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Authors

Long, Yuqin
Feng, Xiaomei
Liu, Hong
et al.

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Effects of anesthetic depth on postoperative pain and delirium: a meta-analysis of randomized controlled trials with trial sequential analysis

Yuqin Long[1,2], Xiaomei Feng[3], Hong Liu[4], Xisheng Shan[1,2], Fuhai Ji[1,2], Ke Peng[1,2]

[1]Department of Anesthesiology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, China;
[2]Institute of Anesthesiology, Soochow University, Suzhou, Jiangsu 215006, China;
[3]Department of Anesthesiology, University of Utah Health, Salt Lake City, UT, USA;
[4]Department of Anesthesiology and Pain Medicine, University of California Davis Health, Sacramento, CA.

Abstract

Background: Whether anesthetic depth affects postoperative outcomes remains controversial. This meta-analysis aimed to evaluate the effects of deep *vs.* light anesthesia on postoperative pain, cognitive function, recovery from anesthesia, complications, and mortality.

Methods: PubMed, EMBASE, and Cochrane CENTRAL databases were searched until January 2022 for randomized controlled trials comparing deep and light anesthesia in adult surgical patients. The co-primary outcomes were postoperative pain and delirium (assessed using the confusion assessment method). We conducted a meta-analysis using a random-effects model. We assessed publication bias using the Begg's rank correlation test and Egger's linear regression. We evaluated the evidence using the trial sequential analysis and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. We conducted subgroup analyses for pain scores at different postoperative time points and delirium according to cardiac or non-cardiac surgery.

Results: A total of 26 trials with 10,743 patients were included. Deep anesthesia compared with light anesthesia (a mean difference in bispectral index of −12 to −11) was associated with lower pain scores at rest at 0 to 1 h postoperatively (weighted mean difference = −0.72, 95% confidence interval [CI] = −1.25 to −0.18, $P = 0.009$; moderate-quality evidence) and an increased incidence of postoperative delirium (24.95% *vs.* 15.92%; risk ratio = 1.57, 95% CI = 1.28–1.91, $P < 0.0001$; high-quality evidence). No publication bias was detected. For the exploratory secondary outcomes, deep anesthesia was associated with prolonged postoperative recovery, without affecting neurocognitive outcomes, major complications, or mortality. In the subgroup analyses, the deep anesthesia group had lower pain scores at rest and on movement during 24 h postoperatively, without statistically significant subgroup differences, and deep anesthesia was associated with an increased incidence of delirium after non-cardiac and cardiac surgeries, without statistically significant subgroup differences.

Conclusions: Deep anesthesia reduced early postoperative pain but increased postoperative delirium. The current evidence does not support the use of deep anesthesia in clinical practice.

Keywords: Anesthetic depth; GRADE level of evidence; Postoperative delirium; Postoperative pain; Trial sequential analysis

Introduction

Monitoring and maintaining brain function are important in daily anesthesia practice.[1,2] The brain functional indices derived from a processed electroencephalogram, such as bispectral index (BIS), auditory evoked potential index, and spectral entropy, have been utilized to evaluate the depth of anesthesia. The advantages of using these indices include prevention of intraoperative awareness, avoidance of excessive anesthetic depth, reduction of hypnotic agents used, and acceleration of postoperative recovery.[3-6]

Effective pain management is crucial to patients' rehabilitation after surgery. Whether deep anesthesia alleviates postoperative pain remains unclear. Faiz *et al*[7] reported that deep anesthesia (BIS values of 35–44) *vs.* light anesthesia (BIS values of 45–55) led to better pain outcomes after laparoscopic cholecystectomy. However, other studies argued that deep anesthesia did not produce

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Yuqin Long and Xiaomei Feng contributed equally to this work.

Correspondence to: Ke Peng, Department of Anesthesiology, First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou, Jiangsu 215006, China
E-Mail: pengke0422@163.com

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clinically useful analgesic effects.[8,9] There has not yet been a meta-analysis of postoperative pain in relationship with the depth of general anesthesia. Furthermore, postoperative pain and opioid-based analgesia are the risk factors for postoperative delirium (POD).[10]

Perioperative neurocognitive disorders are common and serious complications, particularly in elderly patients undergoing surgery. A consensus has been developed for perioperative cognitive changes, including acute events such as POD and cognitive decline up to 30 days postoperatively (delayed neurocognitive recovery [DNR]) and up to 12 months (postoperative neurocognitive disorder).[11] The effects of anesthesia depth on neurocognitive function are controversial in previous randomized controlled trials (RCTs).[8,12] Moreover, the results from meta-analyses are also conflicting,[13-15] without incorporating recently published trials.[16,17] Regarding postoperative mortality, observational studies and relevant meta-analyses showed that intraoperative low BIS was associated with increased postoperative mortality,[18-21] but a recent RCT did not demonstrate such a causal link.[22]

Therefore, we conducted this systematic review and meta-analysis to evaluate the effects of deep *vs*. light anesthesia on postoperative pain, cognitive function, recovery from anesthesia, complications, and mortality. We performed the trial sequential analysis (TSA) to assess the primary results and utilized the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence of this study.

