Effect of desflurane and sevoflurane on postoperative cognitive dysfunction A meta-analysis of randomized controlled trials

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Research Article

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Abstract

Background

This meta-analysis was conducted to evaluate the effects of desflurane and sevoflurane on postoperative cognitive dysfunction(POCD).

Methods

Randomized controlled trials (RCTS) investigating the application of desflurane and sevoflurane in the maintenance of POCD in patients under general anesthesia were retrieved through a computer search on the PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure(CNKI), Wanfang Database and Technology Periodical Database (VIP) for studies published until October 2022. The identified literature were analyzed using the Revman5.3 system evaluation software.

Results

A total of 10 studies met the inclusion criteria, which comprised 966 patients, including 483 in the desflurane group and 483 in the sevoflurane group. It was observed that the score of Mini-Mental State Examination (MMSE) decreased preoperative (SMD = 0.00, 95%CI = -0.14-0.15), 1h after surgery (SMD = 1.78, 95%CI = 0.68–2.88), and 3h after surgery (SMD = 0.46, 95%CI = 0.09 ~ 0.82), 6h after surgery (SMD = 1.11, 95%CI =-0.15 ~ 2.37), and 24h after surgery (SMD = 0.16, 95%CI =-0.01 ~ 0.30), and eye opening time (SMD = -3.30, 95%CI = -4.65-1.96) and extubation time (SMD = -3.54, 95%CI = -5.44-1.63) in desflurane group were shorter compared with values in the sevoflurane group.

Conclusions

Desflurane results in shorter eye opening and extubation times compared with sevoflurane when used as the maintenance therapy of general anesthesia with inhalation anesthetics. Both anesthetics may lead to a reduction in cognitive function among surgical patients, and this is particularly higher the sevoflurane than for desflurane treatment.

Registration number:CRD42023390692.

1. Introduction

Postoperative cognitive dysfunction (POCD) is a kind of central nervous system complications after surgical anesthesia. Common symptoms of patients include short-term memory, mental concentration, language communication ability, recognition ability and other mental impairment[1]. POCD usually lasts for weeks to months, and in some patients the symptoms are mild and subtle[2]. POCD was first recognized as a complication after heart surgery[3]. Further studies showed that POCD was also very common in non-cardiac surgery, with an incidence of 30.4% to 41.4% in patients over 18 years of age[4]. At present, the pathogenesis of POCD has not been fully clarified, which may be the enhancement of inflammatory response, the decrease of central cholinergic system function, the theory of neurodegeneration (deposition of Aβ, the formation of age spots), the hyperphosphorylation of Tau protein in brain tissue, the increase of apolipoprotein E, the imbalance of brain oxygen metabolism[5, 6]. Identifying the etiology of POCD and the influence of anesthetics on it is helpful to develop prevention strategies for POCD, so as to make early intervention, reduce the incidence and improve the postoperative quality of life of patients[7]. Compared with traditional inhalation anesthetics , desflurane and sevoflurane provide good controllability and are superior in terms of recovery quality. Thus, they are widely used as inhalation anesthetics in clinical practice. It has been demonstrated that surgery can induce cognitive impairment, which may be due to increased hippocampal complement C3 after surgery [8]. There is no clear evidence-based medical evidence on which inhalation anesthesia has less impact on cognitive function damage and recovery in clinical use of desflurane or sevoflurane. This study aims to compare the effects of sevoflurane and desflurane on cognitive function after general anesthesia and postoperative anesthesia resuscitation, so as to provide a more reasonable drug reference for general anesthesia.

2. Materials And Methods

This meta-analysis was conducted in accordance with the guidelines and protocols of the Priority Reporting Project for System Evaluation and Meta-Analysis (PRISMA) and registered in the PROSPERO database (CRD42023390692)

2.1 Data Sources

This meta-analysis was performed on randomized controlled trials (RCTS) investigating the changes in POCD after intraoperative maintenance of general anesthesia with desflurane and sevoflurane, regardless of whether the study was randomized. A search was conducted on the PubMed, Embase, Cochrane Library, CNKI, Wanfang Database and Technology Periodical Database (VIP) with Chinese and English to identify studies published until October 2022, with no restrictions on publication year. Selected combinations of Medical Subject Headings (MeSH) terms were used to conduct the search on PubMed, and EMTREE terms were applied for the search on Embase. Keyword search terms for desflurane, sevoflurane, quality of recovery, postoperative cognitive dysfunction, and randomized controlled trials were applied in all databases. In the analysis, we excluded duplicate reports, dissertations, review reports, news articles, animal studies, retrospective studies, case reports, conference proceedings, ongoing trials, unpublished trials, and studies that did not explore postoperative recovery indicators. Among the included studies, sevoflurane or desflurane were the main intraoperative drugs used to maintain anesthesia, regardless of whether preoperative induction drugs and methods were the same.

Two independent reviewers(MBL and JC) performed the initial screening of literature by reading the titles. At this stage, duplicate studies and those that did not meet the eligibility criteria were excluded. Studies listed in relevant systematic reviews or meta-analyses were also screened.

If there was any discrepancy in the selection of studies by the two reviewers, a third examiner(ZJY) was consulted. The studies selected in the initial screening were then further examined by reading the abstract, and trials that met the inclusion criteria were analyzed in detail by reading the full text.

2.2 Data Extraction

The full text of the included studies was read by two independent authors(MBL and JC). The following data were extracted from each study: first name of author, year of publication, country, ASA grade, age, type of operation, number of cases in the sevoflurane and desflurane groups, type of intraoperative airway entry (laryngeal mask airway or endotracheal tube), eye opening time, extubation time, score of Mini-Mental State Examination (MMSE) (preoperative and 1h, 3h, 6h, 24h postoperatively).

