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Efficacy and safety of sevoflurane vs propofol in combination with remifentanil for anesthesia maintenance during craniotomy

A meta-analysis

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Abstract

Background: The purpose of this study was to evaluate the efficacy and safety of sevoflurane-remifentanil (SR) vs propofol-remifentanil (PR) as inhalation anesthesia or total intravenous anesthesia in patients undergoing craniotomy, respectively.

Methods: Electronic databases included PubMed, ScienceDirect, Embase, Cochrane library, CNKI, and Wanfang data were searched using suitable search items. Randomized clinical controlled trials comparing the combination of SR and PR as anesthetics for neurosurgery were included. The outcomes included wake-up time, spontaneous respiration time, extubation time, and safety.

Results: Seventeen studies were included in this meta-analysis. There were no statistically significant differences in wake-up time ($P = .25$, standardized mean difference (SMD) = 0.29, 95% CI −0.20 to 0.77), extubation time ($P = .1$, SMD = 0.52, 95% CI −0.11 to 1.14) and spontaneous respiration time ($P = .58$, SMD = 0.43, 95% CI −1.07 to 1.93) when patients with SF and PF for anesthesia maintenance. Moreover, the changes of hemodynamic parameters are similar between the 2 groups. During anesthesia maintenance, SF could significantly increase the incidence of hypotension and brain edema than PF ($P = .02$, SMD = 1.68, 95% CI 1.07 to 2.62; $P < .0001$, SMD = 3.37, 95% CI 1.86 to 6.12), PF markedly promoted the incidence of hypertension ($P = .001$, SMD = 0.55, 95% CI 0.39 to 0.79). The postoperative adverse reactions were similar between the 2 groups ($P > .05$), but the incidence of postoperative nausea and vomiting proved to be higher in SF group ($P < .0001$, SMD = 2.12, 95% CI 1.47 to 3.07).

Conclusions: SR and PR as anesthetics in patients underwent craniotomy had similar effects, but PR was superior to SR in terms of safety of intraoperation and postoperation.

Abbreviations: DBP = diastolic blood pressure, MAP = mean arterial hypertension, PONV = postoperative nausea and vomiting, PR = propofol-remifentanil, RCTs = randomized controlled trials, SBP = systolic blood pressure, SMD = standardized mean difference, SR = sevoflurane-remifentanil.

Keywords: craniotomy, meta-analysis, propofol, remifentanil, sevoflurane

1. Introduction

During the craniotomy procedures, the recognized goals for the anesthetic management included maintaining hemodynamic stability, protecting the autoregulation function of cerebral blood vessel, and providing good operating conditions and rapid recovery.[1,2] The ideal anesthetic drugs could not only maintain appropriate intracranial pressure and cerebral perfusion pressure, provide good relaxation for brain and preserve carbon dioxide reactivity, but also have short recovery time and no interference with neurophysiological monitoring, so as to assess the neurological function and detect intracranial complications after surgery.[3,4] At present, the anesthetics for craniotomy were mainly inhaled anesthetics and opioids, which could ensure intraoperative unconsciousness, pain control, and early palinesthesia.[5]

Sevoflurane is a short-acting and well-tolerated inhaled anesthetic with low blood/gas partition coefficient, and could be rapidly inducted and lead to early recovery from general anesthesia.[6] Recent studies revealed that inhaled anesthetics had been widely used in neurosurgical anesthesia, sevoflurane, and desflurane had shorter recovery time and extubation time than isoflurane, while the incidences of their respective adverse reactions were similar in neurosurgical patients.[7,8] Propofol is a general anesthetic agent with rapid onset and short duration of anesthesia, and used in the process of anesthesia induction and maintenance. It could interact with neurotransmitter receptors, constrict cerebral vessels and protect the auto-regulated function of cerebral vessels.[9] However, the injection of propofol alone was related to increasing pain, so it could achieve better

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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anesthetic effect when used in combination with opioids. Remifentanil is a short-acting opioid receptor agonist with rapid emergence and shorter half-life of elimination, and has been commonly used for craniotomy. During the procedures of patients with awake craniotomy, the addition of remifentanil to propofol infusion could enhance sedation, increase patients' satisfaction, and maintain hemodynamic stability.[10,11]

Previous study found that sevoflurane had longer recovery time and the time of response to verbal commands than propofol in patients undergoing supratentorial craniotomy, and the number of patients with hypertension was larger using sevoflurane.[12] A systematic review and meta-analysis compared the effects of propofol with volatile anesthetic agents for maintenance of anesthesia in patients undergoing craniotomy, and the results indicated that propofol had better effects in lowering the mean intracranial pressure and increase cerebral perfusion pressure given that patients had similar brain relaxation when propofol and volatile agents were used for maintained anesthesia.[13] Some studies had verified that both sevoflurane and propofol in combination with remifentanil have better anesthetic effect in elective neurosurgery, but propofol-remifentanil (PR) was more likely to cause lactic acidosis and hypertension.[14,15] Currently, multiple clinical studies with small sample sizes had compared the effects of sevoflurane and propofol with that of remifentanil for maintenance of anesthesia in patients undergoing craniotomy, but the results were controversial. Hence, the aim of this meta-analysis was to comprehensively assess the efficacy and safety of sevoflurane-remifentanil (SR) vs PR for maintained anesthesia in patients undergoing neurosurgery.

