REVIEW ARTICLE

Effects of sevoflurane and propofol for elderly patients: A systematic review and meta-analysis

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Background: To evaluate the safety of propofol and sevoflurane for general anesthesia in elderly. **Materials and Methods:** All studies on sevoflurane, propofol, and hyperamylasemia from the establishment of Embase, Ovid, Cochrane Library, and Google Scholar from database establishment to December 2024 were searched. Literatures were screened, and data were extracted on the grounds of inclusion and exclusion criteria. Review Manager (RevMan) (Version 5.4. The Cochrane Collaboration.) was used for statistical analysis. Outcomes assessed included time to spontaneous eye opening, extubation time, incidence rate of postoperative cognitive dysfunction (POCD), postoperative delirium, agitation, nausea and vomiting. **Results:** Fourteen trials were identified and included in this meta-analysis. The results showed no significant difference in time to spontaneous eye opening (P = 0.54), the incidence of POCD (P = 0.07), postoperative delirium (P = 0.37), and postoperative nausea and vomiting (P = 0.8) between the sevoflurane and propofol groups. Compared with propofol groups, extubation time (P < 0.0001) was significantly shortened by sevoflurane groups. Conversely, compared with sevoflurane, the incidence of postoperative agitation in the propofol group was significantly reduced (P = 0.04). **Conclusion:** There was no difference in time to spontaneous eye-opening, the incidence of POCD, postoperative delirium, postoperative nausea, and vomiting between the sevoflurane and propofol groups. However, compared with propofol, sevoflurane can significantly shorten intubation time. The incidence of postoperative agitation (P = 0.04) was significantly lower in the propofol group compared with sevoflurane.

Key words: Aged, meta-analysis, postoperative cognitive dysfunction, postoperative nausea and vomiting, propofol, sevoflurane

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INTRODUCTION

Propofol and sevoflurane are commonly used general anesthetics in clinical practice. Propofol, an intravenous general anesthetic, with the characteristics of fast onset and strong anesthetic effect, without side effects such as cough and involuntary muscle movements.[1] Propofol can enhance gamma-aminobutyric acid (GABA) to type A receptors achieves sedative and hypnotic effects by inhibiting excitation transmission through intracellular hyperpolarization. However, its inhibition on the circulatory system is severe, with a significant decrease in blood pressure and a decrease in myocardial blood perfusion.[2] Furthermore, propofol has a certain inhibition on the respiratory system and circulatory system, but it helps the rapid recovery of the body after anesthesia.[3]

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Sevoflurane is a volatile inhaled general anesthetic, which have the characteristics of smooth and rapid induction. It has no significant impact on the respiratory tract and circulatory systems. Relevant studies have confirmed that patients using sevoflurane anesthesia for anesthesia induction have good tolerance and a low incidence of airway complications. However, there is evidence to suggest that exposure of humans and animals to sevoflurane-based anesthetics, especially repeated exposure, can cause neuropathological changes in the brain and long-term cognitive impairment.[4] The neurotoxic effects of sevoflurane may be mediated by neuroinflammation, neurotransmitter imbalance, and/or decreased concentrations of brain-derived neurotrophic factor.[5]

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At present, there are many researches about the effects of sevoflurane and propofol in elderly patients. The elderly population often experiences poor health, with many underlying diseases and disordered self-regulation mechanisms, leading to decreased organ function. In addition, as age increases, there can be changes in pharmacokinetics and pharmacodynamics, making the elderly more susceptible to complications from anesthesia after surgery. As a result, it is crucial to exercise caution when selecting anesthetic drugs for this demographic. The choice of anesthetics may affect cognitive outcome after surgery, but results from clinical studies always been contradictory. Some researchers reported worse cognitive outcomes after inhalational anesthesia than intravenous.[6] Other studies have found no significant differences in cognitive outcomes between propofol and sevoflurane anesthesia.[7,8] In contrast, another study found better cognitive outcome after sevoflurane than after propofol anesthesia in patients with impaired cerebral oxygenation.[9]

Therefore, we took a meta-analysis to evaluate whether propofol was superior over sevoflurane in the incidences of time to spontaneous eye opening, extubation time, the incidence of postoperative cognitive dysfunction (POCD), postoperative delirium, agitation, and postoperative nausea and vomiting for general anesthesia in elderly. The information would be used in clinical practice to select the appropriate anesthetics for elderly surgery.

