Review Article

Perioperative approaches to prevent delayed neurocognitive recovery and postoperative neurocognitive disorder in older surgical patients: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background and Aims: Delayed neurocognitive recovery (DNR) and postoperative neurocognitive disorder (P-NCD) are common postoperative complications affecting older patients. This review evaluates perioperative approaches for preventing DNR and P-NCD in older noncardiac surgical patients.

Material and Methods: We searched databases for relevant articles from inception through June 2022 and updated in May 2023 (PROSPERO ID CRD42022359289). Randomized controlled trials (RCTs) utilizing intervention for DNR and/or P-NCD were included.

Results: We included 39 RCTs involving anesthetic (25 RCTs, 7422 patients) and other pharmacological and nonpharmacological approaches (14 RCTs, 2210 patients). Seventeen trials investigating four interventions were included in the meta-analysis for DNR. Perioperative dexmedetomidine (relative risk [RR]: 0.59, 95% confidence interval [CI]: 0.35–0.97; $P = 0.04$) and propofol-based total intravenous anesthesia (TIVA) (RR: 0.81, 95% CI: 0.66–0.98; $P = 0.03$) significantly decreased the risk of DNR versus control. There was no significant decrease in the risk of DNR with regional anesthesia (RA) versus general anesthesia (GA) (RR: 0.89, 95% CI: 0.63–1.26) or bispectral index (BIS) monitoring (RR: 0.79, 95% CI: 0.60–1.04) versus the control groups. Evidence regarding the effects of interventions on P-NCD is limited. Although all included trials were at low risk of bias, the quality of meta-analysis pooled estimates was low.

Conclusions: Our meta-analysis of RCTs showed that dexmedetomidine and TIVA decrease the risk of DNR in older patients undergoing noncardiac surgery by 41% and 20%, respectively, versus control. Further RCTs of adequate power and methodology on the effects of interventions on DNR and P-NCD are warranted.

Keywords: Anesthesia, delayed neurocognitive recovery, older patients, postoperative neurocognitive disorder, surgery

Key Messages: Our meta-analysis of RCTs showed that dexmedetomidine and TIVA decrease the risk of DNR in older patients undergoing noncardiac surgery by 41% and 20%, respectively, versus controls, whereas RA and BIS monitoring do not.

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Introduction

Our population is rapidly aging. By 2030, one in six people will be 60 years or older.[1] Older adults represent 10% of the world's population, but account for 50% of surgeries.[2,3] Older surgical patients are at a higher risk of developing postoperative complications due to preexisting medical conditions and exaggerated proinflammatory states.[4] One possible complication is cognitive decline postsurgery, which is of major concern to older adults.

Historically, "postoperative cognitive dysfunction" has been used to describe any cognitive impairment (CI) postsurgery. In 2018, the Nomenclature Consensus Working Group refined this definition.[5] The group recommended "postoperative cognitive dysfunction" to be part of perioperative neurocognitive disorders (PNDs), which are defined as "CI or change identified in the preoperative or postoperative period." PND consists of 1) preoperative CI, 2) postoperative delirium (POD), 3) delayed neurocognitive recovery (DNR), CI during the first 30 days postsurgery, and 4) postoperative neurocognitive disorder (P-NCD), CI occurring between 30 days and 1-year postsurgery.[4] While DNR signifies a temporary decline in cognitive function that occurs shortly after surgery, P-NCD suggests a more prolonged decline, emerging beyond the immediate postoperative period. Although POD is classified in the category of PND, it is a unique clinical syndrome with specific criteria like fluctuating attention and mental status.[4]

About 5%–55% of older patients undergoing major noncardiac surgeries experience DNR and P-NCD.[6] This large percentage range is explained by differences in statistical thresholds to define PND.[6] DNR and P-NCD are associated with increased postoperative complications, including functional decline, and increased mortality and morbidity.[7] The high prevalence and risks of complications make DNR and P-NCD a target for prevention and intervention.

Perioperative approaches such as dexmedetomidine and bispectral index (BIS) monitoring for the prevention of DNR and P-NCD have been reported in systematic reviews and meta-analyses.[8,9] A meta-analysis of eight randomized controlled trials (RCTs) revealed that dexmedetomidine was associated with a significantly reduced risk of postoperative cognitive decline in older surgical patients compared to controls with a risk ratio (RR) of 0.47 ($P < 0.001$).[8] A meta-analysis of 10 RCTs found that light compared to deep anesthesia showed significantly lower incidence of postoperative cognitive decline on day 1 with an RR of 0.14 ($P > 0.10$) and on day 90 with an RR of 0.7 ($P > 0.10$).[9] The evidence is insufficient to support or disprove the effect of depth of anesthesia on postoperative cognitive decline.[9]

While there is a growing body of literature exploring diverse perioperative approaches to prevent DNR and P-NCD, a comprehensive synthesis of studies on dexmedetomidine versus placebo, total intravenous anesthesia (TIVA) versus inhalational anesthesia, depth of anesthesia, and regional anesthesia (RA) versus general anesthesia (GA) in a systematic review and meta-analysis is absent. Our systematic review and meta-analysis of RCTs is aimed to assess different anesthetic and other pharmacological and nonpharmacological techniques, to prevent DNR and P-NCD in older patients undergoing noncardiac surgery. Our review seeks to bridge this gap and provide a comprehensive overview on perioperative approaches to prevent DNR and P-NCD in older surgical patients. It provides a foundation that can guide clinicians in implementing effective strategies to mitigate PNDs, thereby improving patient outcomes.