2. Methods

2.1. Search strategy

We searched the electronic databases including PubMed, ScienceDirect, Embase, the Cochrane library, CNKI, and Wanfang data, the publication deadline was up to March 31, 2020 and without language restriction. Searches were conducted using the following terms: "remifentanil" and "propofol" or "total intravenous anesthesia" and "sevoflurane" or "inhalation anesthesia" and "craniotomy" or "neurosurgery".

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: First, adult patients with intracranial tumor or other pathologies underwent elective neurosurgery were included. Second, all patients received remifentanil for anesthesia induction before operation, and propofol, sevoflurane were used for maintained anesthesia. Third, the types of the studies were prospective and randomized controlled trials (RCTs), and all the researches compared the efficacy and safety of SR with PR for maintained anesthesia.

Exclusion criteria were: patients with severe traumatic brain injury that underwent craniotomy were excluded; repeated published research, the protocols and studies with no interest data were excluded.

2.3. Data extraction

All data were extracted by Z Zhou and MF Ying individually and verified by R Zhao. The details of all selected studies included sample sizes; the baseline characteristics of patients, interventions, dosage of drugs, and the outcomes were extracted using a standardized data extraction form. The primary outcomes were wake-up time, spontaneous respiration time, and extubation time. Secondary outcomes included hemodynamic changes and safety. Any disagreements in the process of data extraction were resolved by discussion or consultation.

2.4. Quality assessment

Two authors (Z Zhou and MF Ying) independently graded the chosen studies using the Cochrane risk of bias tool. The contents of the risk assessment included 7 different items of bias, and they were selection bias, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each study has a Jadded score, and the scores quantify the quality of included studies. For this study, ethical approval and informed consent were not required.

2.5. Statistical analysis

This meta-analysis was performed using Review Manager 5.3 software (The Cochrane Collaboration, UK). The results were presented as the odds ratio with 95% confidence intervals (95% CI) for dichotomous data, and standardized mean difference (SMD) with 95% CI for continuous data. Forest plots were used to assess the outcomes. The heterogeneity was estimated by I^2 statistic. If I^2 values $<50\%$, there showed no significant heterogeneity was showed between the 2 groups, and fixed-effects model was used to assess the outcomes. The data were heterogeneous when I^2 values $>50\%$, and random effect model was used. Besides, sensitivity analysis or subgroup analysis was used to eliminate methodological heterogeneity, funnel plot was performed to assess the risk of bias, and significant statistical differences were considered when P values were less than.05.

3. Results

3.1. Search results and description of included studies

A total of 698 articles were obtained through searching the electronic databases, and 630 records including duplicate publications, review, observational trials, meta-analysis, and clinical guidelines were excluded (Fig. 1). Sixty-eight full-text

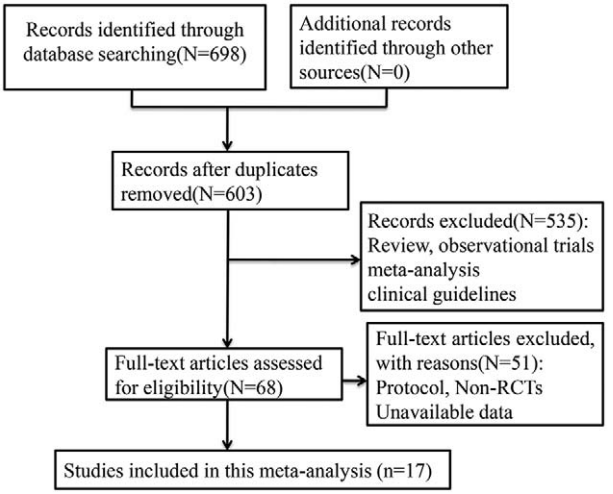

Figure 1. Flow diagram of screening studies in this meta-analysis.

Table 1

Characteristics of the included studies.