MATERIALS AND METHODS

Search strategy

A comprehensive search was conducted in PubMed, Embase, Ovid, Cochrane Library, and Google Scholar from database establishment to December 2024. The search terms included "propofol or diprivan or propofolum," sevoflurane, and "elderly or aged or older." Searches were limited to English articles. The full search strategies employed for the four databases and Google Scholar are shown in Supplementary Table 1. Two authors screened the titles and abstracts of the retrieved articles. Reference lists were imported to Endnote software ×9, and duplicate articles were removed.

Inclusion and exclusion criteria

For inclusion, articles were selected based on the following criteria: (1) elderly patients aged (60 years); (2) patients were treated by propofol or sevoflurane; (3) The outcomes include: The incidence of POCD, the incidence of postoperative delirium, time to spontaneous eye opening, time to extubation, the incidence of postoperative nausea and vomiting, hypertension or hypotension.

Review articles, case reports, case series, letters to the editor, commentaries, proceedings, laboratory science studies, and all other irrelevant studies were excluded. In addition, studies that failed to report the outcomes of interest were excluded.

Data extraction

The following data were extracted by two authors (Qi Wang and Wenli Yu) from eligible articles using standard forms: (1) first author, (2) publication year, (3) sample size, (4) patient characteristics (ratio of men to women and age distribution), (5) details of drug administration (dose, route, and timing of medication) and control, (6) time to spontaneous eye opening, (7) extubation time, (8) the incidence of POCD, (9) the incidence of postoperative delirium and agitation, (10) the incidence of postoperative nausea and vomiting. If there is a disagreement between the data extracted by Qi Wang and Wenli Yu, a third person, Jing Luan will be introduced to analyze the data, and the data of the two people who agree will be analyzed.

Study quality analysis

The Cochrane Risk of Bias Assessment Tool was used by two authors (Jing Luan and Wenli Yu).[10] The assessment included the following items: random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and additional potential practices. Based on the results of the risk of bias judgment, formal overall risk of bias judgment was characterized as "low," "middle," and "high."

Statistical analysis

All statistical analyses were performed using Review Manager (Version 5.4, Cochrane Collaboration, Oxford, UK). All outcomes were calculated odds ratio (OR), mean difference (MD) values, and their 95% (confidence interval [CI]), and use P values and I^2 values measure whether there is heterogeneity in the statistics of the same study. The homogeneity test level is set as $P > 0.1$ and $I^2 < 50\%$. If there is no heterogeneity, use a fixed effects model; if there is heterogeneity, analyze the reasons, conduct subgroup analysis or sensitivity analysis, and use a random effects model for analysis. If meta-analysis is not possible, conduct a descriptive analysis.

RESULTS

Literature search

The PubMed, Embase, Ovid, Cochrane Library, and Google Scholar were searched in this study. After screening based on inclusion and exclusion criteria, 650 articles were retrieved as eligible, the detailed literature searching process can be found in Figure 1. After removing duplicates and screening the titles and abstracts, 37 articles were deemed

potentially eligible. Twenty-one studies were excluded for the following: review (n = 3); irrelevant data (n = 7); and incomplete data (n = 11). Finally, 16 articles[3,6-8,11-22] involving were ultimately eligible for final meta-analysis. No additional citations were found from the references reviewed.

Figure 2 summarizes the details of the bias assessment risk of the included researches. All researches were assessed as low risk based on the appropriate random sequence. However, many relative information in the studies was not available, such as allocation concealment and blinding of participants and personnel, and blinding of outcome assessment. Nevertheless, the overall methodological quality was generally fair.