Methods

Protocol and registration

We prospectively registered the review protocol at PROSPERO International Prospective Register of Systematic Reviews (identifier: CRD42019127973) on April 8, 2019. We conducted this systematic review and meta-analysis by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [Supplementary Table 1, http://links.lww.com/CM9/B335].[23]

Search strategy

Two review authors independently performed the literature search in PubMed, EMBASE, and Cochrane CENTRAL databases from inception to February 20, 2021, and the search results were updated on January 6, 2022. We used the following search strategy for PubMed: (((((((bispectral index [Title/Abstract]) OR (bispectral index monitor [Title/Abstract])) OR (anesthesia depth [Title/Abstract])) OR (anesthetic depth [Title/Abstract])) OR (spectral entropy [Title/Abstract])) OR (depth of anesthesia [Title/Abstract])) OR (bis [Title/Abstract])) AND ((((((((((postoperative outcome) OR (postoperative complication)) OR (complications)) OR (pain)) OR (death)) OR (mortality)) OR (cognitive)) OR (cognition)) OR (delirium)) OR (POCD))) AND "Randomized Controlled Trial"[pt]. The search strategies for all databases are shown in Supplementary Table 2, http://links.lww.com/CM9/B335. We did not use language or other restrictions for the literature search. We manually checked the references of included studies to identify additional records.

Trial selection

We included studies that met the following criteria: (1) study design: RCT; (2) participants: adult patients undergoing cardiac or non-cardiac surgery; (3) intervention: light anesthesia *vs*. deep anesthesia (a mean between-group difference ≥5 in BIS [0–100] or ≥3 in auditory evoked potential index [0–60]); and (4) postoperative outcomes: pain intensity, cognitive function, postoperative nausea and vomiting (PONV), time to emergence from anesthesia, time to extubation from anesthesia, length of stay, postoperative major complications, and mortality. The exclusion criteria were: (1) non-RCT, (2) duplicate publications, (3) surgical procedures under sedation other than general anesthesia, or (4) no specific results. Any discrepancy during the trial selection process was resolved by re-evaluation of the study and group discussion with other review authors.

Data extraction

Two review authors independently extracted data from each study, including the first author's name, publication year, region, type of surgery, type of anesthesia with anesthetic doses, intervention groups, mean age, number of patients, mean or median BIS values, and main outcomes reported. Any discrepancy during the data extraction process was resolved by re-checking the study data and group discussion.

Primary outcomes

The co-primary outcomes were postoperative pain scores at rest at 0–1 h postoperatively and the incidence of POD up to 1 week postoperatively or until discharge. Postoperative pain was measured using the visual analogue scale (VAS, 0–10). POD was assessed using the confusion assessment method. The definitions of perioperative neurocognitive disorders (NCDs, including POD, DNR, and postoperative NCD) are listed in Supplementary Table 3, http://links.lww.com/CM9/B335.

Secondary outcomes

The secondary outcomes were exploratory, including postoperative VAS pain scores at 8 h and 24 h postoperatively, intraoperative sufentanil consumption, postoperative rescue analgesia, persistent pain during 3 to 12 months postoperatively, DNR during 1 to 7 days postoperatively, NCD during 1 to 3 months postoperatively, Mini-mental State Examination (MMSE) scores, time to emergence from anesthesia, time to extubation from anesthesia, orientation recovery time, length of post-anesthesia care unit (PACU) stay, length of intensive care unit stay, length of hospital stay, quality of recovery on postoperative day 1, 90-day physical and mental recovery scores, clinically significant hypotension (necessitating fluid and/or drug intervention), PONV, any major

complication, such as myocardial infarction, sepsis, stroke, and wound infection, intraoperative awareness, 1-year cancer recurrence, mortality within 30 to 90 days postoperatively, and 1-year mortality.

Quality assessment

Two review authors independently conducted quality assessments using the Cochrane evaluation tool.[24,25] We evaluated the risk of bias for each study in seven domains: random sequence generation, allocation concealment, blinding of participants and personal information, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. After a judgment of low, high, or unclear risk of bias in each domain, we rated the study to be at a low risk of bias (if all domains were at low risk), a high risk of bias (if high risk in ≥1 domain), or unclear risk of bias (if unclear risk in ≥1 domain without any domain at a high risk). Furthermore, we assessed the quality of evidence for the main outcomes using the GRADE approach.[26,27] We assessed the certainty of evidence in six domains: study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. Based on the assessment, we rated the level of evidence as high, moderate, low, or very low. Any discrepancy during the quality assessment process was resolved by group discussion with other review authors.

Statistical analysis

We conducted the meta-analysis using the RevMan software (version 5.4, Cochrane Collaboration, Copenhagen, Denmark). For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were analyzed using the Mantel–Haenszel method. For continuous outcomes, weighted mean differences (WMDs) with 95% CIs were analyzed using the Inverse Variance method. Considering clinical heterogeneities, we applied a random-effects model for data pooling.[28] We used the I^2 statistic test to evaluate heterogeneity among studies, with $I^2 > 50\%$ indicating significant heterogeneity.[25,29] We assessed publication bias using the Begg's rank correlation test and Egger's linear regression test with the STATA software (version 14.0, Stata Corp, College Station, TX, USA).[27,30,31] Begg's funnel plot was also generated for visual inspection. For the two co-primary outcomes, we performed multiple testing using the Bonferroni method, with $P < 0.025$ indicating a statistical significance (i.e., 0.05/2). We conducted subgroup analyses for pain scores at different postoperative time points and POD according to cardiac or non-cardiac surgery. For the exploratory secondary outcomes, no multiple testing correction was applied.