Study	Study design	No of centres	Sample size SR/PR	Mean age SR/PR	Specification of lesions	Dosage of maintenance anesthesia		Outcomes	Jadad score
						S+R	P+R		
Sneyd et al, 2005	RCTs	1	26/24	58/56	Not mentioned	2%+ 0.5 μg/kg min	2 μg/ml+0.5 μg/kg min	1/2/3	5
Citerio et al, 2012	RCTs	14	130/124	–	Supratentorial neoplasm	(0.75–1.25)% + 0.25 μg/kg min	6 mg/kg h+(0.05–0.1) μg/kg min	2/7/8	4
Lauta et al, 2010	RCTs	3	149/153	53.1/58.1	Glioma meningioma	(0.7–2)% +(0.1– 0.25) μg/kg min	(6–10) mg/kg h+ (0.1–0.25) μg/kg min	1/2/7/8	5
Hernandez et al, 2006	RCTs	1	45/45	–	Brain neoplasm	0.4MAC + 0.25 μg/kg min	2.5 μg/ml+0.25 μg/kg min	1/2/8	3
Pu et al, 2014	RCTs	1	30/30	44.5	Tumor	(0.75–1.25)MAC+(2–4.5) ng/ml	3 μg/ml+6ng/ml	1	2
Huang et al, 2018	RCTs	1	58/57	54.8/56.4	Not mentioned	(0.75–1.25)MAC+(3–4)ng/ml	(3–4) μg/ml+(3–4)ng/ml	1/2/4/5/6/8	4
Wu et al, 2016	RCTs	1	43/43	45.2/46.3	Craniocerebral trauma	1.5%+3 μg/l	2 mg/kg+3 μg/l	1/2/3/9	3
Wang et al, 2018	RCTs	1	30/30	52.22/52.39	Not mentioned	(0.75–1.25)MAC +(3–5)ng/ml	(3–5) μg/ml+(3–5)ng/ml	1/2/8	2
Lin et al, 2008	RCTs	1	20/20	–	Tumor	2%+(0.2–0.4) μg/kg min	3 μg/ml+(0.2–0.4) μg/kg min	2/4/5/6	2
Meng et al, 2009	RCTs	1	41/40	52	Tumor	MAC≤1 + 2.0 ng/ml	2.5 mg/ml+2.0 ng/ml	1/2/9	2
Ouyang et al, 2010	RCTs	1	20/20	–	Tumor	(0.5–1.5)%+ (0.06–0.15) μg/kg min	(2–4) mg/kg h+(0.06–0.15) μg/kg min	6/8/9	3
Lei et al, 2017	RCTs	1	45/49	38.06/37.64	Craniocerebral trauma	1.5%+(0.1–0.3) μg/kg min	(2–4)mg/kg h+(0.1–0.3) μg/kg min	1/2/3/6/9	2
Yang et al, 2019	RCTs	1	77/78	55.8/56.2	Craniocerebral trauma	(0.75–1.25)MAC +(3–5) ng/ml	(3–5) μg/ml+(3–5)ng/ml	1/2/4/5/6/8	3
Ren et al, 2008	RCTs	1	25/25	52/54	Tumor	1%+0.25 μg/kg min	3 μg/ml+μg/kg min	1/2/7/8	2
Han et al, 2015	RCTs	1	20/20	–	Not mentioned	2%+ 0.2 μg/kg min	(4–12) mg/kg h+ 0.2 μg/kg min	1/2/4/5/6/8/9	3
Jin et al, 2015	RCTs	1	49/49	48.2/48.6	Tumor	MAC=1+0.2 μg/kg min	(1.5–2)mg/kg+ 0.2 μg/kg min	1/2/4/5/6/8	2
Bai et al, 2015	RCTs	1	70/58	–	Tumor	MAC=1.1–2.5+(0.1–0.2) μg/kg min	(4–5)mg/kg h + (0.1–0.25) μg/kg	1/2/3/8	2

Note: 1, wake-up time; 2, extubation time; 3, spontaneous respiration time; 4, SBP = systolic blood pressure; 5, DBP = diastolic blood pressure, 6, heart rate; 7, brain relaxation score; 8, side effects; 9, MAP= mean arterial hypertension. MAC= Maximum alveolar concentration, PR = propofol-remifentanil, SR = sevoflurane-remifentanil.

articles were screened, of which 51 articles were excluded because of unavailable data, non-RCTs and protocol restrictions. Finally, 17 studies[16–32] were eligible to be included in this meta-analysis. Among these studies, 4 articles were published in English, and the remaining articles were in Chinese. One of 17 eligible trials failed to provide the basic information of patients. The main characteristics of all included studies were showed in Table 1. Two trials were conducted in multi-centers, and the others were single-center clinical trials. A total of 1753 patients were included and underwent craniotomy for supratentorial neoplasm, glioma, meningioma or cerebral trauma, etc. Anesthesia was induced with remifentanil, midazolam, cisatracurium, propofol or sevoflurane. The dosages of anesthesia agents were showed in Table 1.

The quality of all included RCTs were evaluated by Jadad score form, of which 4 studies were scored more than or equal to 4, and they were considered as high-quality studies, and the rest were low-quality studies. In addition, asymmetric funnel plot was showed in Figure 2, and we inferred that potential publication bias existed. Then we performed Egger test to identify the publication bias, and the results indicated that detectable publication bias was observed ($P=.041$).