Description of included studies

The 14 included studies were published between 2004 and 2024, with sample sizes ranging from 30 to 1195 subjects. All the participants were aged elder than 65 years. The types of surgery in the meta-analysis mainly include gynecological or urological surgery, laparoscopic surgery, rectal resection, tumor resection, spine surgery, and so on. In the sevoflurane group, the maintenance anesthetic was sevoflurane. In the propofol group, the maintenance anesthetic was propofol [Table 1].

Time to spontaneous eye opening

Four articles reported the time of eye-opening. The homogeneity analysis indicates that there is significant heterogeneity among the trials (I^2 = 95%, P < 0.00001). A random effect model was performed, and the result revealed that there was no significance between the time of postoperative eye-opening of sevoflurane group and propofol groups [MD = −0.78; 95% CI = −3.27 − 1.72; P = 0.54, Figure 3a].

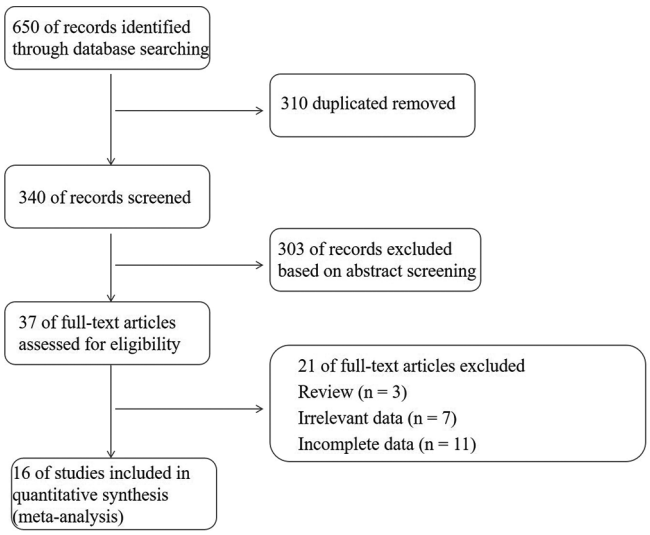

Figure 1: The flow diagram about the study retrieval process

Extubation time

Three articles reported the extubation time. The homogeneity analysis indicates that there are no statistical differences in results among the trials (I^2 = 16%, P = 0.3). Fixed-effects model was performed, and the result showed a significant decrease in the extubation time for sevoflurane groups compared to propofol groups [MD = 0.95, 95% CI = 0.5 − 1.39; P < 0.0001, Figure 3b].

The incidence of postoperative cognitive dysfunction

Five articles reported the incidence of POCD. The homogeneity analysis indicates that there are no statistically differences in results among the trials (I^2 = 18%, P = 0.3). Fixed-effects model was performed, and the result revealed that there was no significance between the incidence of POCD of sevoflurane group and propofol groups [OR = 0.73; 95% CI = 0.52 − 1.02; P = 0.07, Figure 4a].

The incidence of postoperative delirium and agitation

Five articles reported the incidence of postoperative delirium. The homogeneity analysis indicates that there is significant heterogeneity among the trials (I^2 = 76%, P = 0.002). Random effect model was performed, and the result revealed that there was no significance between the incidence of postoperative delirium of sevoflurane group and propofol groups [OR = 0.69; 95% CI = 0.31–1.55, P = 0.37, Figure 4b].

Two articles reported the incidence of postoperative agitation. The homogeneity analysis indicates that there are no statistically differences in results among the trials (I^2 = 0%, P = 0.76). Fixed-effects model was performed, and the result revealed that sevoflurane could significantly decrease the incidence of postoperative agitation, compared to propofol groups [OR = 0.49, 95% CI = 0.25–0.95, P = 0.04, Figure 4c].