Material and Methods

This systematic review and meta-analysis protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022359289). It followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines.[10]

Search strategy

Comprehensive, structured literature searches were conducted by an information specialist (ME) on June 7, 2022, using OVID for MEDLINE, MEDLINE In-Process/ePubs, Embase/Embase Classic, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials; ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were also searched. Preliminary searches were conducted, and full-text literature was mined for potential keywords and appropriately controlled vocabulary terms (such as Medical Subject Headings for MEDLINE). The Yale MeSH Analyzer was used to assess target citations.[11] The search strategy concept blocks were built on the topics of "Cognitive Impairment" AND "Non-Cardiac Surgery" AND "Elderly" AND "Randomized Controlled Trials," with each component being fleshed out with controlled vocabularies, text word terms, and synonyms. Results were limited to English studies, humans, and adults, and conference abstracts were removed at source, where possible.

Supplemental searching was conducted by team members using citation search via Google Scholar, PubMed, and the reference lists of included studies to identify any additional articles missed in the initial yield. In addition, continued

literature surveillance was conducted until May 2023 to ensure that we followed the most updated literature.

Inclusion and exclusion criteria

The inclusion criteria were 1) studies having patients aged ≥60 years undergoing noncardiac surgery, 2) studies in which patients receive intervention for DNR and/or P-NCD, 3) RCTs with a comparator group and sample size of ≥100 patients, 4) studies with outcomes of DNR and/or P-NCD, and 5) English language articles. The exclusion criteria were 1) studies with nonsurgical or ICU patients, 2) studies examining only delirium (no DNR and/or P-NCD outcomes), and 3) studies with overlapping or duplicate data.

Study selection and data extraction

Title, abstract, and full-text screening was performed by two reviewers (YA, WL) independently on an online review platform, Rayyan.[12] Disagreements were resolved by discussion and consensus between the two reviewers or by a third reviewer (EY). Data were extracted by two independent reviewers (YA, WL) and summarized into Excel spreadsheets.

Risk of bias assessment

Trials were assessed using the Cochrane risk-of-bias tool by two independent reviewers (WL, ZE), and conflicts were resolved by discussion with a third reviewer (YA).[13] The traffic plots were generated using the robvis package on R.[14]

Statistical analysis

We conducted qualitative and quantitative analyses. The qualitative analysis consisted of descriptions of study characteristics and DNR and P-NCD outcomes. We also performed a meta-analysis of the interventions to prevent DNR compared to controls. Due to the small number of trials examining P-NCD and its heterogenous assessment time points, we could not conduct a meta-analysis evaluating interventions for it.

Dichotomous data were extracted and summarized as RRs and 95% confidence intervals (CIs). We calculated the predictive interval, absolute risk reduction (ARR), and number needed to treat (NNT) with 95% CI. Analysis was performed using the Review Manager Software (version 5.3; RevMan, Copenhagen, Denmark). A random effects analysis was chosen over fixed effects analysis to model the amount of between-study heterogeneity. Heterogeneity was quantified by the Chi-square test and by calculating I^2 according to the method reported by Higgins *et al.*[15] Publication bias was explored using the visual inspection of funnel plots and from Begg's and Egger's tests. All reported P values were two-sided, and a $P < 0.05$ was considered statistically significant. Overall, the certainty of the evidence was assessed using the GRADE approach.

Results

Search strategy

A total of 15,335 articles were identified from the databases [Figure 1a]. After removing duplicates, title and abstract screening, and citation review, 74 full texts were assessed for eligibility. Thirty-eight trials were excluded due to study design, age, nonsurgical patients, etc. With two additional trials from citation search and one from an updated search of databases [Figure 1b], 39 trials were included for qualitative analysis and 17 for meta-analysis.[16–54]

Study characteristics

Demographic data and study characteristics are presented in S-Tables 1 and 2. Trials were conducted in Asia (n = 32), Europe (n = 5), South America (n = 1), and Australia (n = 1). The trials were stratified based on the perioperative approaches: 1) anesthetic techniques and approaches [S-Table 1] and 2) other pharmacological and nonpharmacological approaches [S-Table 2].

Anesthetic techniques and approaches comprised 25 trials with 7422 patients. These included TIVA versus inhalational anesthesia (n = 6),[16–21] RA versus GA (n = 6),[22–26] anesthesia depth (n = 4),[27–30] dexmedetomidine (n = 6),[31–37] and analgesics (n = 3).[38–40] The mean age was 70 ± 7 years, and 41% were female.

Fourteen trials with 2210 patients consisted of other pharmacological approaches (n = 9)[41–49] and nonpharmacological approaches (n = 5).[50–54] The mean age was 73 ± 7 years, and 51% were female.

Risk-of-bias assessment

According to the Cochrane risk-of-bias assessment, 16 trials had an unclear overall risk of bias and 11 trials had a high risk of bias [Figure 2, S-Figure 1].