2.3 Bias Risk Evaluation

The Cochrane systematic review criteria was adopted to determine the level of bias among the studies by two researchers (MBL and JC) working independently. The assessment was conducted in line with six different criteria: selection bias (generation of random sequences, assignment hiding), implementation bias (implement-participant double-blindness), measurement bias (blindness in outcome assessment), loss of follow-up bias (incomplete outcome data), publication bias (selective reporting), and other sources of bias. According to the above criteria, two reviewers(MBL and JC) assigned a score of bias for each study independently. In case of different opinions, a third researcher (ZJY) was consulted to reacha consensus.

2.4 Result Recording

The main outcomes recorded were MMSE score (preoperative, postoperative 1h, 3h, 6hand 24h), eye opening time and extubation time. In cases of missing data from eligible studies, the authors were contacted.

2.5 Statistical Analysis

The MMSE scores of patients at various study time points, such as preoperative, 1h, 3h, 6h and 24h after surgery, eye opening time and extubation time were analyzed using the RevMan5.3 software. The data were statistically analyzed using the fixed effects model or random effects model. The X^2 test was employed to determine whether there was heterogeneity among various studies based on the data type. At the $P > 0.1$ and $I^2 < 50\%$, no heterogeneity or little heterogeneity was considered. At a $P < 0.1$ and $I^2 \geq 50\%$, the random effects model should be used for combined calculation.

3. Results

3.1 The Basic Information of the Included Literature

A total of 966 trials were identified using the selected search terms. Studies that did not meet the inclusion criteria were removed after reading the title. A further reading of the abstract and full text, 10 RCTS[9–18] were deemed eligible for the study. The search strategy and exclusion procedure are shown in Fig. 1. Overall, 966 patients were randomized to receive maintenance anesthesia with desflurane or sevoflurane during the operation (483 and 483, respectively). Table 1 summarizes the features and characteristics of the included studies.

Table 1
Characteristics of included studies

Study	Year	Country	ASA	Age	Airway	Surgical type	DES/SEVO(N)	Cognitive function scale
Celalettin Altun	2015	Turkey	1	≥ 18	ET	C.S	25/25	MMSE
Telugu SeeTharam Deepak	2013	India	1 ~ 3	≥ 65	NR	Mixed	30/30	MMSE
Halit Çobanoğlu	2013	Turkey	1 ~ 3	≥ 65	ET	Mixed	20/20	MMSE
Dingling Deng	2018	China		≥ 65	LAM	TURP	60/60	MMSE
Xiaoli Xu	2021	China	1 ~ 2	≤ 12	NR	Paediatric surgery	55/55	MMSE
Qixing Yang	2017	China		≥ 60	ET	Mixed	60/60	MMSE
Xueying Zhang	2022	China	1 ~ 2	65–79	ET	Abdominal operation	30/30	MMSE
Amit Kumar Verma	2022	India	1 ~ 2	18–65	NR	MED	25/25	MMSE
Chunhui Zheng	2020	China	1 ~ 2	65–80	ET	Mixed	80/80	MMSE
Xuenan Chang	2016	China	1 ~ 2	≥ 60	ET	Mixed	98/98	MMSE

Note: ASA, American Society of Anesthesiologists physical status scale; NR, not reported; ET, Endotracheal Tube; LAM, Laryngeal mask intubation; C.S, Caesarean section; TURP, transurethral prostatectomy; MED, microendoscopic discectomy Des, desflurane; Sev, sevoflurane; MMSE, mini-mental state examination.

3.2 Bias Risk Assessment for Included Studies

The Cochrane Handbook5.1 bias risk assessment criteria was utilized to determine the bias risk of the selected 10 RCTS. "High risk" represented high risk bias level, "Low risk" indicated low risk bias level, and "Unclear" indicated insufficient or uncertain information about the bias risk of a study. The majority of the RCTS had low or unclear risk of bias. The evaluation results of bias levels are shown in Figs. 2 and 3.

3.3 Effect of Desflurane and Sevoflurane on Postoperative Cognitive Function

3.3.1 Preoperative Cognitive Function Analysis of Patients in Desflurane Group and Sevoflurane Group

The included studies adopted the MMSE cognitive scoring method. As shown in Fig. 4, eight studies reported the preoperative MMSE scores for all patients. It was observed that there was no significant difference between the two groups, and no heterogeneity was observed in the studied ($P = 0.23$, $I^2 = 25\%$). Therefore, the fixed-effect model was applied in the calculation and analysis. Preoperative cognitive function of patients was comparable among the studies (SMD = 0.00, 95%CI = -0.14-0.15).

3.3.2 Comparison of Cognitive Function Changes in Desflurane Group and Sevoflurane Group at 1h After Surgery

Figure 5 demonstrates that nine studies compared the changes in cognitive function among patients 1h after surgery. The results showed that there was no significant difference between the two groups, and the level of heterogeneity was high ($P < 0.00001$, $I^2 = 97\%$). Thus, the random effects model was adopted in the calculation and analysis. It was found that the MMSE score of the desflurane group was higher than that of the sevoflurane group (SMD = 1.78, 95%CI = 0.68 ~ 2.88).

3.3.3 Comparison of Cognitive Function Changes in Desflurane Group and Sevoflurane Group at 3h After Surgery

Data shown in Fig. 6, indicate that seven studies provided the comparison results for the changes in cognitive function among patients 3h after surgery. The results revealed that there were significant differences between the two groups, and heterogeneity was high ($P = 0.0005$, $I^2 = 73\%$). Therefore, the random effects model was adopted in the calculation and analysis. The MMSE score of the desflurane group was higher than that of the sevoflurane group (SMD = 0.46, 95%CI = 0.09–0.82) 3h after surgery.