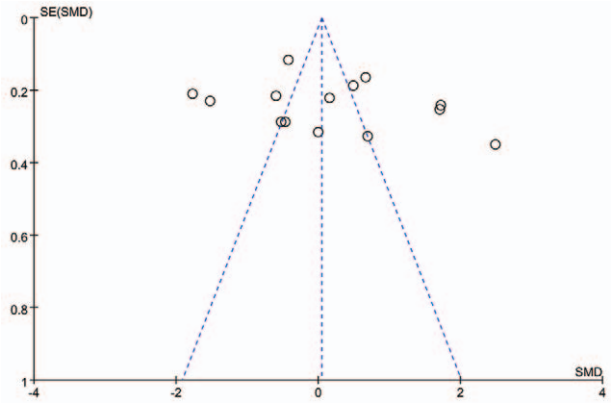

Figure 2. Funnel plot for assessing the risk of bias. SMD = standardized mean difference, SE = standard error.

3.2. Pooled results

3.2.1. Wake-up time. Thirteen studies involving 1349 participants compared the wake-up time between the SR and PR group. Random effect model was used as marked heterogeneity was observed ($P<.00001$, $I^2=94\%$) (Fig. 3). The results indicated that no statistically significant difference in the wake-up time was found between the 2 groups ($P=.25$, SMD = 0.29, 95% CI –0.20 to 0.77).

3.2.2. Extubation time and spontaneous respiration time. Fifteen trials with 1450 patients were studied to assess each anesthetic group in terms of extubation time. The heterogeneity was significant and random effect model was used to analyze the outcomes ($P<.00001$, $I^2=97\%$) (Fig. 4A). There was no marked difference in declining the extubation time between SR and PR group ($P=.1$, SMD = 0.52, 95% CI –0.11 to 1.14). With regard to spontaneous respiration time, only 4 trials evaluated outcome in this respect. The pooled results showed that random effect model was used ($P<.00001$, $I^2=98\%$), and no statistically significant difference was observed in patients undergoing craniotomy when used SR or PR for maintenance of anesthesia ($P=.58$, SMD = 0.43, 95% CI –1.07 to 1.93) (Fig. 4B).

3.2.3. Hemodynamic parameters. Five studies assessed the changes of mean arterial hypertension (MAP) and systolic blood pressure (SBP), and 3 studies evaluated the levels of diastolic blood pressure (DBP) during anesthesia maintenance. As shown in Figure 5A, random effect models were used to analyze the levels of MAP and SBP because the heterogeneity was remarkable (MAP, $P<.00001$, $I^2=86\%$; SBP, $P<.0001$, $I^2=86\%$). Fixed effect model was used to evaluate the change of DBP as low heterogeneity was showed ($P=.91$, $I^2=0\%$) (Fig. 5B). Compared to PR group, no significant changes of the levels of MAP, SBP and DBP were observed in SR group ($P=.87$, SMD = 0.05, 95% CI –0.55 to 0.65; $P=.73$, SMD = 0.09, 95% CI –0.43 to 0.61; $P=.14$, SMD = –0.17, 95% CI –0.39 to 0.06). Additionally, 6 trials with 530 patients assessed the levels of heart rate. High heterogeneity

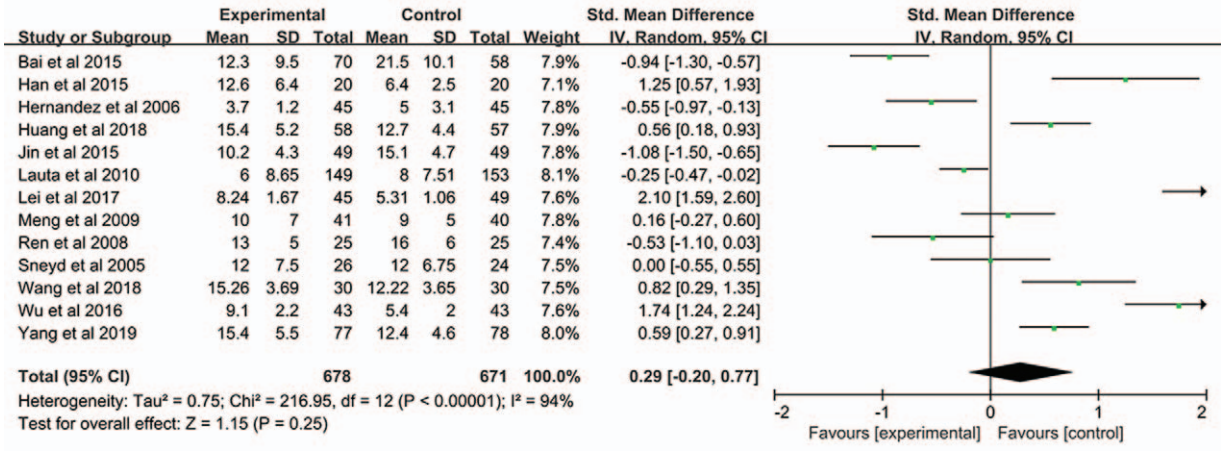

Figure 3. The effect of sevoflurane-remifentanil vs propofol-remifentanil on wake-up time.

existed among these studies ($P < .00001$, $I^2 = 88\%$). There was no significant change in the level of heart rate in the process of anesthesia maintenance ($P = .06$, SMD = 0.51, 95% CI –0.02 to 1.05).