Measures and assessment time points of DNR and P-NCD

Most trials incorporated more than one validated cognitive assessment tool for DNR and P-NCD assessment (n = 26),[16–23,25–30,34,36,38–40,42,45,47,48,51–53] with the most common being the Mini-Mental State Examination (MMSE) (n = 20) [S-Tables 3 and 4].[17,18,24–26,30–33,35–37,41,43–47,49,54] Other notable assessment tools included the Digit Symbol Substitution Test (DSST) (n = 11)[16,18,19,25,29,34,36,39,40,47,48] and the Stroop Color and Word Test (SCWT) (n = 9) [S-Tables 3 and 4].[16,20,22,27,34,36,38,48,53]

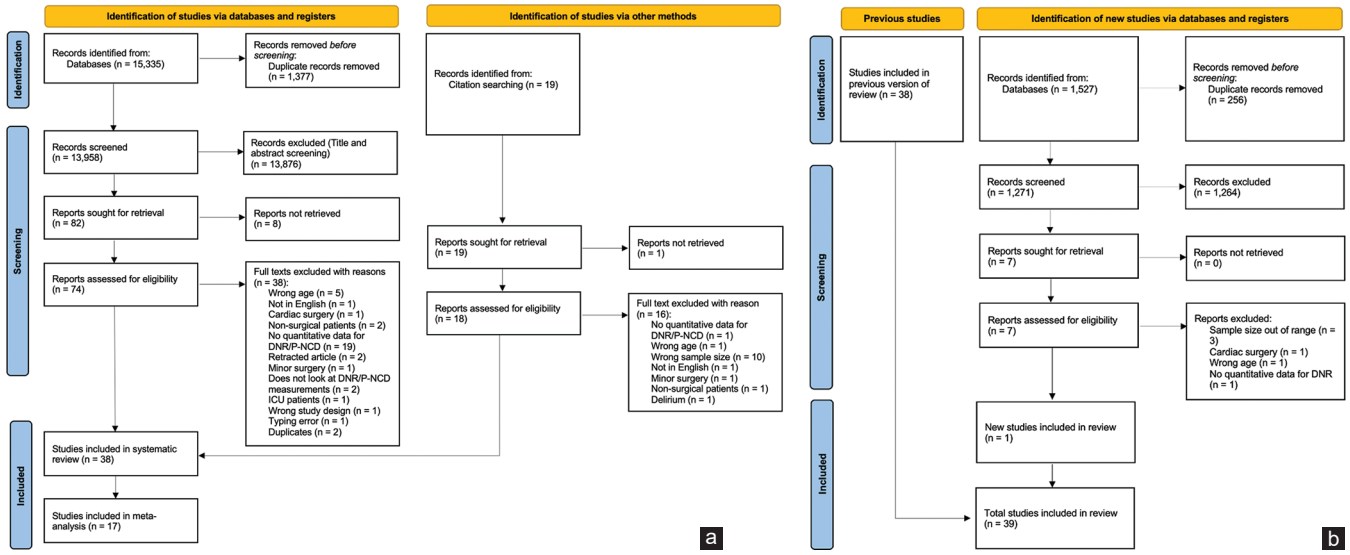

Figure 1: PRISMA flow diagram. (a) Original PRISMA flow diagram. (b) Updated PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic review and Meta-Analyses

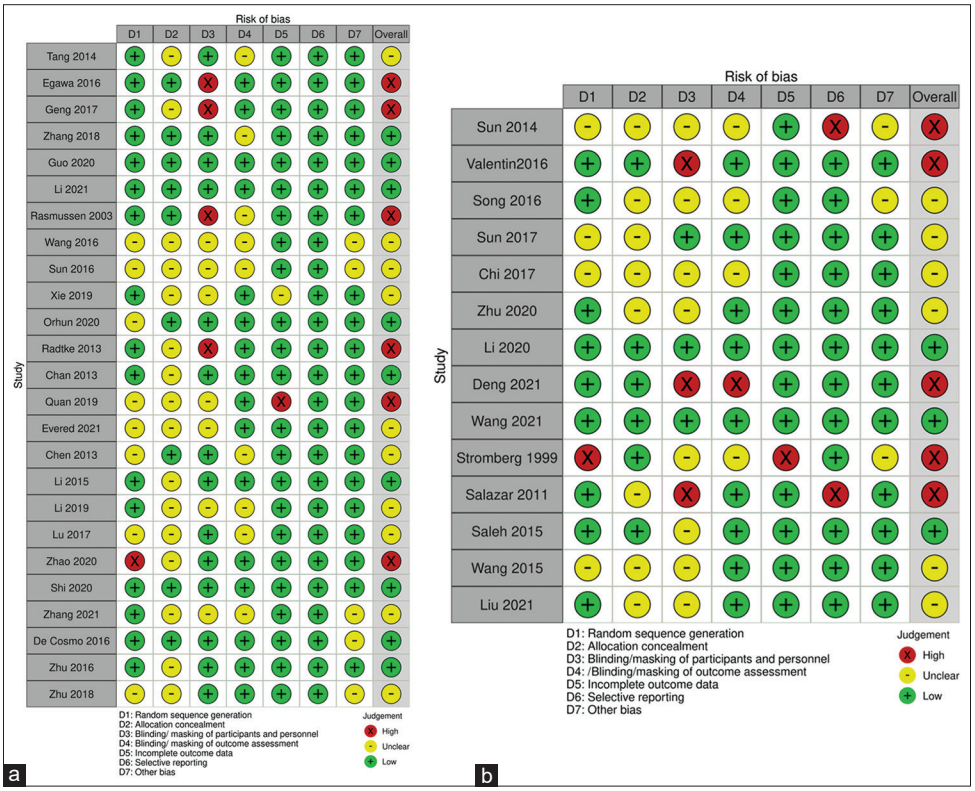

Figure 2: Risk of bias among the studies. (a) Risk of bias for studies in anesthetic techniques and approaches. (b) Risk of bias for studies in other pharmacological and non-pharmacological approaches

Twenty-eight trials assessed cognitive performance on day 7, 12 at 3 months, and two at 1 year [S-Tables 5 and 6]. Other time points included day 1 (n = 14) and day 3 (n = 9).