3.3.4 Comparison of Cognitive Function Changes in Desflurane Group and Sevoflurane Group at 6h After Surgery

As shown in Fig. 7, four studies reported the comparison results of changes in cognitive function among the patients 6h after surgery. The results showed that: there were significant differences between the two groups, and heterogeneity was high ($P < 0.00001$, $I^2 = 95\%$), Therefore, the random effects model was used for calculation and analysis. Notably, the MMSE score of the desflurane group was higher than that of the sevoflurane group (SMD = 1.11, 95%CI =-0.15 ~ 2.37).

3.3.5 Comparison of Cognitive Function Changes in Desflurane Group and Sevoflurane Group at 24h After Surgery

The data shown Fig. 8 show that four studies provided the comparison results on the changes in cognitive function among patients 24h after surgery. There were significant difference in between the two groups, and heterogeneity was moderate (P = 0.55, I^2= 0%). Therefore, the fixed effect model was used for calculation and analysis. MMSE scores in the desflurane group were higher than those in the sevoflurane group 24 hours after surgery (SMD = 0.16, 95%CI = -0.01-0.30).

3.3.6 Analysis of Eye Opening and Extubation Time in Desflurane Group and Sevoflurane Group

As shown in Figs. 9 and 10, nine studies reported the comparison results of postoperative eye opening time among the patients, and five studies reported postoperative extubation time of patients, these results were statistically significant. Due to the large heterogeneity among the studies, the random effects model was used for calculation. It was observed that postoperative eye opening time and extubation time in sevoflurane group were shorter than those in sevoflurane group (SMD (eye opening) = -3.30, 95%CI = -4.65-1.96, SMD (extubation) = -3.54, 95%CI = -5.44-1.63).

4. Discussion

A total of 10 RCTS were included in this meta-analysis to compare the effects of sevoflurane and desflurane on POCD in patients undergoing general maintenance anesthesia. For the 5-time nodes in which MMSE score was performed, significant differences were observed at 1, 3 and 24h after surgery, but this was not the case for he comparison between preoperative and 6h after surgery. In this meta-analysis, we discovered that more effectively desflurane reduced the incidence of POCD more effectively compared with sevoflurane when applied as the to maintenance general anesthesia. Moreover, it was superior to sevoflurane in terms of time to recovery. The results, revealed no heterogeneity between desflurane and sevoflurane in preoperative MMSE score, but there was some differences between desflurane and sevoflurane at the first, third, sixth and 24h after surgery, and the MMSE score of desflurane was higher than that of sevoflurane. MMSE is a long-term test that is currently used to assess the severity and monitor the progress of cognitive impairment. It tests orientation, memory, attention and numeracy, recall, and language. These six variables are often referred to as cognitive areas, with a maximum score of 30 and a normal score of 27–30. Scores < 27 are classified as cognitive dysfunction [19]. The analysis found, no significant difference in the preoperative MMSE score between the two groups. The incidence of POCD in the desflurane group was lower than that in the sevoflurane group within 24h after the operation, but the difference between the two groups was significantly decreased at

24h after the operation compared with the first hour after the operation. However, the desflurane group had less effect on POCD. For patients, whether there is a difference in the long-term incidence of POCD after the use of two drugs deserves further exploration.

POCD is a common postoperative complication. Although numerous studies have investigated the mechanisms underlying its occurrence in the past decade, its exact mechanism and pathology have not been fully understood. There are many risk factors contributing to the occurrence of POCD, including patient, surgical and anesthetic factors. Anesthesia is an important and integral part of any surgical procedure. The risk factors of POCD include the type of anesthesia, decreased intraoperative brain saturation, and neurotoxic effects of postoperative anesthesia. The use of narcotic drugs may also alter the cognitive function of patients, especially the elderly, because the residual effects of drugs can modify the activity of the central nervous system. Such drugs can influence tau protein modification, inflammatory process calcium regulation and mitochondrial function to alter cognitive function [20, 21]. Anesthetics primarily act on the central nervous system. Currently, the commonly used inhalation anesthetics such as isoflurane, sevoflurane, and desflurane are considered to be safe anesthetics. They have been shown to reduce mortality and morbidity during cardiac surgery, but there is no consensus on which inhalation is more effective [22]. Desflurane is a volatile inhalation anesthetic with a minimum MAC of 6%, low blood gas partition coefficient, and rapid onset and elimination, which leads to faster eye opening and extubation times in the desflurane group than in the sevoflurane group [23]. In animal studies, inhalation of sevoflurane in mice resulted in increased apoptosis of hippocampal neurons and induced hippocampal METTL3 inactivation leading to POCD[24, 25]. However, short exposure time to sevoflurane did not affect cognitive function in mice[26]. In pediatric anesthesia, the incidence of COPD increases significantly after sevoflurane anesthesia for more than 3 hours, as do serum inflammatory cytokines, which peak during the recovery period[27]. In animal studies, Zheng et al. demonstrated that rats anesthetized with desflurane showed decreased levels of neuroinflammation and learning and memory impairments [28]. However, Kilicaslan et al. exposed young adult mice to sevoflurane and desflurane and found that their spatial memory was not impaired [29]. But higher doses of desflurane anesthesia affected learning and memory in adult rats, and more so in older rats, but these effects were temporary and reversible. 10 Chen et al. found that compared with sevoflurane, desflurane caused a shorter extubation, reorientation, and exit from the recovery room, but no significant differences were observed in postoperative cognitive function or time to eye opening after anesthesia [30]. Lertkovit et al. reported that desflurane protected against cognitive decline after anesthesia and was an independent protective factor in POCD, whereas sevoflurane was an independent predictor of POCD [20]. Contrary to our findings, a prospective cohort study in Korea found that desflurane increased the risk of dementia in patients and sevoflurane decreased the risk of dementia [31].