We assessed the reliability of two primary results using the TSA viewer software (version 0.9.5.5 beta, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).[27,32] In a TSA diagram, a *Z*-curve crossing the trial sequential monitoring boundary or futility boundary suggests that the current evidence is sufficient for a conclusion and that further studies are unlikely to change the inference. On the contrary, a *Z*-curve not crossing any boundary suggests an insufficient level of evidence. To calculate the monitoring and futility boundaries, the following parameters were used: conventional test boundary (boundary type: two-sided; Type I error = 5%), Alpha-spending boundaries (hypothesis testing [boundary type: two-sided; Type I error = 5%; α-spending function: O'Brien-Fleming; Information axis: sample size], inner wedge [β-spending function: O'Brien-Fleming; Power = 80%], and required information size [information size: estimate; Power = 80%; Heterogeneity correction: model variance based]), and law of the Iterated logarithm (boundary type: two-sided; Type I error = 5%; Penalty = 2.0). We also reported the adjusted 95% CIs by TSA for each outcome.

Results

Literature search

We initially identified a total of 2996 publications. After excluding duplicates and irrelevant articles, 99 studies were included for full-text review. Thereafter, we excluded 73 articles due to non-RCT, pediatric use, BIS not used in the control group, lack of specific outcomes, or surgery performed under sedation and spinal anesthesia. Finally, we included a total of 26 RCTs in this meta-analysis [Figure 1].[7-9,12,16,17,33-52]

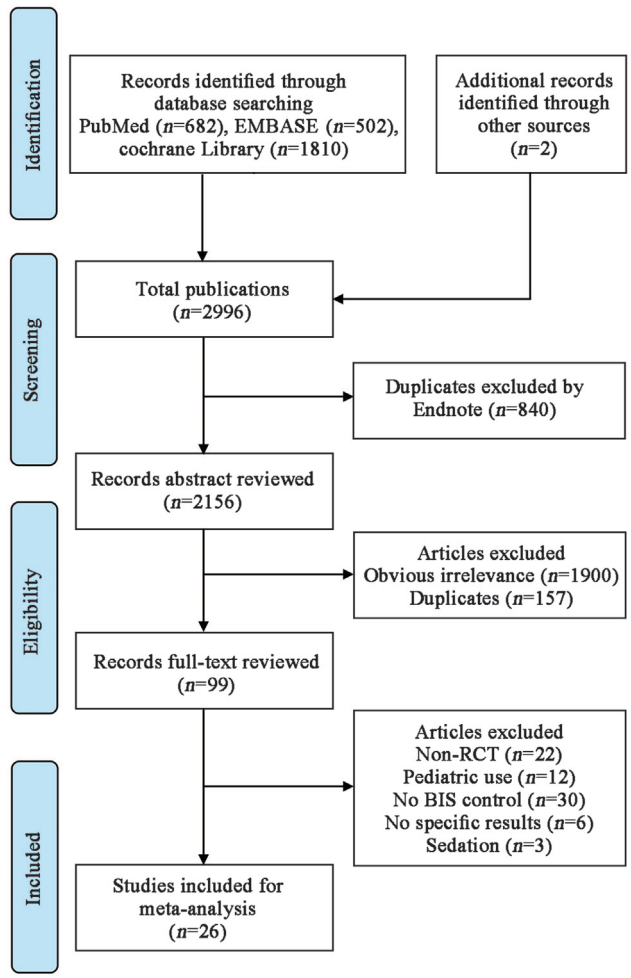

Figure 1: Flowchart of literature inclusion criteria of studies on effects of anesthetic depth on postoperative pain and delirium. BIS: Bispectral index; RCT: Randomized controlled trials.

Trial characteristics

Table 1 shows the trial characteristics. These RCTs were published between 1997 and 2021, involving 10,743 patients undergoing cardiac or non-cardiac surgery. Among 22 trials on non-cardiac surgery, 9 trials used volatile-based anesthesia (sevoflurane, isoflurane, or desflurane),[9,33-36,38-41] 8 trials used total intravenous anesthesia with propofol,[7,8,42,44-48] and 5 trials used propofol anesthesia combined with volatiles.[12,49-52] Two studies included both cardiac and non-cardiac surgeries using volatile-based anesthesia.[16,17] Two studies included patients undergoing cardiac surgery; isoflurane anesthesia was used in one study and propofol anesthesia was used in the other study.[37,43]

Supplementary Figure 1, http://links.lww.com/CM9/B334 depicts the risk of bias in the included studies. Of these, 12 RCTs had a low risk of bias, 13 had an unclear risk of bias, and one had a high risk of bias.

Primary outcomes

The VAS pain score at rest at 0–1 h postoperatively was significantly lower in the deep anesthesia group than that in the light anesthesia group (WMD = −0.72, 95% CI = −1.25 to −0.18, $P = 0.009$, $I^2 = 33\%$; Supplementary Table 4, http://links.lww.com/CM9/B335 and Figure 2A), with a moderate level of GRADE evidence [Supplementary Table 5, http://links.lww.com/CM9/B335]. The mean difference of BIS values between groups was −12 in the included studies. There was no publication bias with the Begg's funnel plot ($P = 1.000$; Figure 2B) or Egger's test ($P = 0.894$). In the TSA diagram, the *Z*-curve (blue) crossed the trial sequential monitoring boundary (red) and conventional benefit boundary (brown), suggesting sufficient evidence for this result [Figure 2C]. For this pain outcome, the adjusted 95% CI by TSA was from −1.32 to −0.12.