Meta-analysis on DNR

Seventeen trials (5409 patients) were included in the meta-analysis, investigating the effects of TIVA,[16,17,19–21] RA,[22,23,26] BIS-guided monitoring,[27–29] and dexmedetomidine.[31–33,35–37] Table 1 summarizes the data on the effect of the anesthetic interventions on the incidence of DNR and the quality of evidence rating using the GRADE approach.

Five trials assessed the risk of DNR after TIVA.[16,17,19–21] One study used propofol 1.5–2 mg/kg,[16] another used a

Table 1: Summary of Findings: The quality of evidence ratings according to the GRADE approach for DNR in patients undergoing noncardiac surgery

Intervention	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Predictive interval	Adjusted risk reduction, % (95% CI)	Number needed to treat (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with (control)	Risk with (intervention)							
TIVA	246 per 1000	200 per 1000 (163–241)	RR 0.81 (0.66–0.98)	0.59–1.10	4.95 (0.55–9.35)	21 (11–182)	1364 (5 RCTs)	⊕⊕◯◯ Low[b,c]	TIVA may decrease the risk of DNR in older patients undergoing noncardiac surgery. However, we are uncertain
RA	282 per 1000	251 per 1000 (177–355)	RR 0.89 (0.63–1.26)	0.02–26.50	2.70 (-3.90 to 9.30)	37 (+10 to -25)	686 (3 RCTs)	⊕⊕◯◯ Low[b,c]	RA may decrease the risk of DNR in older patients undergoing noncardiac surgery. However, we are uncertain
BIS monitoring	197 per 1000	156 per 1000 (118–205)	RR 0.79 (0.60–1.04)	0.04–13.40	3.50 (0.25–6.90)	28 (14–397)	2043 (3 RCTs)	⊕⊕◯◯ Low[b,c]	BIS may decrease the risk of DNR in older patients undergoing noncardiac surgery. However, we are uncertain
Dexmedetomidine	242 per 1000	143 per 1000 (85–235)	RR 0.59 (0.35–0.97)	0.11–2.90	10.5 (5.80–15.30)	10 (6–17)	1095 (6 RCTs)	⊕⊕◯◯ Low[b,c]	Dexmedetomidine may decrease the risk of DNR in older patients undergoing noncardiac surgery. However, we are uncertain

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [b]Different surgical procedure and different duration of anesthesia. [c]Predictive intervals not significant. BIS=bispectral index, CI=confidence interval, RA=regional anesthesia, RR=risk ratio, TIVA=total intravenous anesthesia. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

target-controlled infusion of 3–4 μg/ml of propofol,[17] one maintained an infusion of 50–150 μg/kgmin of propofol,[21] and the remaining did not provide dosage information.[19,20] Pooled evidence showed that TIVA significantly decreased the risk of DNR versus inhalational anesthesia (19.6% vs. 24.6%; relative risk [RR], [95% confidence interval {CI}: 0.81 {0.66–0.98}], I^2: 0%; $P = 0.03$) [Table 1, Figure 3]. The funnel plot suggests the absence of publication bias [S-Figure 2a].

Three trials compared the risk of DNR between RA and GA, where RA was employed as either spinal anesthesia (SA) or epidural anesthesia (EA) ± epidural analgesia.[22,23,26] Pooled estimates showed that RA did not significantly reduce the risk of DNR compared to GA (25.4% vs. 28.1%; RR [95% CI]: 0.89 [0.63–1.26], I^2: 45%; $P = 0.50$) [Table 1, Figure 3]. S-Figure 2b suggests the absence of publication bias.

The meta-analysis evaluated three trials on the risk of DNR with BIS monitoring.[27–29] Two trials used intraoperative BIS-guided management[27,28] and the remaining compared different BIS target values: 30–45 for deep anesthesia and 45–60 for light anesthesia.[29] BIS-guided management or light anesthesia did not significantly decrease the risk of DNR compared to control (16.1% vs. 19.7%; RR [95% CI]: 0.79 [0.60–1.04], $I^2 = 44\%$; $P = 0.1$) [Table 1, Figure 3]. The funnel plot suggests the absence of publication bias [S-Figure 2c].

Six trials on dexmedetomidine included in the meta-analysis varied considerably in methods and drug dosage [S-Table 1].[31–33,35–37] Pooled estimates showed that dexmedetomidine significantly decreased the risk of DNR compared to placebo (13.5% vs. 24.1%; RR [95% CI]: 0.59 [0.35–0.97], I^2: 69%; $P = 0.04$) [Table 1,