Due to the limited sample size of the study, the relationship between desflurane and sevoflurane and POCD deserves further investigations. There are several shortcomings in the included studies in terms of methodology: (1) Implementation bias and selection bias may exist in the included studies, which decreases the quality of the obtained results. Only 4 studies adopted the random number table method, and the rest only mentioned random allocation. Moreover, the specific randomization method was not explained in detail: only 2 studies used the opaque envelope method to hide the randomization. Therefore, future clinical trials should consider this limitation. (2) The included studies were all published Chinese or English articles, and this may introduce publication bias due to incomplete literature inclusion and missing grey data. (3) Different examiners were involved in the included studies, and the depth of anesthesia was not controlled using a common method, which may weaken the comparison results among indicators; (4) Different types of surgeries were included in the study, which included pediatric surgery, gynecological surgery and orthopedic surgery, among others. Different surgical methods or sites may have exert different effects on the results of the study. These shortcomings and biases can be prevented by inclusion of many studies involving one type of single surgery.

5. Conclusion

In summary, this analysis shows that desflurane induces faster recovery of patients and reduces the incidence of POCD compared with sevoflurane. However, in clinical practice, the rational choice or combination of these two anesthetic drugs should be based on the actual situation of patients and their respective advantages and disadvantages. In addition, given the the limited data in the original literature included in this study, the strength of the research results is uncertain, and further high-quality RCTSwith reasonable design, strict execution and multi-center and large samples are needed to further verify our conclusions.

Abbreviations

POCD= Postoperative cognitive dysfunction, RCTS= Randomized controlled trials, CNKI=China National Knowledge Infrastructure, VIP =Technology Periodical Database, MeSH =Medical Subject Headings, MMSE =Mini-Mental State Examination.

Declarations

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

MBL and ZJY designed/performed most of the investigation and data analysis MBL,JC and YC wrote the manuscript; MBL and JC extracted data; MBL, ZJY and JC contributed to interpretation of the data and analyses. All of the authors have read and approved final manuscript.

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Authors’ contributions

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Manuscript editing: Mingbo Luo, Zhijian You

Methodology: Mingbo Luo, Zhijian You, Jie Chen, Yue Chen

All of the authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Supplemental material

Supplemental material for this article can be requested from the corresponding author for appropriate reasons.