3.2.4. Safety. In the process of anesthesia maintenance and postoperation, a series of adverse reactions were occurred. At present, some studies have been found that the intraoperative adverse reactions mainly included brain edema, hypertension, and hypotension, and the postoperative adverse reactions included postoperative nausea and vomiting (PONV), shivering, seizures, and pain. Fixed effect model was used due to the low heterogeneity ($P > .05$, $I^2 < 50\%$) (Fig. 6). During anesthesia maintenance, PR could remarkably increase the incidence of hypertension in patients undergoing craniotomy when compared to SR group ($P = .001$, SMD = 0.55, 95% CI 0.39 to 0.79), and SR had higher incidence of hypotension and brain edema than PR ($P = .02$, SMD = 1.68, 95% CI 1.07 to 2.62; $P < .0001$, SMD = 3.37, 95% CI 1.86 to 6.12).

During postoperative recovery, the incidence of PONV in SR group was higher than that of the PR group ($P < .0001$, SMD = 2.12, 95% CI 1.47 to 3.07), while no significant difference in the incidence of shivering, seizures, and pain between the 2 groups was observed ($P = .30$, SMD = 0.78, 95% CI 0.48 to 1.25; $P = .55$,

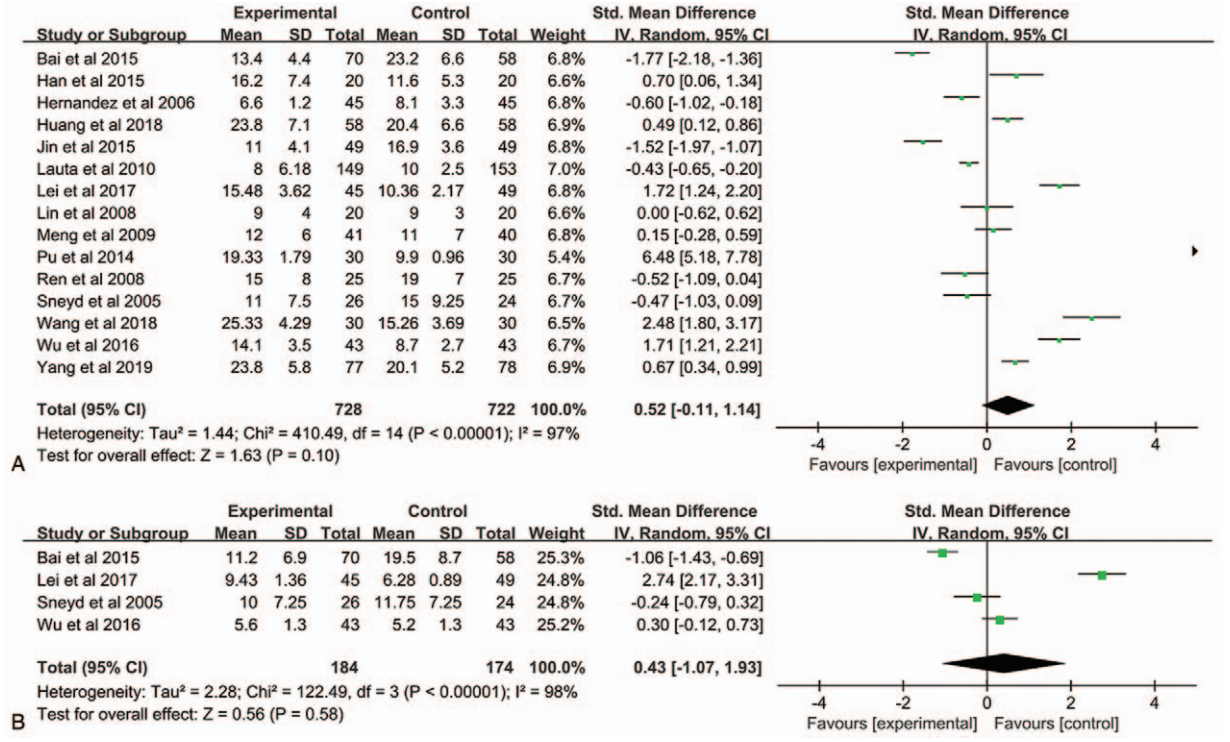

Figure 4. Comparison of the effect of sevoflurane-remifentanil and propofol-remifentanil on extubation time and spontaneous respiration time. A, extubation time; B, spontaneous respiration time.

