0, 92.0)	83.0 (83.0, 92.0)	0.0 (0.0, 0.0)	0.489
Physical functioning	87.0 (85.3, 93.0)	87.0 (98.0, 93.0)	0.0 (0.0, 0.0)	0.327
Role functioning	100.0 (83.0, 100.0)	83.0 (83.0, 100.0)	0.0 (0.0, 0.0)	0.505
Emotional functioning	92.0 (83.0, 92.0)	92.0 (83.0, 100.0)	0.0 (0.0, 0.0)	0.410
Cognitive functioning	83.0 (83.0, 100.0)	100.0 (83.0, 100.0)	0.0 (0.0, 0.0)	0.483
Social functioning	100.0 (83.0, 100.0)	83.0 (83.0, 100.0)	0.0 (0.0, 0.0)	0.490
Symptom scales				
Fatigue	11.0 (11.0, 22.0)	11.0 (11.0, 22.0)	0.0 (0.0, 0.0)	0.441
Nausea and vomiting	17.0 (0.0, 17.0)	17.0 (0.0, 17.0)	0.0 (0.0, 0.0)	0.344
Pain	17.0 (0.0, 17.0)	17.0 (0.0, 17.0)	0.0 (0.0, 0.0)	0.250
Dyspnoea	33.0 (0.0, 33.0)	18.0 (0.0, 33.0)	0.0 (0.0, 0.0)	0.295

Table 6 continued. Secondary outcomes in Group S and Group P.

	Group S (N=110)	Group P (N=110)	Median difference or OR (95% CI)	P value
Insomnia	33.0 (0.0, 33.0)	33.0 (0.0, 33.0)	0.0 (0.0, 0.0)	0.399
Appetite loss	33.0 (0.0, 33.0)	33.0 (0.0, 33.0)	0.0 (0.0, 0.0)	0.565
Constipation	33.0 (0.0, 33.0)	33.0 (0.0, 33.0)	0.0 (0.0, 0.0)	0.289
Diarrhoea	0.0 (0.0, 33.0)	0.0 (0.0, 33.0)	0.0 (0.0, 0.0)	0.540
Financial difficulties	33.0 (33.0, 67.0)	33.0 (33.0, 67.0)	0.0 (0.0, 0.0)	0.713

The results are presented as the number (%) or median (interquartile range). QoR-40 – quality of recovery-40; POD – postoperative day; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

determined by comparing a patient's pre-operative and post-operative performance on a series of neuropsychological tests. The condition is not described in the Diagnostic and Statistical Manual of Mental Disorders [1]. Accordingly, we calculated the appropriate sample size for the patient groups and the control group (the ratio was approximately 4: 1) and required elderly patients to perform applicable neuropsychological tests to evaluate their cognitive function before and after surgery and determine the incidence of POCD.

POCD is a common outcome following general anesthesia and major surgical procedures and is characterized by difficulties remembering and recalling, decreased intellectual performance, inability to complete tasks, difficulty concentrating, impaired language comprehension, and issues with social integration [3,4]. The duration of POCD varies and can be transient, persistent or permanent. Symptoms are subtle, making POCD difficult to detect or easily overlooked by clinicians and family members. In a 1955 landmark discovery, Bedford [29] observed that approximately 10% of surgical patients experienced long-term or persistent neurocognitive deterioration following general anesthesia and surgical procedures; the limitation to that study was that cognitive decline was identified solely based on patient self-report and the testimonies of family and caregivers rather than on the results of neuropsychological tests.

Ageing of the brain is an independent risk factor for POCD [1,2]. Neurogenesis progressively declines with age [10,11], the weight and volume of cerebral white matter decrease with age [30,31], and synaptogenesis is sensitive to the toxic effects of anesthetics [32]. Monk et al. [2] reported that the incidence of POCD at discharge was slightly higher in elderly patients that underwent elective noncardiac surgery compared to young or middle-aged patients; however, the incidence of POCD was significantly higher in elderly patients than in young or middle-aged patients 3 months later. These data suggest that the age-related cognitive decline increases the incidence of prolonged POCD in surgical patients. Therefore, understanding the impact

of anesthesia on the prognosis of elderly cancer patients at 3 months post-operation is essential for clinical decision making.

The integrity of the blood brain barrier (BBB) is associated with biological ageing. There is an aged-related reduction in tight junction proteins that causes an increase in the permeability of the BBB [33]. Animal studies [34,35] indicated that high concentrations of sevoflurane induced serious cognitive dysfunction via an intracerebral oxidative stress response or changing the integrity of the BBB. Accordingly, we maintained an appropriate depth of sedation at a BIS value of 40 to 60 during anesthesia in this trial. The results of the neuropsychological tests suggested that the incidence of POCD after sevoflurane-based anesthesia was not significantly different compared to propofol-based anesthesia at 7 days or 3 months post-operation.

Cerebral hypoperfusion, due to the physiology of ageing or caused by anesthesia, is a significant risk factor for POCD [36,37]. However, a recent clinical study [38] revealed that intraoperative hypotension was not associated with POCD in elderly patients that underwent surgery under general anesthesia. Furthermore, sevoflurane-based (2%) but not propofol-based anesthesia preserved left ventricular function in high-risk coronary surgery patients (older than 70 years of age with 3-vessel disease and an ejection fraction less than 50% with impaired length-dependent regulation of myocardial function) [39]. In the present study, patients' hemodynamic parameters were strictly controlled within the target range during anesthesia and recovery by using etomidate for induction [40], maintaining an appropriate depth of sedation by monitoring BIS values [41], and administering vasoactive drugs to ensure adequate perfusion of vital organs. There were no significant differences in perioperative hemodynamic parameters after sevoflurane-based or propofol-based anesthesia; however, patients did experience hypotension and sinus bradycardia as common adverse events associated with their surgery.

The choice of general anesthetics and their association with POCD remains a controversial topic. A trial in cardiac patients [42] showed that sevoflurane-based anesthesia was associated with better short-term post-operative cognitive performance than propofol-based anesthesia. However, the effects of sevoflurane and propofol on the incidence of POCD in non-cardiac patients varies [43,44]. A recent review [45] concluded that evidence supporting a reduction in the incidence of POCD in elderly patients undergoing non-cardiac surgery with propofol-based total intravenous anesthesia versus inhalational agents was low-certainty.

Although several clinical trials [46,47] have suggested that the choice of general anesthesia did not negatively impact quality of recovery in the early post-operative period in patients undergoing an ambulatory gynecological surgery or otorhinolaryngological surgery, the trials were limited by small sample sizes and/or the study of minor surgery. In the present study, findings showed that sevoflurane-based anesthesia decreased the QoR-40 global score in elderly cancer patients during the first 48 hours after surgery compared to propofol-based anesthesia, suggesting that sevoflurane exposure had a negative impact on quality of recovery in the early post-operative period; however, these short-time negative results did not prolong post-operative length of hospital stay.

In the present study, we followed up with the surviving patients by telephone and administered the EORTC QLQ-C30 to evaluate quality of life. The results revealed that sevoflurane-based anesthesia did not have an adverse effect on prognosis or quality of life at 3 months post-operation.

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Conclusions

This study demonstrated that sevoflurane-based anesthesia caused a mild and brief negative effect on the quality of recovery in the early post-operative period in elderly cancer patients who had undergone surgical resection of solid tumors. Sevoflurane-based anesthesia did not increase the incidence of POCD compared to propofol-based anesthesia at 7 days or 3 months post-operation. The choice of sevoflurane- or propofol-based anesthesia during surgery did not impact short-term post-operative prognosis.

Conflict of interest

None.

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