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Figures

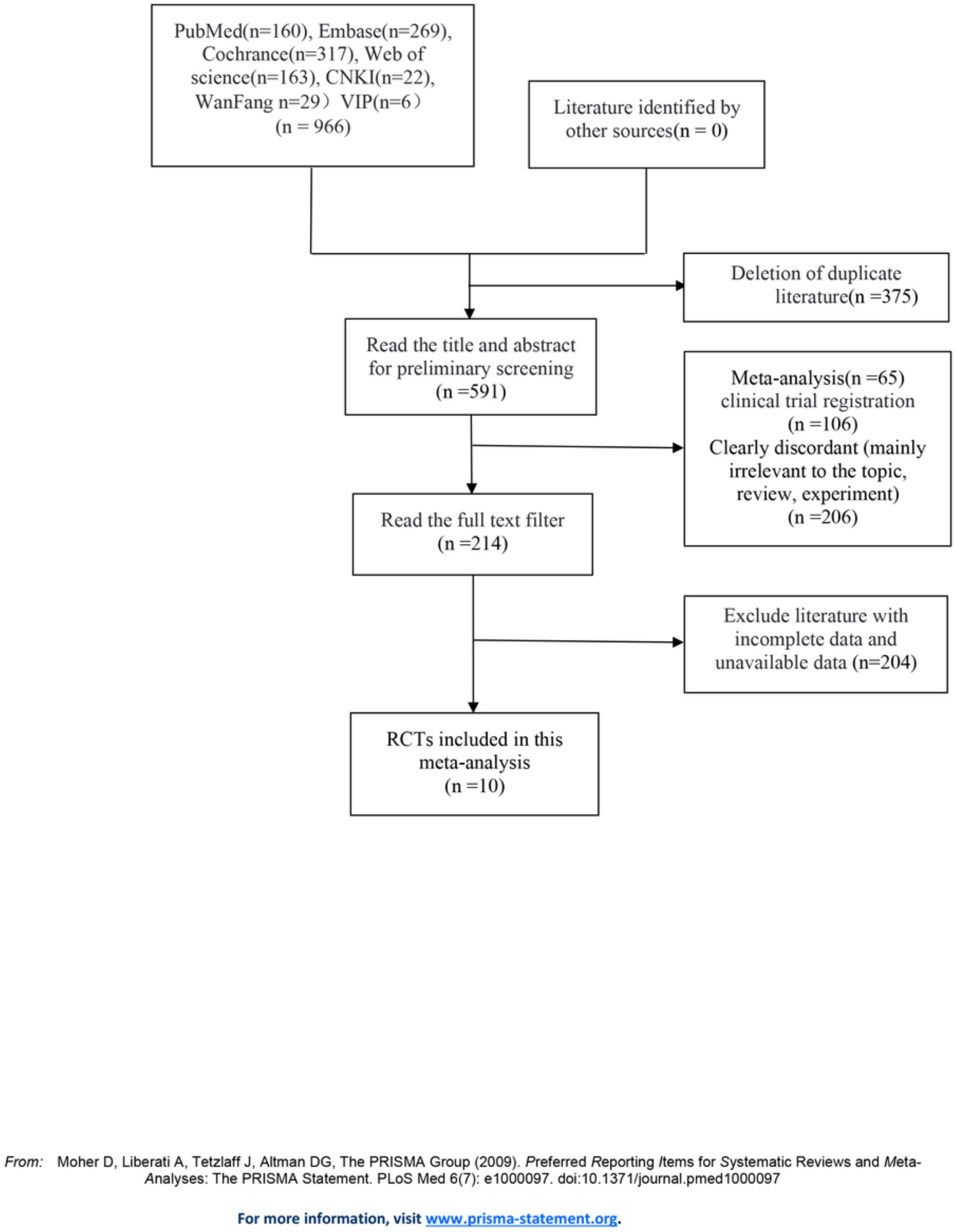

Figure 1

Search strategy and exclusion procedure.

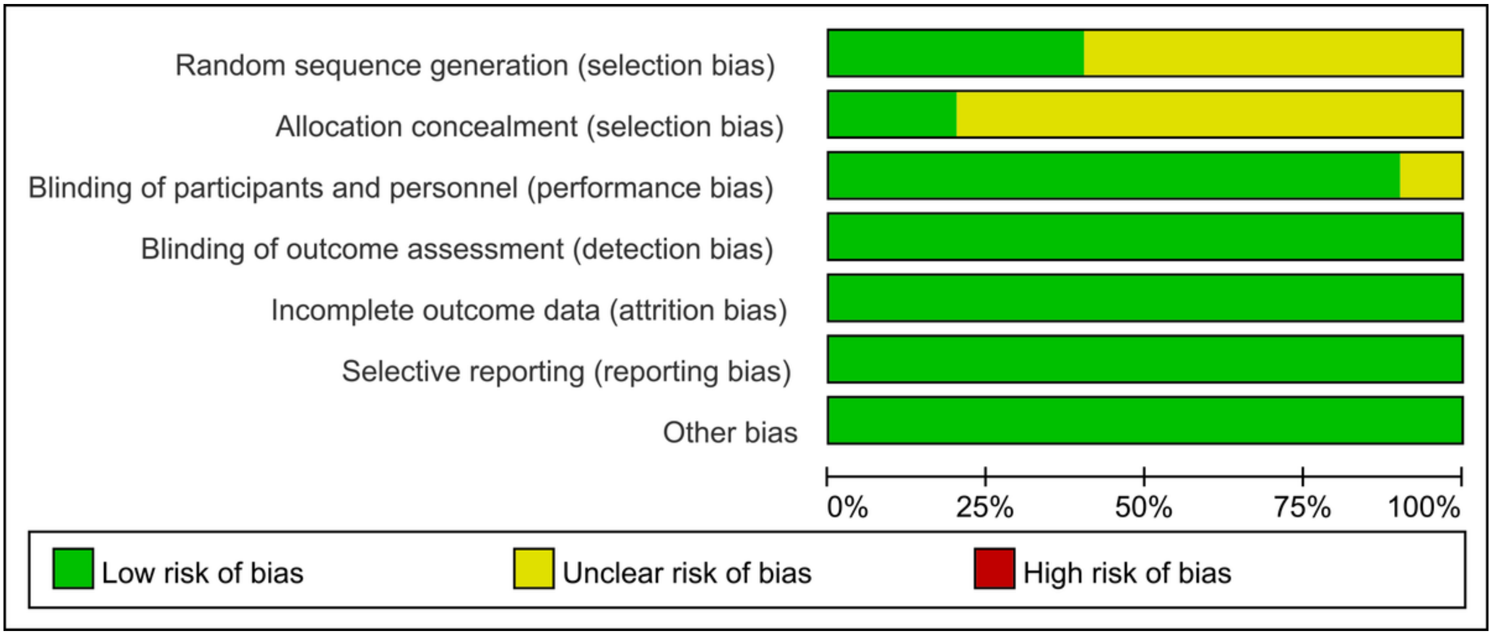

Figure 2

Bias risk map.