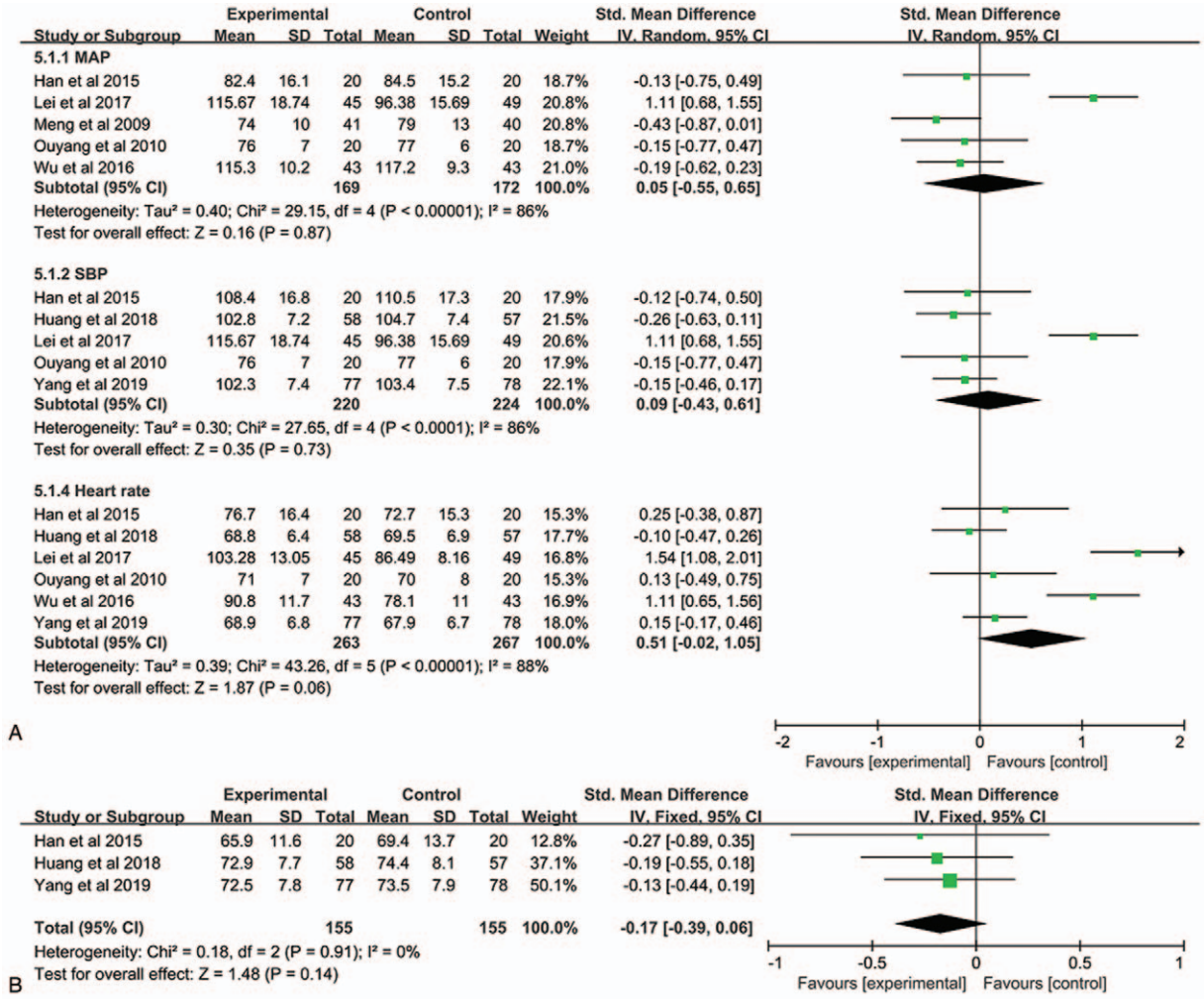

Figure 5. The effect of sevoflurane-remifentanil vs propofol-remifentanil on hemodynamic parameters. A, MAP, SBP, and heart rate; B, DBP. DBP = diastolic blood pressure, MAP = mean arterial hypertension, SBP = systolic blood pressure.

SMD = 1.26, 95% CI 0.60 to 2.65; $P = .24$, SMD = 1.28, 95% CI 0.85 to 1.93).

3.3. Sensitivity analysis

In this study, sensitivity analysis was conducted to evaluate the accuracy of these results. We changed the processing methods of data such as fixed or random effect model, and the results indicated that no significant differences in the values of SMD and odds ratio were observed. In addition, we assessed these outcomes using SMD vs weighted mean difference, and the outputted results were consistent.