The incidence of postoperative nausea and vomiting

Five articles reported the incidence of postoperative nausea and vomiting. The homogeneity analysis indicates that there are no statistically differences in results among the trials (I^2 = 28%, P = 0.23). Fixed-effects model was performed,

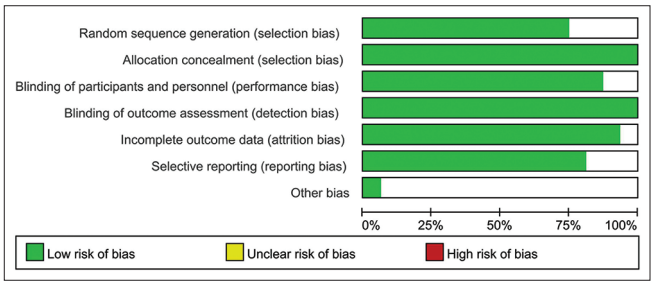

Figure 2: Risk of bias assessment in randomized trials and single-arm studies. Green indicates low risk of bias, yellow indicates medium risk of bias, and red indicates high risk of bias

Table 1: Main characteristics of the studies included in the meta-analysis

Included studies	Type of operation	Studies design	Propofol group	Sevoflurane group	Sample size (P vs. S)	Age (years)	Sex (male/female)
Arar, 2005	Gynecological or urological surgery	Retrospective study	8 mg/kg for the first 30 min, followed by 6 mg/kg for maintenance	MAC sevoflurane	20:20	67.6±2.4:68.5±4.04	13/7:12/8
Chang, 2024	Spine surgery	Retrospective observational study	/	/	141:140	72.4±4.5:72.9±4.7	54/87:64/76
Rohan, 2005	Minor urological or gynecological surgery	Randomized controlled trial	Maintain adequate depth of anesthesia	Tidal volume inhalation	15:15	72.9:73.8	12/3:11/4
Egawa, 2016	Lung surgery	Prospective study	3–4 μg/mL	1–2 mg/kg	72:72	69:72	48/23:39/33
Cao, 2023	Cancer surgery	Multicenter randomized trial	/	/	598:597	72:71	396/202:377/220
Geng, 2017	Laparoscopic cholecystectomy	Prospective, randomized, double-blind clinical trial	0.2–0.3 μg/kg/min	1.0–1.5 MAC	50:50:00	/	20/30:22/28
Guo, 2020	Tumor resection	double-blinded randomized controlled trial	/	/	117:117	69:69	71/46:76/41
Ishii, 2016	Gastrectomy, colectomy, or rectectomy	Double-blind prospective study	1.5–3 μg/mL	1.0–1.5 MAC	29:30:00	77.3±4.6:76.5±4.5	20/9:20/10
Li, 2021	Laparoscopic abdominal surgery	Randomized, double-blind, parallel, controlled study	50–150 μg/kg/min	1.0–1.5 MAC	272:272	64:65	199/72:184/88
Luntz, 2004	Ophthalmic surgery	Prospective randomized study	2 mg/kg	0.6%–1.2% end-tidal concentration	32:32:00	74±7:77±7	/
Mei, 2020	Total hip/knee replacements	Randomized clinical trial study	629.8±255.0 mg	1%–4%	106:103	70.9±6.7:71.5±6.8	34/72:27/76
Micha, 2016	Noncardiac operation	Randomized controlled trial	/	/	36:37:00	64:65.62	19/17:20/17
Nishikawa, 2004	Laparoscopic surgery	Randomized controlled trial	4 mg/mL	5% sevoflurane	25:25:00	71±8:71±7	13/12:12/13
Tang, 2014	Radical rectal resection	Prospective, double-blind, randomized clinical trial	1.5–2.0 mg/kg	8%	101:99	69.6±4.8: 70.0±4.3	26/75:32/67
Yu, 2017	Thoracic surgery	Randomized controlled trial	2 mg/kg	2%–4%	500:500	/	/
Zhang, 2018	Cancer surgery	Randomized controlled trial	/	/	195:192	72.8±5.5:72.4±5.6	135/60:128/64

MAC=Minimum alveolar concentration

and the result revealed that there was no significance between the incidence of postoperative nausea and vomiting of sevoflurane group and propofol groups [OR = 0.97; 95% CI = 0.75 – 1.24; P = 0.8, Figure 4d].

Publication bias

The publication bias is important for interpreting the conclusions. As shown in Figure 5, the funnel plots had good symmetry, indicating that there had no selectivity and publication bias.