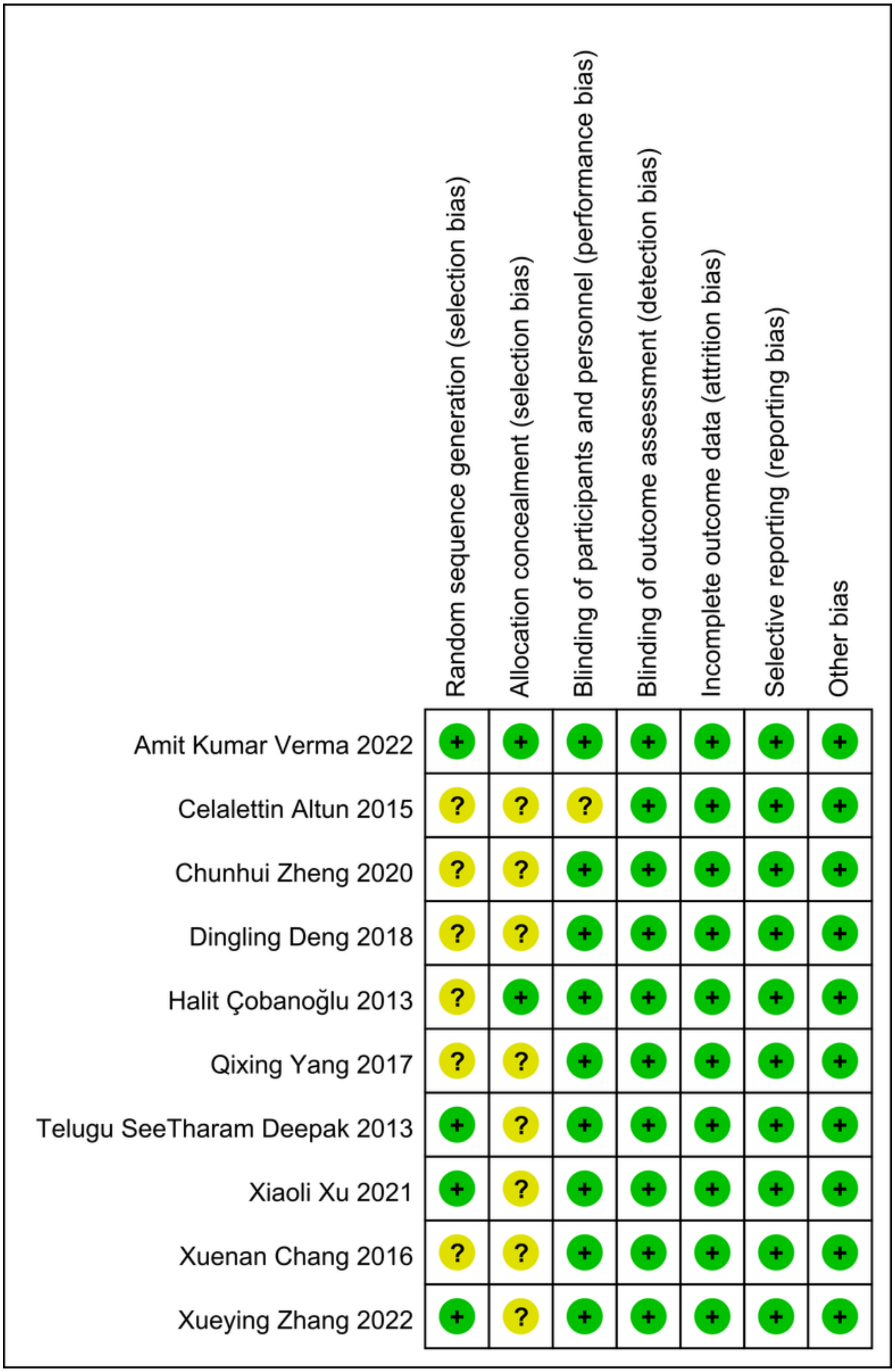

Figure 3

Bias risk summary.

Study or Subgroup	DES Mean	DES SD	DES Total	SEVO Mean	SEVO SD	SEVO Total	Weight	Mean Difference IV, Fixed, 95% CI
Celalettin Altun 2015	24.04	2.57	25	24.72	2.34	25	1.1%	-0.68 [-2.04, 0.68]
Chunhui Zheng 2020	30.91	1.38	80	30.74	1.22	80	12.9%	0.17 [-0.23, 0.57]
Dingling Deng 2018	29.5	0.8	60	29.6	0.7	60	29.2%	-0.10 [-0.37, 0.17]
Halit Çobanoğlu 2013	27.8	2.2	20	27	2.1	20	1.2%	0.80 [-0.53, 2.13]
Qixing Yang 2017	28.73	1.77	60	28.36	1.92	60	4.8%	0.37 [-0.29, 1.03]
Telugu SeeTharam Deepak 2013	28.6	1.276	30	28.97	0.964	30	6.4%	-0.37 [-0.94, 0.20]
Xuenan Chang 2016	29.1	0.9	98	29.2	1	98	29.7%	-0.10 [-0.37, 0.17]
Xueying Zhang 2022	29.6	0.7	30	29.3	0.8	30	14.6%	0.30 [-0.08, 0.68]
Total (95% CI)			**403**			**403**	**100.0%**	**0.00 [-0.14, 0.15]**

Heterogeneity: Chi² = 9.29, df = 7 (P = 0.23); I² = 25%
Test for overall effect: Z = 0.04 (P = 0.97)

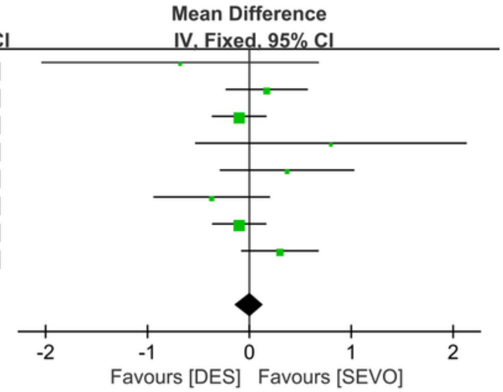

Figure 4

This forest maps are analysis of MMSE scores of patients preoperative and at 1h.3h.6h.24h after surgery.