4. Discussion

General anesthesia is the most commonly used method for craniotomy, and the main goals of anesthesia management are to maintain the balance of cerebral blood flow and brain metabolism, avoiding the increase of intracranial pressure and maintaining a stable hemodynamics, thus providing good surgical conditions and promoting rapid recovery.[5,33] This is convenient for postoperative evaluation of early neurological function, and timely discovery intracranial hematoma, cerebral hernia formation, cerebral ischemia and other intracranial complications. At present, there is no consensus on which anesthesia option is the most suitable for craniotomy, and it is still controversial whether to use intravenous anesthesia or inhalation anesthesia during craniotomy.

In our study, we conducted a meta-analysis to compare the efficacy and safety of SR and PR for maintained anesthesia in patients undergoing craniotomy. A total of 17 RCTs were included, and some of these studies suggested that SR led to shorter recovery time than PR for anesthesia maintenance. However, our results indicated that there were no significant differences in wake-up time, extubation time and spontaneous respiration time when patients with SF or PF for anesthesia maintenance. The reason might be related to the dosage of these anesthetics, the drug tolerance of patient and the physical fitness. In addition, because sevoflurane and propofol are short-active anesthetics, and their anesthetic effects and postoperative recovery time are related to the duration of anesthesia. Previous clinical trial found that the recovery times were similar in patients with sevoflurane and propofol anesthesia for elective supratentorial craniotomy.[18] Moreover, Talke et al[34] found that no

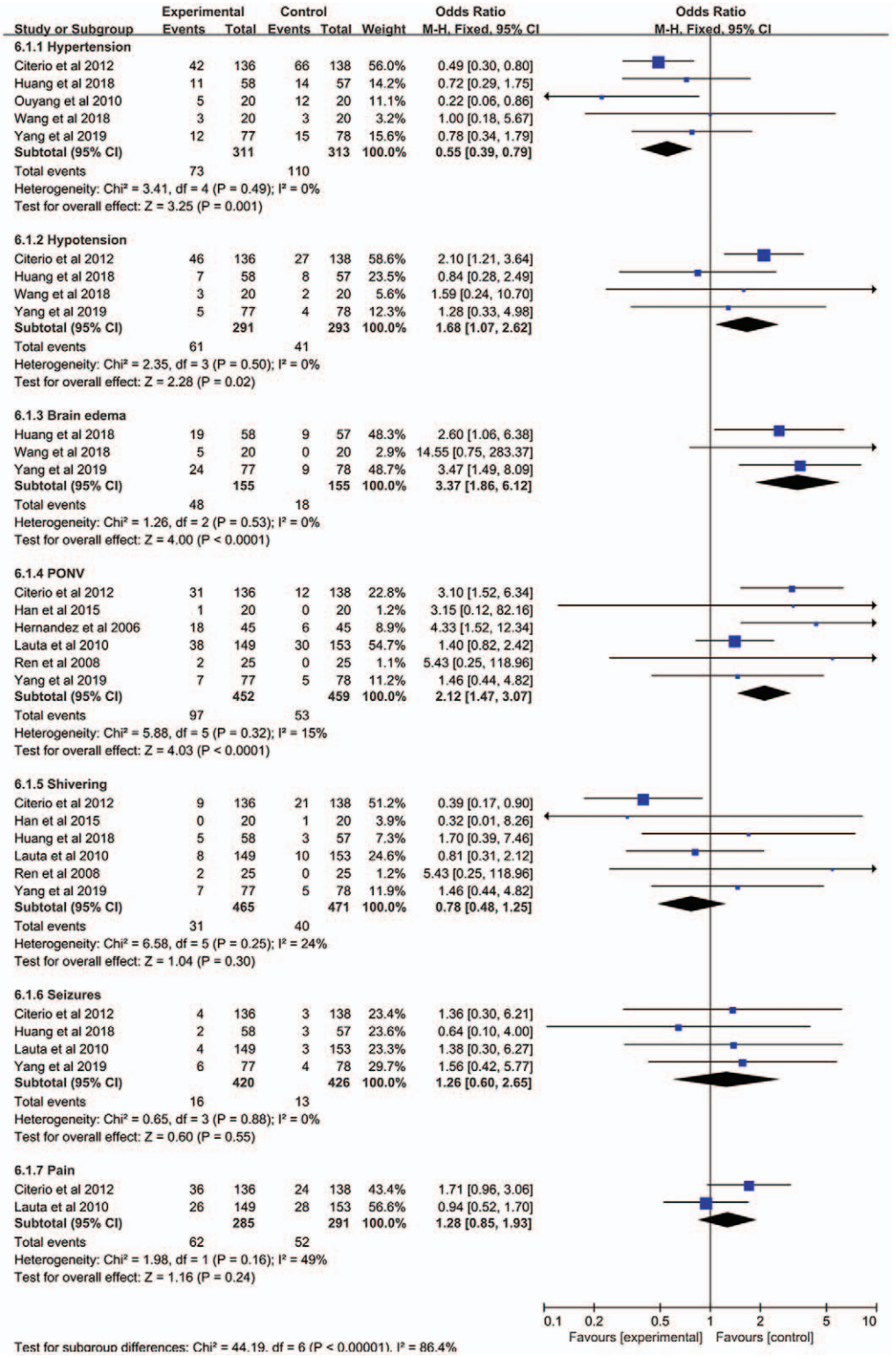

Figure 6. The incidence of adverse reactions in patients undergoing craniotomy when used sevoflurane-remifentanil and propofol-remifentanil for anesthesia maintenance.