DISCUSSION

With the improvement of global medical standards and changes in population structure, the number and proportion of elderly people are increasing. Compared with young people, the elderly often have poor health, more underlying diseases, disordered self-regulation mechanisms, and decreased organ function. Age increases can also cause changes in pharmacokinetics and pharmacodynamics. The incidence and mortality of complications caused by anesthesia after surgery are also much higher than those of normal healthy adults. Therefore, the selection of anesthetic drugs and doses for the elderly needs to be more cautious. To the best of our knowledge, only one meta-analysis[23] compared the effects of propofol and sevoflurane on POCD in elderly lung cancer patients. This article only analyzed POCD, and the results were simple. Our meta-analysis innovatively investigated the effects of propofol and sevoflurane on "time to spontaneous eye opening," "extubation time,"

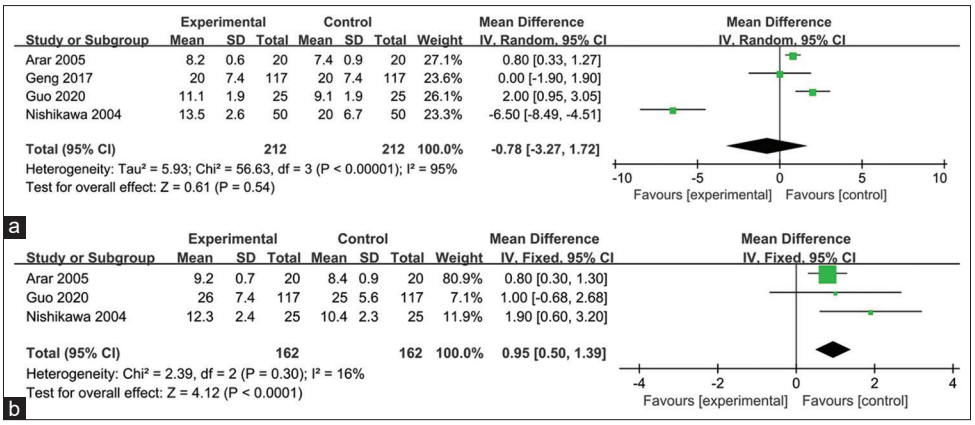

Figure 3: (a) Pooled estimate of the time to spontaneous eye opening (min) between sevoflurane and propofol groups for general anesthesia in elder patients, (b) Pooled estimate of the extubation time (min) between sevoflurane and propofol groups for general anesthesia in in elder patients. CI: Confidence interval, SD: Standard deviation, IV: Intravenous