Study or Subgroup	DES Mean	DES SD	DES Total	SEVO Mean	SEVO SD	SEVO Total	Weight	Mean Difference IV, Random, 95% CI
Amit Kumar Verma 2022	26.68	2.39	25	26.2	2.43	25	10.1%	0.48 [-0.86, 1.82]
Celalettin Altun 2015	24.12	2.76	25	24.36	2.16	25	10.0%	-0.24 [-1.61, 1.13]
Chunhui Zheng 2020	28.92	1.77	80	22.33	1.89	80	11.5%	6.59 [6.02, 7.16]
Dingling Deng 2018	26.9	0.9	60	24.9	0.5	60	11.8%	2.00 [1.74, 2.26]
Halit Çobanoğlu 2013	27.1	1.9	20	25.9	1.4	20	10.7%	1.20 [0.17, 2.23]
Qixing Yang 2017	25.42	2.31	60	23.51	2.11	60	11.2%	1.91 [1.12, 2.70]
Telugu SeeTharam Deepak 2013	26.53	1.737	30	27.17	1.234	30	11.2%	-0.64 [-1.40, 0.12]
Xuenan Chang 2016	27.8	1.2	98	25.6	1.1	98	11.7%	2.20 [1.88, 2.52]
Xueying Zhang 2022	26.7	0.7	30	24.7	0.9	30	11.7%	2.00 [1.59, 2.41]
Total (95% CI)			**428**			**428**	**100.0%**	**1.78 [0.68, 2.88]**

Heterogeneity: Tau² = 2.66; Chi² = 308.93, df = 8 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.17 (P = 0.002)

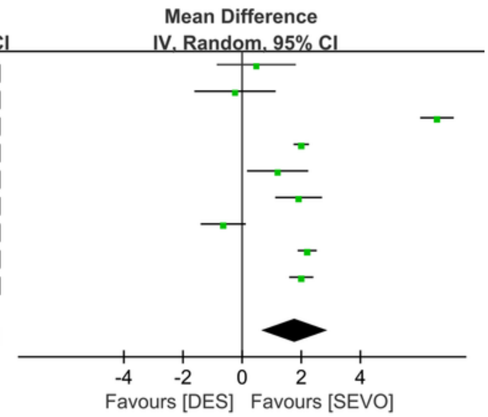

Figure 5

This forest maps are analysis of MMSE scores of patients preoperative and at 1h.3h.6h.24h after surgery.

Study or Subgroup	DES Mean	DES SD	DES Total	SEVO Mean	SEVO SD	SEVO Total	Weight	Mean Difference IV, Random, 95% CI
Amit Kumar Verma 2022	28.24	1.56	25	27.8	1.5	25	10.4%	0.44 [-0.41, 1.29]
Celalettin Altun 2015	24.8	2.72	25	24.92	2.16	25	5.5%	-0.12 [-1.48, 1.24]
Dingling Deng 2018	29	0.5	60	28.3	0.8	60	21.5%	0.70 [0.46, 0.94]
Halit Çobanoğlu 2013	27.9	2.2	20	27.2	1.6	20	6.8%	0.70 [-0.49, 1.89]
Qixing Yang 2017	27.89	2.98	60	25.97	2.26	60	9.2%	1.92 [0.97, 2.87]
Telugu SeeTharam Deepak 2013	27.7	1.368	30	27.97	1.066	30	14.1%	-0.27 [-0.89, 0.35]
Xiaoli Xu 2021	25.21	2.29	55	24.86	2.34	55	10.2%	0.35 [-0.52, 1.22]
Xuenan Chang 2016	29.1	0.7	98	28.9	0.6	98	22.3%	0.20 [0.02, 0.38]
Total (95% CI)			**373**			**373**	**100.0%**	**0.46 [0.09, 0.82]**

Heterogeneity: Tau² = 0.15; Chi² = 25.84, df = 7 (P = 0.0005); I² = 73%
Test for overall effect: Z = 2.43 (P = 0.01)

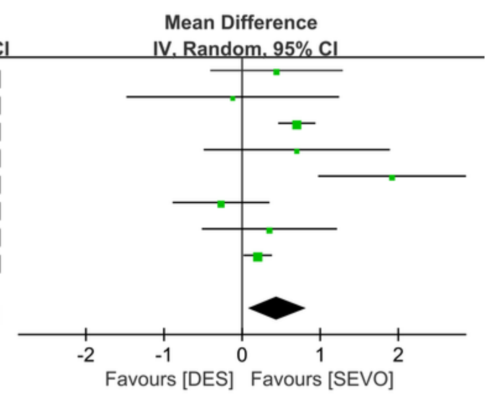

Figure 6

This forest maps are analysis of MMSE scores of patients preoperative and at 1h.3h.6h.24h after surgery.

Study or Subgroup	DES Mean	DES SD	DES Total	SEVO Mean	SEVO SD	SEVO Total	Weight	Mean Difference IV, Random, 95% CI
Qixing Yang 2017	28.32	2.32	60	27.93	2.65	60	23.5%	0.39 [-0.50, 1.28]
Telugu SeeTharam Deepak 2013	28.4	1.102	30	28.67	0.959	30	25.4%	-0.27 [-0.79, 0.25]
Xiaoli Xu 2021	27.85	1.16	55	25.89	1.04	55	25.9%	1.96 [1.55, 2.37]
Xueying Zhang 2022	28.2	1.1	30	25.9	1.2	30	25.2%	2.30 [1.72, 2.88]
Total (95% CI)			**175**			**175**	**100.0%**	**1.11 [-0.15, 2.37]**

Heterogeneity: Tau² = 1.55; Chi² = 59.85, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.72 (P = 0.08)

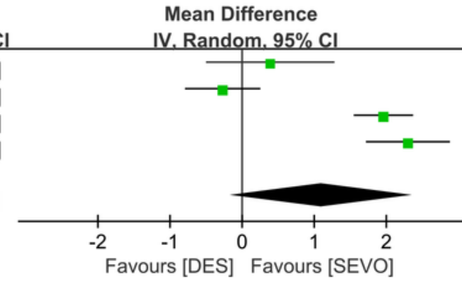

Figure 7

This forest maps are analysis of MMSE scores of patients preoperative and at 1h.3h.6h.24h after surgery.