The deep anesthesia group had a significantly higher incidence of POD (24.95%) compared with the light anesthesia group (15.92%; risk ratio [RR] = 1.57, 95% CI = 1.28–1.91, $P < 0.0001$, $I^2 = 0\%$; Supplementary Table 4, http://links.lww.com/CM9/B335 and Figure 3A), with a high level of GRADE evidence [Supplementary Table 5, http://links.lww.com/CM9/B335]. The mean difference of BIS values between groups was −11. We did not detect significant publication bias in the Begg's funnel plot ($P = 0.308$; Figure 3B) or Egger's test ($P = 0.196$). In the TSA diagram, the *Z*-curve crossed the monitoring boundary and conventional benefit boundary, suggesting that the current evidence is sufficient [Figure 3C]. For the POD outcome, the adjusted 95% CI by TSA was 1.17–2.09.

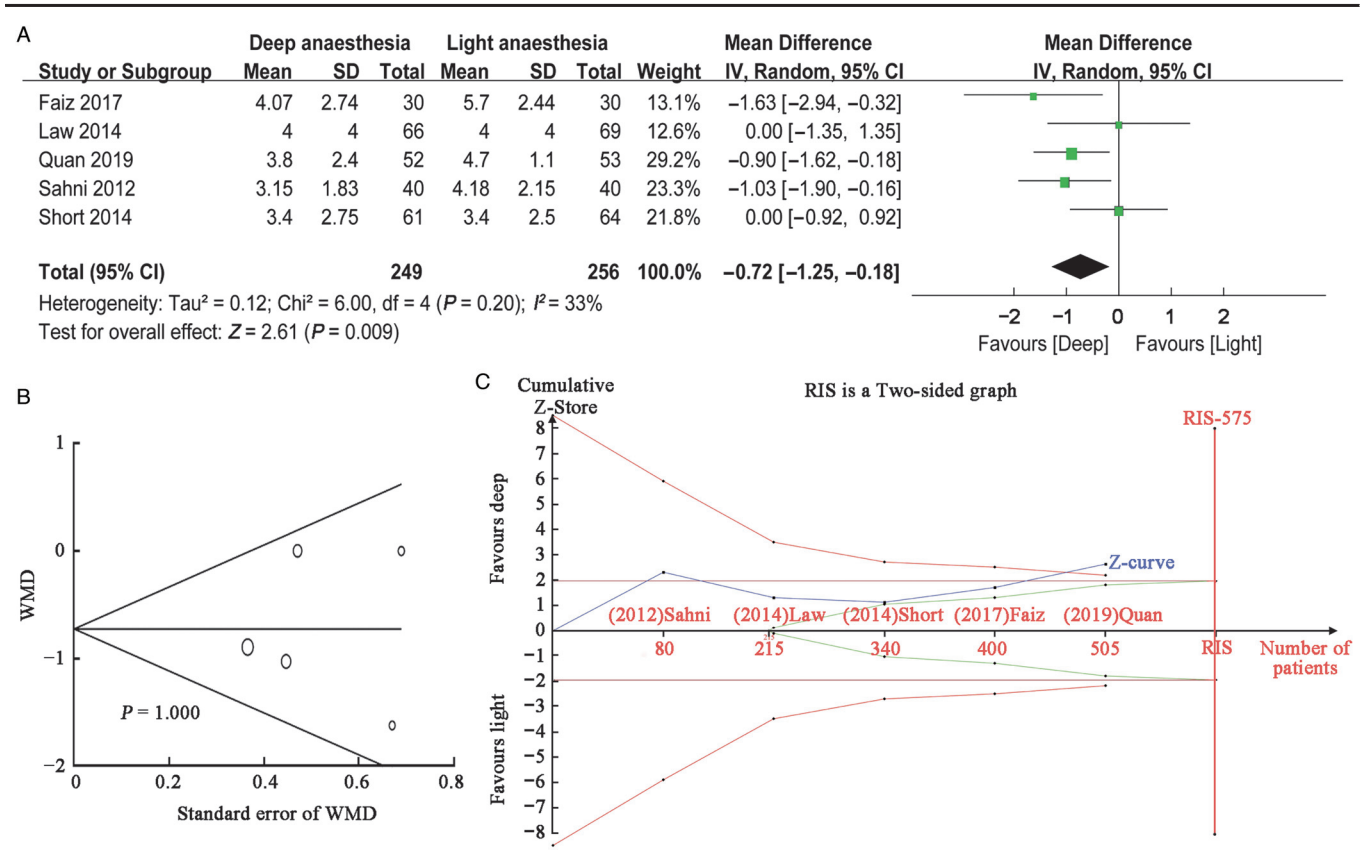

Figure 2: Deep *vs.* light anesthesia on postoperative pain at rest at 0–1 h postoperatively. (A) forest plot; (B) Begg's funnel plot; and (C) TSA. Pain intensity was assessed using the VAS (0–10). Red lines indicate the trial sequential monitoring boundary; green lines indicate the futility boundary; brown lines indicate the conventional benefit boundary; blue line is the Z-curve; CI: Confidence interval; IV: Inverse variance; RIS: Required information size; SD: Standard deviation; TSA: Trial sequential analysis; VAS: Visual analogue scale; WMD: Weighted mean difference.

Table 1: Trial characteristics of included studies comparing deep and light anesthesia.