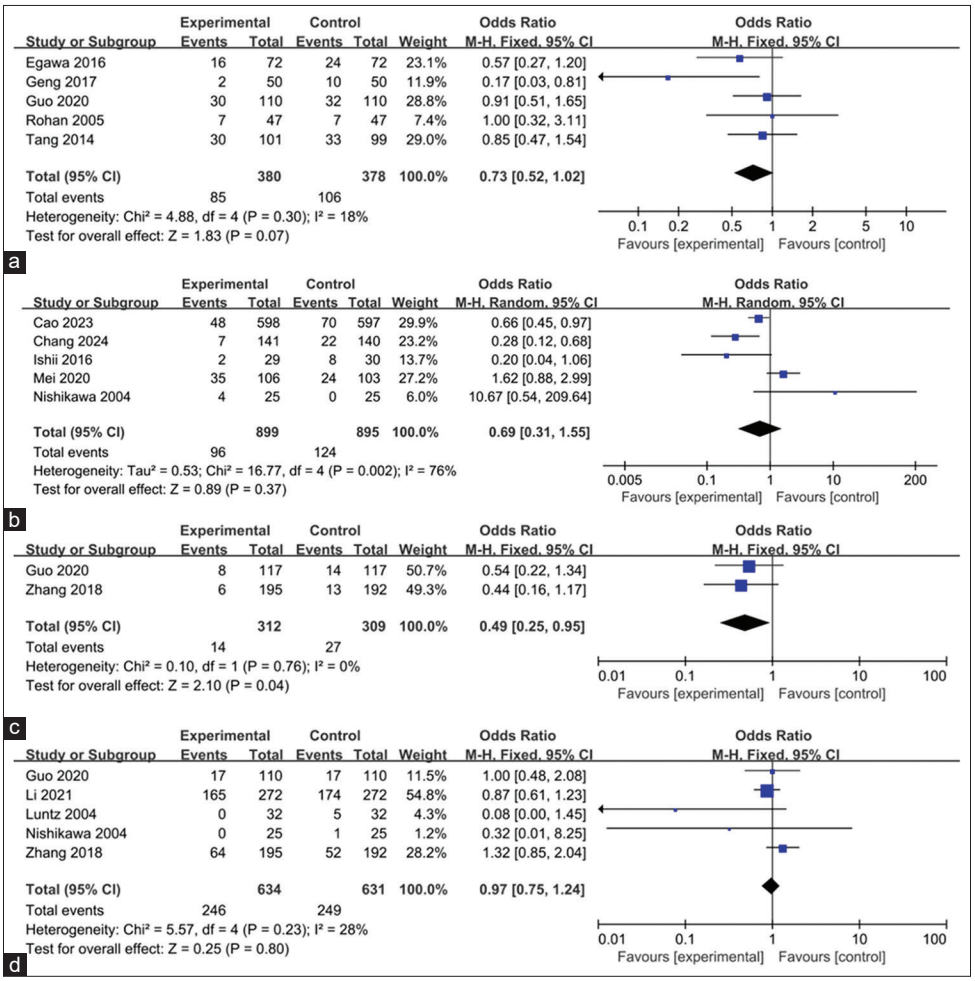

Figure 4: (a) Pooled estimate of the incidence of postoperative cognitive dysfunction between sevoflurane and propofol groups for general anesthesia in elder patients, (b) Pooled estimate of the incidence of postoperative delirium between sevoflurane and propofol groups for general anesthesia in elder patients, (c) Pooled estimate of the incidence of postoperative agitation between sevoflurane and propofol groups for general anesthesia in elder patients, (d) Pooled estimate of the incidence of postoperative nausea and vomiting between sevoflurane and propofol groups for general anesthesia in elder patients. CI: Confidence interval

"the incidence of POCD," "the incidence of postoperative delirium and agitation," and "the incidence of postoperative nausea and vomiting" in elderly patients, which can better help clinicians choose appropriate anesthetic drugs. The results of this study showed no significant difference in time to spontaneous eye opening ($P = 0.54$), the incidence of POCD ($P = 0.07$), postoperative delirium ($P = 0.37$), and postoperative nausea and vomiting ($P = 0.8$) between the

two groups. Compared with propofol groups, extubation time ($P < 0.0001$) was significantly shorted by sevoflurane groups. Conversely, compared with sevoflurane, the incidence of postoperative agitation in the propofol group was significantly reduced ($P = 0.04$).

Studies have shown that the shorter duration of extubation in intensive care unit (ICU) patients can not only reduce the incidence of complications such as ventilator-related pneumonia and ventilator-related lung injury, but also shorten the ICU stay and total hospital stay.[24] Soukup *et al*.[25] have reported that ICU patients sedated with sevoflurane >48 h may return to spontaneous breathing faster, while the quality of sedation is comparable to a propofol-based sedation regime. Our study found that sevoflurane significantly shortened the extubation time of patients, indicating that sevoflurane should be the first choice for anesthesia for patients in ICU.

Postoperative agitation is a common reversible mental disorder in clinical practice, which often occurs 15 min after extubation. It manifests as restlessness, memory impairment, disorientation, and brief blurring of consciousness. Patients may involuntarily twist their limbs due to restlessness, which can easily cause incision cracking, increased heart rate, and high blood pressure, greatly damaging the patient's body and affecting the effectiveness of surgical treatment.[26] Propofol is one of the pharmacological interventions that can decrease the incidence of agitation after sevoflurane anesthesia. Most propofol agitation trials showed benefit delivered propofol by infusion throughout the maintenance of anesthesia.[27] Our study also revealed that propofol could markedly reduce the incidence of postoperative agitation, compared with sevoflurane. For elderly patients with greater mental stress, propofol can be the first choice for anesthesia.