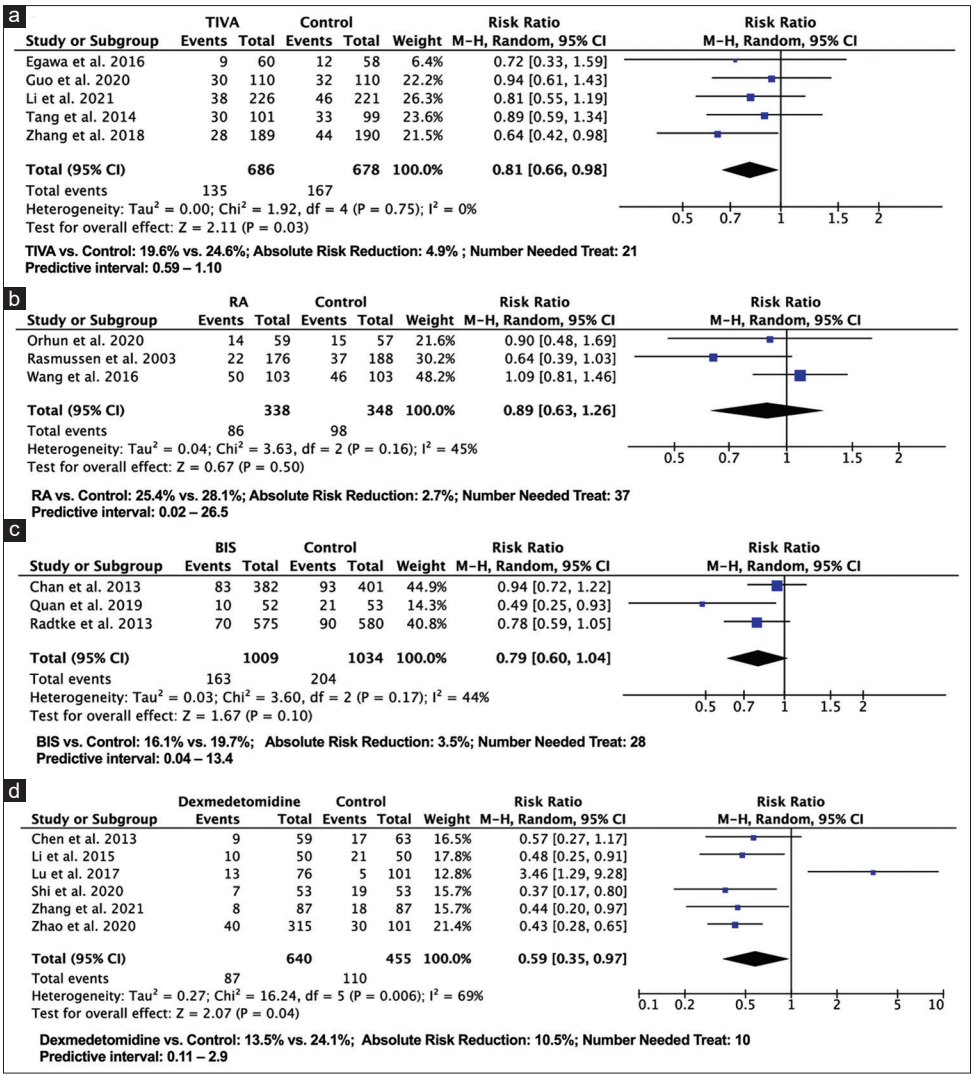

Figure 3: Forest plot for pooled incidence of DNR across different anesthetic interventions. BIS = bispectral index, DNR = delayed neurocognitive recovery, C = confidence interval, TIVA = total intravenous anesthesia, M-H = Mantel-Haenszel

Figure 3]. The funnel plot suggests the presence of one outlier [S-Figure 2d].[33] After removal of this outlier, the effect estimate decreased from 0.59 to 0.45, 95% CI narrowed (0.34–0.59), heterogeneity decreased from 69% to 0%, and the *P* value decreased from 0.04 to <0.00001.

All trials included were RCTs with some or no concerns with their quality of evidence [Table 1]. To assess imprecision, the effect estimates of the relative interventions lower than one and greater than one were considered clinically significant. The data published in the literature were collected from different clinical settings and countries at varying time intervals, and our meta-analysis model showed some incoherence. Overall, the interventions were rated down for imprecision, heterogeneity, and incoherence (inconsistency); thus, the quality of evidence for the effect estimates was low using the GRADE approach.

Qualitative analysis results

Among the anesthetic techniques and approaches [Table 2, S-Table 5], two trials showed no significant difference in the incidence of P-NCD at 3 months between TIVA and inhalational anesthesia groups.[17,20] For anesthesia depth, one study found a lower incidence of P-NCD at 3 months in BIS-guided than non–BIS-guided anesthesia [Table 2, S-Table 5].[28] Another trial detected no significant difference,[27] but one found reduced P-NCD at 1 year in the lighter (BIS 50) versus deeper (BIS 35) anesthetic group.[30] Finally, two trials studying cyclooxygenase-2 (COX-2) inhibitors found no significant reduction of P-NCD at 3 months [Table 2, S-Table 5].[39,40]

Among the other pharmacological approaches [Table 3, S-Table 6], various medications and nonmedications were investigated in single studies. These medications demonstrated