significant differences in the recovery event times (open eyes, extubation, and follow commands) were observed between propofol and isoflurane anesthesia.

During anesthesia maintenance, stabilizing the stable hemodynamics is an important part of craniotomy. Intraoperative hypertension was related to increased intracranial pressure, which could cause intracranial hemorrhage and cerebral edema; hypotension could affect cerebral perfusion pressure and MAP.[35] Sevoflurane is a preferred inhalational agent, and has the effects on cerebral vasodilatory in a dose-dependent manner,

whereas propofol leads to cerebral vasoconstriction.[36] Previous study showed that sevoflurane and isoflurane might have better effect on hemodynamic control than propofol during craniotomy for cerebral tumors; moreover, sevoflurane combined with remifentanil was more likely to cause hypotension than propofol combined with remifentanil when patients with craniotomy.[37] Later, Bastola et al[12] found that propofol, sevoflurane, and desflurane had similar effects on hemodynamics for neuroanesthesia in patients undergoing elective supratentorial craniotomy. In our study, the results suggested that there were no significant difference in the levels of MAP, DBP, SBP, and heart rate when patients with SR and PR for anesthesia maintenance. Additionally, other research found that no significant hemodynamic changes were observed through transcranial Doppler sonography at the time of deep anesthesia and recovery when used sevoflurane and propofol anesthesia in patients undergoing intracranial tumors resection surgery.[38] Therefore, we could identify that SR and PR anesthetics had similar hemodynamic control in patients undergoing craniotomy.

Regarding side effects, hypertension, hypotension, and brain edema are quite common during neurosurgery. In the process of surgery, choosing optimal neuroprotective strategies could maintain the balance between cerebral perfusion and oxygenation, ensure the stability of blood pressure, prevent brain edema and reduce the occurrence of post-operative side effects. In our study, the results indicated that PR could remarkably increase the incidence of hypertension in patients undergoing craniotomy when compared to SR group, while SR had higher incidence of hypotension and brain edema than PR. Therefore, appropriate drugs to control blood pressure and reduce cerebral edema are needed during surgery.

One RCT assessed the post-operative complications in patients who received sevoflurane or propofol in conjunction with remifentanil and rocuronium for anesthesia maintenance, and the results found that no significant differences in the post-operative hypertension, edema, and vomiting were observed.[14] Other study found that there were still no significant differences in the incidence of post-operative PONV, shivering, pain, hypertension, and hypotension.[39] However, our results suggested that the incidence of PONV in SR group was higher than that of the PR group, while no significant difference in the incidence of shivering, seizures, and pain between the 2 groups. We inferred that PR was more comfortable for patients, and more researches are still needed to confirm the correlation between postoperative complications and anesthetics.

However, this study has some certain limitations. Most of the included studies had small sample size, and the concentration, dosage of anesthetics and supplementary medications were quite different, both of which undermined the accuracy of the results to some extent. Second, most of the included studies came from Chinese, and the methods of allocation concealment, blinding, and following-up were not elaborate, which might have high risk of bias. Third, some included studies were low quality, which may affect the accuracy of the outcomes. Therefore, more high-quality RCTs are necessary to further evaluate the efficacy and safety of SR vs PR as inhalation anesthesia in patients undergoing craniotomy.

To conclude, SR as inhalation anesthesia had similar effect with PR as total intravenous anesthesia in patients undergoing craniotomy, but SR had higher incidence of intraoperative hypotension, brain edema and post-operative PONV. PR may be more comfortable than SR for patients undergoing craniotomy, and this will provide a medication reference for the use of anesthetics.

Author contributions

Conceptualization: Rui Zhao.
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Formal analysis: Zheng Zhou.
Investigation: Zheng Zhou, Miaofa Ying.
Methodology: Zheng Zhou, Miaofa Ying.
Project administration: Zheng Zhou.
Resources: Zheng Zhou, Miaofa Ying.
Software: Zheng Zhou.
Supervision: Miaofa Ying, Rui Zhao.
Validation: Zheng Zhou, Miaofa Ying.
Visualization: Zheng Zhou, Miaofa Ying.
Writing – original draft: Zheng Zhou.
Writing – review & editing: Rui Zhao.

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