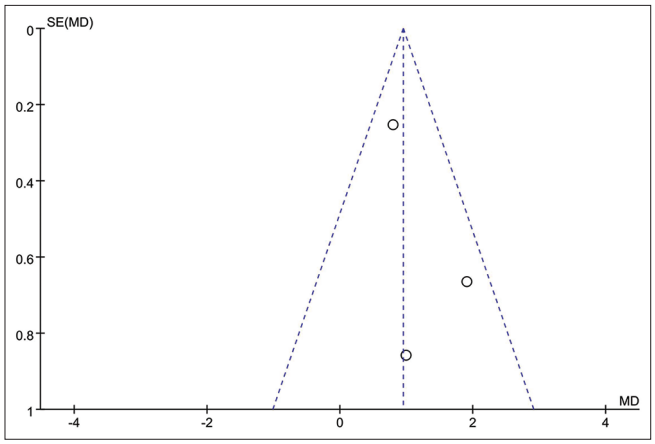

Figure 5: Begg's funnel of included studies. The shape of the funnel plot did not reveal any evidence of obvious asymmetry. Indicating that there was no publication bias that could affect the results of the meta-analysis

POCD is one of the common complications of postoperative anesthesia in elderly patients, mainly manifested as changes in their surgical cognitive and social abilities, mental disorders, and memory impairment. Severe cases of POCD may even lose their language expression ability, affecting surgical outcomes, prolonging hospital stay, reducing quality of life decline, and increasing the economic burden on patients.[28] The mechanism of propofol is mainly occupying the $GABA_A$ receptor site, directly activating the $GABA_A$ receptor and enhancing its inhibitory effect. In addition, propofol blocks nociceptive transmission by inhibiting N-methyl-D-aspartate (NMDA) receptors, reducing excitatory synaptic transmission, or regulating NMDA receptor activity in spinal dorsal horn neurons and inhibiting spinal facilitation status. Sevoflurane can directly inhibit the NMDA receptor. The roles of $GABA_A$ and NMDA receptors are closely related to the formation of cognitive functions such as learning and memory. Both can enhance the long-term expression of synapses in hippocampal Cornu Ammonis 1 cells, thereby affecting various aspects of cognitive function in patients.[29] In this study, the incidence of POCD did not show difference between propofol and sevoflurane. Zhang *et al*.[14] reported that compared to patients under propofol anesthesia, patients undergoing cancer surgery under sevoflurane anesthesia had a higher incidence of POCD 7 days after surgery. Sun *et al*.[23] compared the effects of propofol and sevoflurane anesthesia on postoperative cognitive function in elderly patients with lung cancer, and the results suggested that propofol has a greater adverse effect on cognitive function in the elderly patients with lung cancer than sevoflurane. In this meta-analysis, we included gynecological or urological surgery patients, laparoscopic surgery patients, rectal resection patients, and tumor resection patients. Our study was more convincing.

Postoperative delirium refers to acute and reversible cognitive impairment, decreased consciousness level, lack of concentration, chaotic sleep cycle, and other mental state changes that occur after surgery. It is a common complication after surgery, and the elderly population is more sensitive and less tolerant to anesthetic drugs, making delirium more likely to occur after general anesthesia.[30] Postoperative delirium patients have an increased risk of dementia, and a 2–20-fold increased risk of mortality, with hospital mortality rates of 25%–33%.[31] In this study, the incidence of postoperative delirium did not show a difference between propofol and sevoflurane.

Postoperative nausea and vomiting are one of the adverse effects caused by sevoflurane, which may lead to complications such as aspiration pneumonia.[32] However,

this meta-analysis did not show that sevoflurane increased the risk of postoperative nausea and vomiting, which does not exclude other analgesic drugs or vomiting agents, so further studies are needed to confirm it.