Table 2: Major findings of DNR and P-NCD in anesthetic techniques and approaches

First author year	Type of surgery (number of patients)	Comparison groups	Major findings
TIVA			
Tang 2014	GI (200)	TIVA propofol versus sevoflurane	DNR between groups NS Severe DNR lower in propofol (P=0.01)
Egawa 2016	Lung (144)	TIVA propofol versus sevoflurane	NS
Geng 2017	GI (150)	TIVA propofol versus sevoflurane versus isoflurane	DNR lower in propofol versus isoflurane on D1, 3 (P<0.001) DNR lower in propofol versus sevoflurane on D1 (P=0.012), D3 (P=0.013) DNR lower in sevoflurane versus isoflurane D1 (P=0.041), D3: NS
Zhang 2018	Mixed (387)	Propofol infusion versus sevoflurane	DNR lower in propofol (P=0.038)
Guo 2020	Mixed (234)	Propofol versus sevoflurane	NS
Li 2021	GI (447)	Propofol infusion versus sevoflurane	NS
RA			
Rasmussen 2003	Mixed (428)	RA versus GA	NS
Wang 2016	Mixed (206)	SA + epidural + epidural analgesia versus GA + IV analgesia	NS
Sun 2016	Orthopedic (193)	Epidural versus GA	D1: DNR lower in epidural anesthesia (P<0.05) D3: NS
Xie 2019	Thoracic (120)	TPVB-GA versus epidural block-GA versus GA	DNR lower in TPVB-GA and epidural-GA versus GA (P<0.05)
Orhun 2020	Mixed (116)	Epidural analgesia + GA versus GA	NS
Anesthesia depth			
Radtke 2013	Mixed (1155)	BIS guided versus BIS blinded	NS
Chan 2013	Mixed (902)	BIS guided versus routine care	D7: NS 3 m: P-NCD lower in BIS-guided group (P=0.02)
Quan 2019	GI (120)	BIS 30–45 versus BIS 45–60	D7: DNR lower in BIS 30–45 (P=0.032) 3 m: NS
Evered 2021	Mixed (515)	BIS 35 versus BIS 50	1 m: NS 1 year: P-NCD lower in BIS-50 (P<0.001)
Dexmedetomidine			
Chen 2013	GI (122)	Dex versus control	NS
Li 2015	GI (100)	Dex versus control	D1: mild DNR lower in dex (P=0.026)
Lu 2017	Orthopedic (152)	PCA dex versus PCA without dex	DNR lower in PCA with dex versus without dex within D7
Li 2019	Orthopedic (164)	Dex versus propofol versus midazolam	D7: DNR lower in propofol versus dex (P=0.012) and midazolam (P<0.001) 1 year: NS
Zhao 2020	Mixed (416)	PCA dex 0 versus 100 μg versus 200 μg versus 400 μg	Dex 200 and 400 μg lower DNR versus Dex 0 and 100 μg within D7 (P<0.05) Dex 200 μg lower DNR versus Dex 0 μg D1–3 (P<0.01) Dex 400 μg lower DNR versus Dex 0 μg on D1–3, 7 (P<0.05) Dex 200 and 400 μg lower DNR versus Dex 100 μg D1–3, 7 (P<0.05) Dex 400 μg group lower DNR versus Dex 200 μg group within D7 (P=0.04)
Shi 2020	Thoracic (106)	Dex versus control	DNR lower in dex within D7 (P=0.006)
Zhang 2021	Mixed (174)	Dex versus control	DNR lower in dex (P=0.038)
Analgesics			
De Cosmo 2016	GI (571)	Remifentanil versus fentanyl	NS
Zhu 2016	Orthopedic (122)	Parecoxib versus control	D7: DNR lower in parecoxib (P<0.05) 3 m: NS
Zhu 2018	Orthopedic (178)	Celecoxib versus control	D7: DNR lower in celecoxib (P<0.001) 3 m: NS

Mixed surgery: spinal, urological, gastrointestinal, rectal, thoracic, general, genitourinary, gynecologic, orthopedic, gastric, colon, colorectal, head and neck, vascular, otorhinolaryngological, oral and maxillofacial, cancer, and others. BIS=bispectral index, Dex=dexmedetomidine, DNR=delayed neurocognitive recovery, GA=general anesthesia, GI=gastrointestinal, NS=not significant, PCA=patient-controlled analgesia, P-NCD=postoperative neurocognitive disorder, RA=regional anesthesia, SA=spinal anesthesia, TIVA=total intravenous anesthesia, TPVB=thoracic paravertebral block

a role in decreasing DNR incidence when administered in various doses,[41–43,45–49] except methoxamine which increased the incidence of DNR when infused.[44]

For nonpharmacological trials [Table 3, S-Table 6], variable ventilation (defined as a ventilatory mode distinguished by the oscillation of one or more respiratory parameters, which aims to mimic variability seen in physiological ventilation and the natural pattern of breathing) reduced the incidence of DNR versus mechanical ventilation,[53] whereas intraoperative warming increased DNR.[51] Interestingly, three 1-h sessions of preoperative cognitive training significantly reduced DNR on day 7 after surgery.[52]

Postoperative outcomes associated with interventions

Among six trials that examined mortality from hospitalization up to 1 year postoperatively,[19,20,22,27,29,50] only one found a slight decrease in overall 3-month mortality with RA versus GA (0.0% vs. 1.8%, $P = 0.05$).[22]

Eighteen trials assessed the effects of interventions on hospital length of stay (LOS).[19–21,26–29,39,40,45–47,49–53,55] Only one study found a significantly shorter LOS of the scopolamine group than the control group (4.4 ± 2.8 vs. 7.3 ± 1.7 days, $P < 0.05$).[45]