Study or Subgroup	DES Mean	DES SD	DES Total	SEVO Mean	SEVO SD	SEVO Total	Weight	Mean Difference IV, Fixed, 95% CI
Celalettin Altun 2015	24.76	2.68	25	25	2.1	25	1.2%	-0.24 [-1.57, 1.09]
Chunhui Zheng 2020	30.38	1.74	80	29.96	1.87	80	6.8%	0.42 [-0.14, 0.98]
Xiaoli Xu 2021	29.02	0.43	55	28.91	0.47	55	75.3%	0.11 [-0.06, 0.28]
Xueying Zhang 2022	29.4	0.6	30	29.1	0.8	30	16.7%	0.30 [-0.06, 0.66]
Total (95% CI)			**190**			**190**	**100.0%**	**0.16 [0.01, 0.30]**

Heterogeneity: Chi² = 2.10, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)

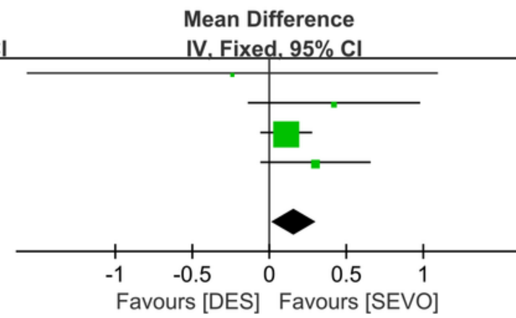

Figure 8

This forest maps are analysis of MMSE scores of patients preoperative and at 1h.3h.6h.24h after surgery.

Study or Subgroup	DES Mean	DES SD	DES Total	SEVO Mean	SEVO SD	SEVO Total	Weight	Mean Difference IV, Random, 95% CI
Amit Kumar Verma 2022	8.18	2.26	25	8.88	2.25	25	10.8%	-0.70 [-1.95, 0.55]
Celalettin Altun 2015	3.76	1.74	25	8.08	1.71	25	11.3%	-4.32 [-5.28, -3.36]
Chunhui Zheng 2020	7.88	2.17	80	11.21	3.28	80	11.4%	-3.33 [-4.19, -2.47]
Dingling Deng 2018	8.2	0.9	60	14.1	0.5	60	11.9%	-5.90 [-6.16, -5.64]
Halit Çobanoğlu 2013	8.4	2.7	20	8.4	2.2	20	10.3%	0.00 [-1.53, 1.53]
Qixing Yang 2017	7.12	1.87	60	11.42	2.57	60	11.4%	-4.30 [-5.10, -3.50]
Telugu SeeTharam Deepak 2013	5.37	0.999	30	7.93	1.53	30	11.6%	-2.56 [-3.21, -1.91]
Xiaoli Xu 2021	7.65	1.52	55	10.62	2.38	55	11.5%	-2.97 [-3.72, -2.22]
Xueying Zhang 2022	8.37	2.33	30	13.77	4.55	30	9.8%	-5.40 [-7.23, -3.57]
Total (95% CI)			**385**			**385**	**100.0%**	**-3.30 [-4.65, -1.96]**

Heterogeneity: Tau² = 3.95; Chi² = 230.02, df = 8 (P < 0.00001); I² = 97%
Test for overall effect: Z = 4.81 (P < 0.00001)

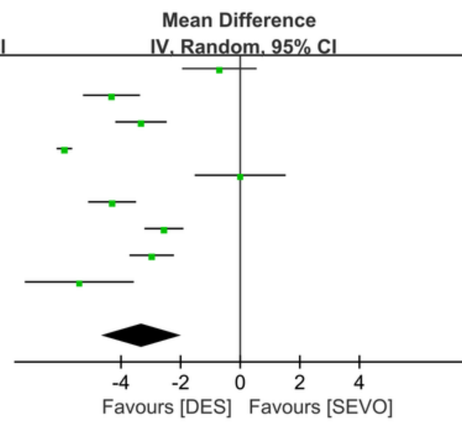

Figure 9

This forest maps are analysis of eye opening time and extubation time.

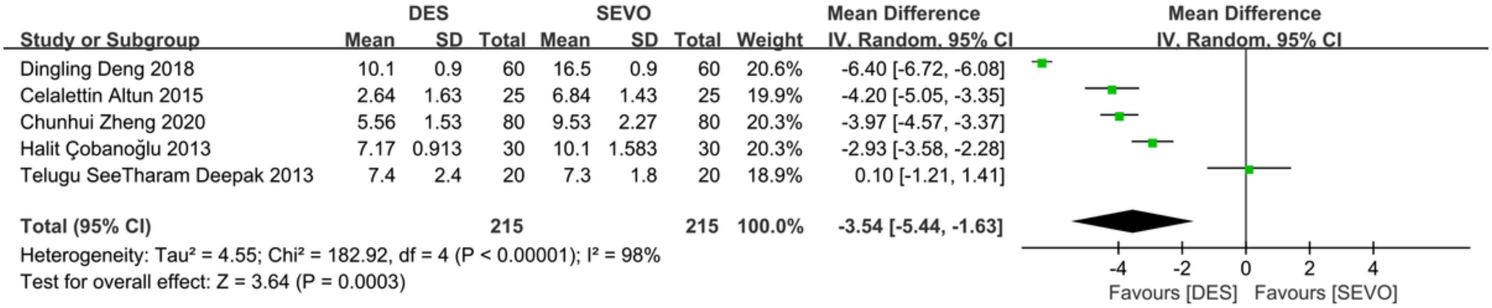

Figure 10

This forest maps are analysis of eye opening time and extubation time.