The present study includes some limitations. First, the included articles included various surgeries: gynecological or urological surgery, laparoscopic surgery, rectal resection, tumor resection, and so on. Different types of surgery require different amounts and durations of general anesthesia. Second, drug dosage, length of surgery, and use of adjuvant medications also differ among older patients. Third, to avoid erroneous interpretation of the content of the articles and a large deviation, we only included English articles. The missing data may lead to misinterpretation of the results. Given the limitations of our study, our findings support that further large-scale trials are required to understand better the impact of propofol and sevoflurane in elderly patients.

CONCLUSION

There was no difference in time to spontaneous eye opening, the incidence of POCD, postoperative delirium, postoperative nausea, and vomiting between the sevoflurane and propofol groups. However, compared with propofol, sevoflurane can significantly shorten extubation time. The incidence of postoperative agitation (P = 0.04) was significantly lower in propofol group compared with sevoflurane.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Search strategy for each database

Number	Query
	PubMed session results
#1	"propofol"[MeSH Terms]
#2	"diprivan"[Title/Abstract] OR "fresofol"[Title/Abstract] OR "pofol"[Title/Abstract] OR "propofol"[Title/Abstract] OR "recofol"[Title/Abstract]
#3	#1 OR #2
#4	"sevoflurane"[MeSH Terms]
#5	"sevofluran*"[Title/Abstract]
#6	#4 OR #5
#7	" elderly"[MeSH Terms] OR " aged"[MeSH Terms] OR " older"[MeSH Terms] OR " senior"[MeSH Terms]
#8	#3 AND #6 AND #7
	Embase session results
#1	"propofol"/exp OR propofol: ab, ti OR diprivan: ab, ti OR fresofol: ab, ti OR pofol: ab, ti OR recofol: ab, ti
#2	"sevoflurane"/exp OR sevofluran*:ab, ti
#3	" elderly "/exp OR "aged"/exp OR "older "/exp OR " senior "/exp OR elder*:ab, ti OR aged*:ab, ti OR older*:ab, ti OR senior*:ab, ti
#4	#1 AND #2 AND #3
	Ovid session results
#1	"propofol"[MeSH Terms]
#2	"diprivan" mp. [mp=title, abstract, full text, caption text] OR "fresofol" mp. [mp=title, abstract, full text, caption text] OR "pofol" mp. [mp=title, abstract, full text, caption text] OR "propofol" mp. [mp=title, abstract, full text, caption text] OR "recofol" mp. [mp=title, abstract, full text, caption text]
#3	#1 OR #2
#4	"sevoflurane"[MeSH Terms]
#5	"sevofluran*" mp. [mp=title, abstract, full text, caption text]
#6	#4 OR #5
#7	" elderly" mp. [mp=title, abstract, full text, caption text] OR " aged" mp. [mp=title, abstract, full text, caption text] OR "older" mp. [mp=title, abstract, full text, caption text] OR " senior" mp. [mp=title, abstract, full text, caption text]
#8	#3 AND #6 AND #7
	Cochrane session results
#1	MeSH descriptor: [Propofol] explode all trees
#2	(propofol):ti, ab, kw OR (diprivan):ti, ab, kw OR (fresofol):ti, ab, kw OR (pofol):ti, ab, kw OR (recofol):ti, ab, kw
#3	#1 OR #2
#4	MeSH descriptor: [Sevoflurane] explode all trees
#5	(sevofluran*):ti, ab, kw
#6	#4 OR #5
#7	MeSH descriptor: [elder] explode all trees
#8	MeSH descriptor: [aged] explode all trees
#9	MeSH descriptor: [older] explode all trees
#10	MeSH descriptor: [senior] explode all trees
#11	(elder*):ti, ab, kw OR (aged*):ti, ab, kw OR (older*):ti, ab, kw OR (senior):ti, ab, kw
#12	#7 OR #8 OR #9 OR #10 OR #1
#13	#3 AND #6 AND #12
	Google Scholar results
#1	(Propofol) and (Sevoflurane) and (elderly or aged or older or senior)