Nine trials reported on POD.[21,22,27,28,30,35,36,48,53] In contrast to GA and RA,[22] POD incidence was significantly reduced in BIS-guided than non–BIS-guided surgeries in two studies (16.7% vs. 21.4%, $P = 0.036$ and 15.6% vs. 24.1%, $P = 0.01$, respectively).[27,28] Also, a significant reduction was found in lighter (BIS-50) than deeper BIS targets (BIS-35) (18.6% vs. 28.2%, $P = 0.01$).[30] POD was not significantly reduced with different dexmedetomidine infusions.[35,36] However, IV infusion of methylene blue after anesthetic induction significantly reduced POD versus saline (7.3% vs. 24.2%, $P < 0.001$).[48] Also, a significant reduction was found with variable compared to conventional ventilation during open abdominal surgeries (16.5% vs. 28.9%, $P = 0.036$).[53]

Table 3: Major findings of DNR and P-NCD in other pharmacological and nonpharmacological approaches

First author year	Type of surgery (number of patients)	Comparison groups	Major findings
Other pharmacological interventions			
Sun 2014	Orthopedic (124)	Dobutamine 2 versus 4 versus 6 μg/kg min versus control	D1, 3: DNR lower in dobutamine 2 and 4 μg/kg min versus control ($P<0.05$)
Valentin 2016	Mixed (140)	Dexamethasone versus control (BIS 35-45 and BIS 46–55 for each group)	D3: DNR lower in dexamethasone versus control in both BIS levels
Song 2016	Spinal (120)	Edaravone versus control	D1: DNR lower in edaravone ($P<0.05$)
Sun 2017	Orthopedic (300)	Methoxamine 2 versus 3 versus 4 μg/kg min versus control	DNR higher in methoxamine 4 μg/kg min versus all other groups within D7
Chi 2017	Urological (142)	Scopolamine versus control	DNR lower in scopolamine versus control ($P<0.05$)
Zhu 2020	Mixed (120)	Neostigmine 0.04 versus 0.02 mg/kg versus control	DNR lower in both neostigmine 0.04 and 0.02 mg/kg versus control ($P=0.013$)
Li 2020	Thoracic (120)	Nalmefene 1 versus 5 μg/kg versus control	DNR lower in both nalmefene 1 and 5 μg/kg versus control ($P<0.05$)
Deng 2021	Mixed (248)	Methylene blue versus control	D7: DNR lower in intraop methylene blue ($P<0.001$)
Wang 2021	Mixed (120)	Probiotics versus control	DNR lower in probiotics ($P=0.046$)
Nonpharmacological interventions			
Stromberg 1999	Orthopedic (223)	Reorientation measures versus control	NS
Salazar 2011	Orthopedic (150)	Intraop warming versus standard	D4: DNR higher in warmed group (>36°C) versus standard ($P=0.0058$) 3 m: NS
Saleh 2015	GI (141)	Cognitive training versus control	D7: DNR lower in cognitive training versus control ($P=0.007$)
Wang 2015	GI (162)	Variable versus mechanical ventilation	D7: DNR lower in the variable versus conventional ventilation ($P=0.045$)
Liu 2021	GI (100)	TEAS versus control	NS

Mixed surgery: spinal, urological, gastrointestinal, rectal, thoracic, general, genitourinary, gynecologic, orthopedic, gastric, colon, colorectal, head and neck, vascular, otorhinolaryngological, oral and maxillofacial, cancer, and others. BIS=bispectral index, DNR=delayed neurocognitive recovery, GI=gastrointestinal, intraop: intraoperative, NS=not significant, P-NCD=postoperative neurocognitive disorder, TEAS, transcutaneous electrical acupoint stimulation

Discussion

We included 39 RCTs in our systematic review and meta-analysis to evaluate the effects of different perioperative interventions in preventing DNR and P-NCD in older noncardiac surgical patients. We found that dexmedetomidine had the highest risk reduction of 41% for DNR versus placebo. Also, propofol-based TIVA significantly decreased DNR by almost 20% compared to inhalational anesthesia. Conversely, RA did not significantly reduce the risk of DNR compared to GA. Also, BIS-guided management or light anesthesia did not significantly decrease the risk of DNR compared to controls. Qualitative analysis found no significant reduction in P-NCD for TIVA and COX-2 inhibitors, whereas BIS monitoring provided contradicting results, making it not possible to draw a conclusive association. There are limited data on whether these interventions influence postoperative outcomes such as mortality, LOS, and POD.[22,27,28,30,45,48,53] POD incidence was significantly reduced in BIS-guided than non–BIS-guided surgeries in two studies.[27,28] Also, a significant reduction was found in lighter (BIS-50) than deeper BIS targets (BIS-35) in another study.[30]

Anesthetic techniques and approaches

Surgery and anesthesia increase inflammatory markers such as S-100β and tumor necrosis factor-alpha (TNF-α), which are also elevated in neurocognitive disorders, demonstrating the role of the proinflammatory pathway in nerve damage and cognitive dysfunction.[19] Propofol has been shown to lower the levels of circulating inflammatory cytokines, which could be a possible explanation for its neuroprotective effects compared to inhalational anesthetics.[56,57] Experimental animal model studies also suggested potential neurotoxic effects of inhalational anesthetics through increasing mediators of pathways that induce inflammation and apoptosis.[58] Our meta-analysis showed that propofol-based TIVA significantly lowered the incidence of DNR.[16,17,19–21] However, our qualitative review on P-NCD showed no significant difference.[17,20] TIVA propofol may be beneficial in lowering the risk of DNR, but more research is needed for P-NCD.