Reference	Country	Surgery	Drug (dose, MAC)	Aneshesia depth		BIS value (deep *vs.* light)	Main outcomes
				Deep group	Light group		
Abdelmalak *et al*[33]	USA	Major non-cardiac	Sevoflurane (N/A)	187 (65)	194 (63)	44 *vs.* 50*	Any major complication, myocardial infarction, infection, sepsis, stroke, and death (30 days, 1 year)
Abdelmalak *et al*[34]	USA	Major non-cardiac	Sevoflurane (N/A)	159 (64)	167 (64)	35 *vs.* 55*	SF-12 physical/mental scores (30 days)
An *et al*[8]	China	Microvascular decompression	Propofol (1100 mg *vs.* 655 mg)	40 (45)	40 (49)	38 *vs.* 58†	VAS pain scores (1 day, 2 days) and DNR (5 days)
Chan *et al*[12]	China	Major non-cardiac	Propofol + volatile (138 mg *vs.* 136 mg, 0.93% *vs.* 0.57%)	452 (67.6)	450 (68.1)	39 *vs.* 53*	POD, DNR (7 days), NCDs (3 months), time to emergence, time to extubation, PACU stay, hospital stay, any complication, infection, QoR-9 scores, hypotension, and SF-36 physical/mental scores (3 months)
Cotoia *et al*[42]	Italy	Urologic surgery	Propofol (7.7 mg · kg^{-1} · h^{-1} *vs.* 5.07 mg · kg^{-1} · h^{-1})	32 (60)	32 (65)	38 *vs.* 45*	MMSE scores (15 min) and time to extubation
Evered *et al*[16]	USA	Cardiac and major non-cardiac	Volatile (0.79% *vs.* 0.59%)	262 (71.1)	253 (70.8)	38 *vs.* 51†	POD, NCDs (30 days/1 year), PACU stay, hospital stay, and MMSE scores (at discharge)
Faiz *et al*[7]	Iran	Laparoscopic cholecystectomy	Propofol (627 mg *vs.* 624 mg)	30 (44.1)	30 (44.7)	35–44 *vs.* 45–55‡	VAS pain scores (0 h/8 h/16 h/24 h at rest and on movement), rescue analgesia, and PONV
Farag *et al*[35]	USA	Abdominal, spine, and pelvic	Isoflurane (N/A)	36 (63.8)	38 (63.9)	39 *vs.* 51†	PACU stay and NCDs (4–6 weeks)
Hou *et al*[49]	China	Total knee replacement	Propofol + sevoflurane (4.56 mg · kg^{-1} · h^{-1} *vs.* 2.88 mg · kg^{-1} · h^{-1})	30 (67.9)	30 (68.5)	42 *vs.* 63*	Time to emergence, time to extubation, DNR (1 day/3 days/7 days), and VAS pain scores (1 day/3 days/7 days)
Jildenstål *et al*[36]	Sweden	Ophthalmic	Desflurane (3.3% *vs.* 2.5%)	226 (60.5)	224 (60.0)	12 *vs.* 18† (AAI)	DNR (1 day, 7 days), NCDs (1 month), mortality (1 year), and hypotension
Kunst *et al*[37]	United Kingdom	Coronary artery bypass grafting	Isoflurane (N/A)	40 (72.0)	42 (71.6)	35 *vs.* 41*	POD, MMSE scores (3–5 days/6 weeks/1 year), infection, ICU stay, and hospital stay
Law *et al*[9]	New Zealand	Non-emergent	Desflurane (N/A)	66 (42.1)	69 (43.2)	33 *vs.* 42*	VAS pain scores at (PACU, 1 day on movement), hypotension, and morphine consumption (PACU, 24 h)
Lehmann *et al*[43]	Germany	Coronary artery bypass grafting	Midazolam + propofol (N/A)	33 (65)	33 (65)	35–44 *vs.* 45–55‡	Time to extubation, PONV, and hypotension
Quan *et al*[44]	China	Abdominal	Propofol (1308 mg *vs.* 1024 mg)	52 (65.6)	53 (63.9)	39 *vs.* 53*	Time to extubation, hospital stay, VAS pain scores (1–2 h), DNR (7 days), NCDs (3 months), PONV, infection, intraoperative awareness, rescue analgesia, death (7 days, 3 months), cancer recurrence (1 year), and persistent pain

Table 1
(continued).

Reference	Country	Surgery	Drug (dose, MAC)	Aneshesia depth		BIS value (deep *vs.* light)	Main outcomes
				Deep group	Light group		
Sahni *et al*[52]	India	Laparoscopic cholecystectomy	Propofol + isoflurane (0.93% *vs.* 0.90%)	40 (39.5)	40 (38.4)	45 *vs.* 63*	Time to emergence, VAS pain scores (0 h/8 h/16 h/24 h at rest and on movement), PONV, and rescue analgesia
Short *et al*[50]	New Zealand, Australia	Major non-cardiac	Propofol or volatile (4.0 μg/mL *vs.* 3.1 μg/mL, 0.98% *vs.* 0.64%)	61 (74)	64 (72)	39 *vs.* 48*	VAS pain scores (at PACU), PACU stay, hospital stay, QoR-9 scores (1 day/2 days/3 days), any major complication, infection, death (1 year), cancer recurrence (1 year), and hypotension
Short *et al*[17]	International multicenter	Cardiac and major non-cardiac	Volatile (0.88% *vs.* 0.62%)	3328 (72)	3316 (72)	39 *vs.* 47†	PACU stay, hospital stay, intraoperative awareness, PONV, myocardial infarction, infection, sepsis, stroke, persistent pain, cancer recurrence (1 year), and death (1 year)
Shu *et al*[38]	China	Gynecologic laparoscopic	Sevoflurane (N/A)	64 (41)	64 (41.5)	30–40 *vs.* 50–60‡	MMSE scores (1 day)
Song *et al*[39]	USA	Laparoscopic tubal ligation	Sevoflurane (1.2% *vs.* 0.8%);	15 (27);	15 (28);	44 *vs.* 60*; 42 *vs.* 60*	Time to emergence, time to extubation, PACU stay, and intraoperative awareness
			Desflurane (1.5% *vs.* 0.7%)	15 (26)	15 (26)		
Soumpasis *et al*[40]	Greece	Major urological	Sevoflurane (3.2% *vs.* 0.9%)	30 (62)	30 (60)	20–30 *vs.* 50–60‡	Time to emergence, VAS pain scores (8 h, 24 h at rest and on movement), and rescue analgesia
Valentin *et al*[45]	Brazil	Non-cardiac and non-neurological	Propofol (1051–1093 mg *vs.* 855–931 mg)	40 (67.2)	32 (68.7)	38 *vs.* 49*	DNR (3 days, 7 days, 21 days), NCDs (90 days, 180 days), and SF-36 physical/mental scores (21 days, 180 days)
				36 (68.0)	32 (69.2)	36 *vs.* 46*	
Wong *et al*[41]	Canada	Orthopedic	Isoflurane (7.7 mL *vs.* 5.6 mL)	31 (70)	29 (71)	44 *vs.* 51*	Time to emergence, PACU stay, intraoperative awareness, and MMSE scores (30 min/60 min/90 min/120 min, 1 day/2 days/3 days)
Xu *et al*[51]	China	Hip arthroplasty	Propofol + sevoflurane (412 mg *vs.* 360 mg)	40 (72.2)	41 (74.3)	40–49 *vs.* 50–59‡	Time to extubation, PACU stay, DNR (3 h), MMSE score (3 h), and hypotension
Yang *et al*[46]	China	Laparoscopic nephrectomy	Propofol (N/A)	32 (49.7)	33 (51.4)	30–40 *vs.* 50–60‡	MMSE score (1 day)
Zhang and Nie[47]	China	Gynecologic laparoscopic	Propofol (N/A)	51 (36.6)	48 (37.0)	30–40 *vs.* 50–60‡	MMSE score (1 day)
Zhou *et al*[48]	China	Colon radical surgery	Propofol (N/A)	40 (68.9)	41 (68.3)	41 *vs.* 51*	POD, DNR (1–5 days), and hypotension

Data are shown as *n* (average age, years). *mean; †median; ‡range. AAI: Auditory evoked potential index; BIS: Bispectral index; DNR: Delayed neurocognitive recovery; MAC: Minimum alveolar concentration; MMSE: Mini-mental State Examination; N/A: not available; NCDs: Neurocognitive disorders; PACU: Post-anesthesia care unit; POD: Postoperative delirium; PONV: Postoperative nausea and vomiting; QoR: Quality of recovery; SF-12: Health Survey Short Form-12; SF-36: Health Survey Short Form-36; VAS: Visual analogue scale.

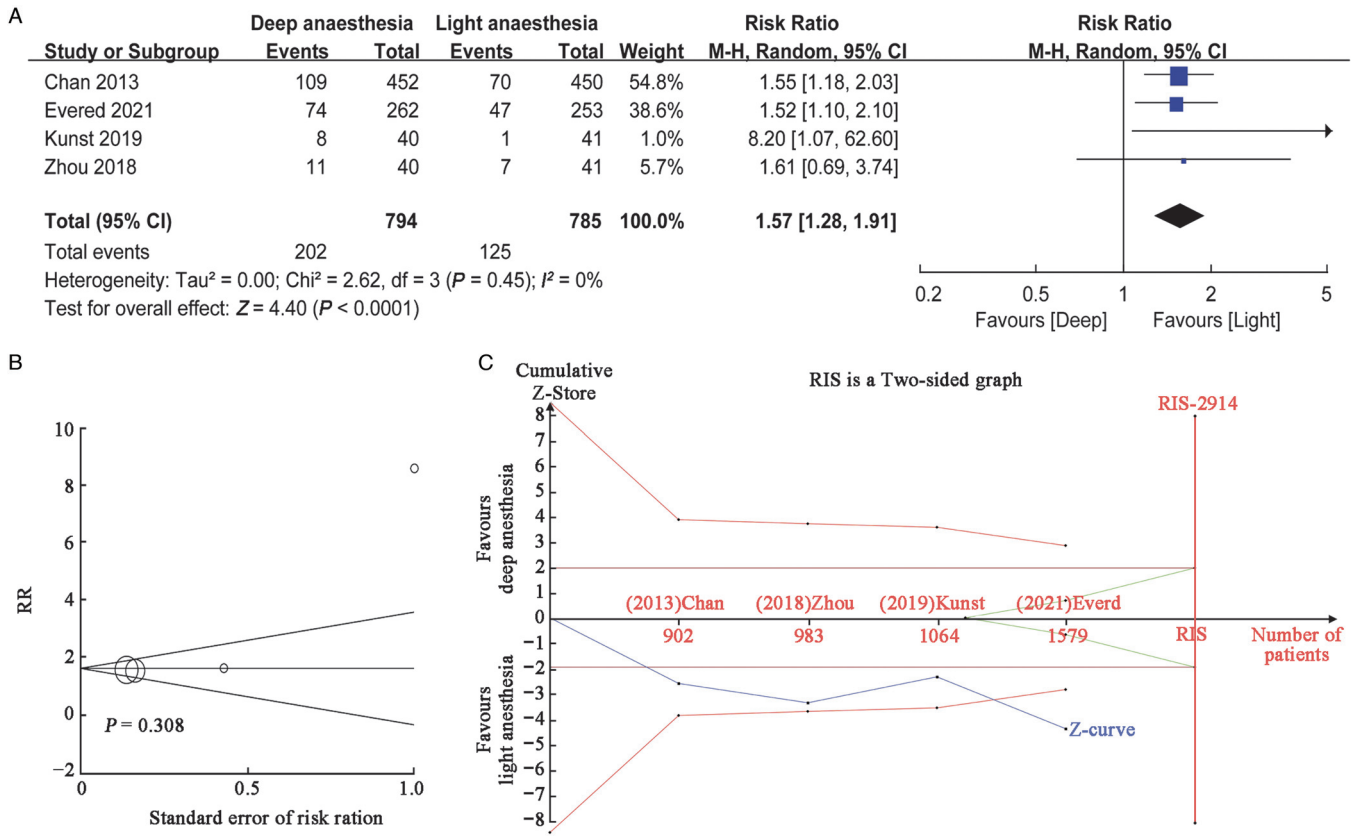

Figure 3: Deep *vs.* light anesthesia on the incidence of POD. (A) forest plot; (B) Begg's funnel plot; and (C) TSA. Red lines indicate the trial sequential monitoring boundary; green lines indicate the futility boundary; brown lines indicate the conventional benefit boundary; blue line is the Z-curve. CI: Confidence interval; M-H: Mantel-Haenszel; POD: Postoperative delirium; RIS: Required information size; RR: Risk ratio; TSA: Trial sequential analysis.

Secondary outcomes

For the secondary pain outcomes [Supplementary Table 4, http://links.lww.com/CM9/B335], the deep anesthesia group had lower VAS pain scores at rest at 8 h (WMD = −1.16, 95% CI = −1.74 to −0.57, $P = 0.0001$) and 24 h postoperatively (WMD = −0.50, 95% CI = −0.94 to −0.06, $P = 0.03$) and on movement at 8 h postoperatively (WMD = −1.25, 95% CI = −1.88 to −0.61, $P = 0.0001$). There were no between-group differences in VAS pain scores on movement at 24 h postoperatively, intraoperative sufentanil consumption, need for rescue analgesia, and persistent pain during 3–12 months postoperatively. For the secondary cognitive function outcomes [Supplementary Table 4, http://links.lww.com/CM9/B335], the two anesthesia groups were comparable in terms of the incidence of DNR during 1–7 days postoperatively (very low-quality evidence; Supplementary Table 5, http://links.lww.com/CM9/B335), NCD during 1–3 months postoperatively (moderate-quality evidence; Supplementary Table 5, http://links.lww.com/CM9/B335), MMSE scores on postoperative day 1, and MMSE scores during 3–5 days postoperatively.

Regarding postoperative recovery [Supplementary Table 4, http://links.lww.com/CM9/B335], the deep anesthesia group had prolonged time to emergence from anesthesia (WMD = 3.65 min, 95% CI = 1.94–5.36 min, $P < 0.0001$), time to extubation (WMD = 3.64 min, 95% CI = 1.39–5.90 min, $P = 0.002$), and orientation recovery time (WMD = 4.51 min, 95% CI = 1.61–7.40 min, $P = 0.002$). In addition, the deep anesthesia group had prolonged length of PACU stay (WMD = 5.85 min, 95% CI = 2.30–9.41 min $P = 0.001$; very low-quality evidence; Supplementary Table 5, http://links.lww.com/CM9/B335) and length of hospital stay (WMD = 1.00 day, 95% CI = 0.14–1.86 days, $P = 0.02$; low-quality evidence; Supplementary Table 5, http://links.lww.com/CM9/B335).

As for postoperative complications and mortality [Supplementary Table 4, http://links.lww.com/CM9/B335], there were no between-group differences in clinically significant hypotension, PONV, any major complication, myocardial infarction, sepsis, stroke, wound infection, intraoperative awareness, 1-year cancer recurrence, mortality within 30–90 days postoperatively, and 1-year mortality. Clinically significant hypotension which necessitated fluid and/or drug intervention was recorded in 23.8% (209/878) and 19.5% (172/881) of patients in the deep and light anesthesia groups, respectively. Two patients in the light anesthesia group experienced intraoperative awareness.

Subgroup analyses

Data on postoperative pain were reported from studies in non-cardiac surgery only. We conducted subgroup analyses for pain scores at different postoperative time points. The VAS pain scores at rest during 24 h postoperatively were significantly lower in the deep anesthesia group than that in

the light anesthesia group (WMD = −0.69, 95% CI = −0.97 to −0.40, $P < 0.0001$, I^2 = 31%), without statistically significant subgroup differences ($P = 0.210$; Supplementary Figure 2, http://links.lww.com/CM9/B334). The VAS pain scores on movement during 24 h postoperatively were also significantly lower in the deep anesthesia group than that in the light anesthesia group (WMD = −0.78, 95% CI = −1.26 to −0.30, $P = 0.002$, $I^2 = 43\%$), without statistically significant subgroup differences ($P = 0.110$; Supplementary Figure 3, http://links.lww.com/CM9/B334).

For the outcome of POD, the subgroup analysis according to cardiac and non-cardiac surgeries showed that deep anesthesia was associated with a higher incidence of POD after non-cardiac surgery (RR = 1.54, 95% CI = 1.26–1.89, $P < 0.0001$, $I^2 = 0\%$) and cardiac surgery (RR = 8.20, 95% CI = 1.07–62.6, $P = 0.04$), without significant subgroup differences ($P = 0.11$; Supplementary Figure 4, http://links.lww.com/CM9/B334).

Discussion

This meta-analysis included 26 RCTs with 10,743 patients to demonstrate the effects of deep *vs.* light anesthesia on postoperative pain, cognitive function, postoperative recovery, complications, and mortality. We found that deep anesthesia led to lower postoperative pain but a higher incidence of POD when compared with light anesthesia. The TSA results suggest that the current evidence is sufficient for the two primary outcomes. Based on the GRADE methodology, the level of evidence was moderate for the VAS pain scores and was high for POD. For the secondary outcomes, the deep anesthesia group had reduced pain up to 24 h postoperatively, prolonged recovery from anesthesia, and prolonged hospital stay, without between-group differences in the incidence of DNR, NCD during 1 to 3 months postoperatively, other major complications, or mortality.

Surgical patients experience a peak of acute postoperative pain during the first 24 h after surgery.[53,54] In our meta-analysis, deep anesthesia provided maximum pain relief at 8 h postoperatively, both at rest (a mean reduction of 1.16 points on the 0–10 VAS) and on movement (a mean reduction of 1.25 points). For these pain outcomes, we did not detect significant heterogeneity among the studies. Generally, these effects are not that large, but the comparable intraoperative sufentanil consumption suggested the differences were mainly attributable to the depth of anesthesia. A possible explanation is that general anesthetics such as sevoflurane and propofol attenuate noxious stimuli.[55-59] In addition, our previous meta-analysis did not support that propofol-based anesthesia significantly reduced postoperative pain than volatile-based anesthesia.[60] Therefore, it is the depth of anesthesia, other than the choice of general anesthetics, that plays a part in postoperative analgesic effects.

Perioperative NCD are often characterized by impairment in attention, memory, mental status, and psychomotor function in patients who are undergoing surgical procedures.[11,61] As a form of the acute event, POD typically occurs from hours to days after surgery, increasing the risks of morbidities and reducing the quality of daily living.[62,63] As for the effects of deep *vs.* light anesthesia on neurocognitive function after surgery, previous meta-analyses have yielded conflicting results.[14,64,65] Lu *et al*[14] investigated the association between anesthetic depth and postoperative cognitive impairment based on four studies. However, only one study was included for POD, comparing depth of sedation (BIS value of 50 *vs.* BIS values ≥80) during spinal anesthesia.[66] In our meta-analysis, we excluded studies on different depths of sedation, because we believed that pooling studies with sedation and those with general anesthesia would introduce significant heterogeneities. Miao *et al*[64] included nine RCTs to suggest that the use of BIS monitoring was not associated with reduced incidences of POD, DNR, and postoperative NCD in older patients. In their study, two trials had a mean difference of BIS values <5 between the BIS-guided and usual care groups.[67,68] In contrast, our meta-analysis included studies with clinically significant separation between BIS values between groups. Regarding long-term neurocognitive outcomes, a recent meta-analysis of 10 RCTs suggested that light *vs.* deep anesthesia was associated with a reduction in postoperative NCD at 90 days after surgery.[15] As the authors mentioned, their results should be treated with caution due to heterogeneity of outcome measures. In our present meta-analysis, we found no between-group differences in the incidences of DNR during 1–7 days postoperatively and NCD during 1 to 3 months postoperatively. We noted that the included studies used different neurocognitive tests, which introduced significant heterogeneities. Thus, more studies are required to investigate the impact of anesthesia depth on long-term postoperative neurocognitive function.

This meta-analysis has several limitations. First, the BIS targets in the deep and light anesthesia groups were not uniform among the included studies, which may have introduced heterogeneities. To better discriminate the deep and light anesthesia groups, we emphasized a mean between-group difference ≥5 in BIS values in our eligibility criteria. Second, the diagnosis of DNR or NCD during 1–3 months postoperatively was based on different neuropsychological tests, which may have confounded these results. Third, while the VAS pain outcomes and POD have a low heterogeneity, several outcomes (including DNR, postoperative recovery, length of PACU and hospital stays, hypotension, and any major complication) are significantly heterogenous, possibly due to different intravenous or inhalational anesthetics used, varied surgical procedures, and different patient populations. Fourth, individual patient data were not available for our meta-analysis. Finally, although there are moderate to high level of evidence for our primary outcomes, the numbers of included studies and patients are relatively small. Hence, we encourage further studies with a large sample size to ascertain these findings.

In conclusion, deep anesthesia compared with light anesthesia was associated with a moderately reduced pain during the early postoperative period but led to an increased incidence of POD. From the current evidence, the risks of maintaining deep anesthesia outweigh its benefits for patients undergoing surgical procedures.

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Conflicts of interest

None.

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