Lack of systemic anesthetic exposure may decrease the likelihood of CI postoperatively.[57] Unlike GA, EA and SA do not cross the blood–brain barrier to exert potential toxic changes in the brain.[59] Also, peripheral nerve blocks (PNBs) help attenuate sympathetic activation by blocking the response to surgical stimuli at the operative site, reducing inflammatory marker production.[60] To date, the optimal technique to prevent CI remains unclear. One systematic review found no difference between RA and GA in postoperative CI,[61] whereas another reported reduced CI using PND in total hip or knee arthroplasty.[62] Our meta-analysis showed that RA did not significantly decrease the risk of DNR.[22,23,26] Only one study investigated P-NCD, and no significant differences were observed.[22] Further research is warranted on the role of RA in reducing DNR and P-NCD.

BIS monitoring has been shown to improve anesthetic delivery and surgical recovery.[63] However, artifacts from electrocautery, electrocardiographic, and electromyographic monitoring can affect signal processing and lead to BIS misinterpretations.[64,65] Nonetheless, practice guidelines from the ASA Brain Health Initiative support the general use of BIS monitors in older adults, as individual RCTs confirmed their effectiveness in reducing postoperative cognitive decline.[66] A previous systematic review found a reduction of DNR, P-NCD, and POD with BIS-guided anesthesia, yet results are limited by heterogeneity and a smaller number of studies.[65] Our meta-analysis showed that BIS-guided management or light anesthesia did not significantly decrease the risk of DNR.[27–29] Our qualitative analysis found the same results on P-NCD.[27,28,30] In addition, whether light or deep anesthesia reduces P-NCD remains inconclusive.

Dexmedetomidine is a selective α_2 adrenoreceptor agonist with anxiolytic, analgesic, sedative, and antisympathetic effects, as well as neuroprotective effects in the older population.[67,68] Consistent with a recent meta-analysis, which concluded that dexmedetomidine is significantly associated with better neurocognitive function postoperatively, we found that dexmedetomidine significantly reduced the incidence of DNR versus control.[67] Dexmedetomidine has been investigated in its effects on POD, with one RCT that examined intraoperative dexmedetomidine infusion versus placebo finding no difference in POD.[69] Another found a low dose of dexmedetomidine from admission until day 1 decreased POD, potentially suggesting the importance of its timing and dose in prevention.[70]

As anti-inflammatory analgesics, COX-2 inhibitors may prevent DNR and P-NCD by reducing inflammation in the central nervous system.[71–73] We found a significant reduction in DNR in two trials.[39,40] Further work is needed in this area.

Although both RA versus GA and BIS monitoring/light anesthesia versus control did not significantly decrease the risk of DNR, both RRs were less than 1, indicating that these interventions may decrease the risk of DNR. We were able to include only three studies for each of RA versus GA and BIS monitoring/light anesthesia versus control. If there were more studies or a larger sample size, the overall RR might have been significant.

Assessment timelines

Multiple screening tools were used to examine DNR and P-NCD. Different assessment time points can influence the type of CI assessed. Screening tests to detect DNR are commonly performed on postoperative day 7, while tests for P-NCD are performed at 3 months and 1 year postsurgery.[4,55] Screening too early (i.e., before day 7 postsurgery) could misdiagnose POD, defined as temporary variations in cognitive function, attention, and awareness, with DNR, leading to an inaccurate incidence for both conditions.[55,74–76] POD usually occurs and is assessed during the initial week postsurgery or until the patient is discharged, which is around the same time that DNR is assessed.[76] While multiple instruments exist to detect POD, the most common is the Confusion Assessment Method (CAM).[76] Other factors such as sleep deprivation and pain could also undermine these tests to examine DNR and P-NCD.[75]

Limitations

Our study is not exempt from potential limitations. First, limited trials exist on the different techniques. Second, we could not perform a meta-analysis to investigate the effects of interventions on P-NCD due to heterogeneity across trials. Third, most trials were done on the older Asian population, potentially affecting the generalizability of our findings. Finally, the types of surgeries, assessment tools, and timeline of assessment contributed to the heterogeneity and differences in the incidence of DNR and P-NCD. Different neuropsychometric tests with different scoring systems and cognitive domains were utilized across studies, potentially creating discrepancies between assessments. A standardized approach with validated tools at specific time points should be implemented in clinical settings for assessing for DNR and P-NCD.

Impact

Although the certainty of the evidence in our meta-analysis is low, this review is an excellent first step toward better understanding the different perioperative approaches to prevent DNR and P-NCD. Our systematic review and meta-analysis comprehensively evaluated all the different approaches – TIVA versus inhalational anesthesia, BIS monitoring/light anesthesia versus control, RA versus GA, and dexmedetomidine versus placebo. To date, our review provides the best available evidence on this topic and adds to the growing body of literature, serving as a knowledge base for all clinicians. It also provides an impetus for further research. Further RCTs of adequate power and methodology on the effects of interventions on DNR and P-NCD are warranted.

Conclusion

In our systematic review and meta-analysis of 39 RCTs, we found that dexmedetomidine had the highest risk reduction of 41% for DNR versus placebo. Second, propofol-based TIVA significantly decreased DNR by almost 20% compared to inhalational anesthesia. Conversely, we found that RA did not significantly reduce the risk of DNR versus GA. Also, BIS-guided management or light anesthesia did not significantly decrease the risk of DNR compared to control. The evidence for perioperative approaches to decrease the risk of DNR and P-NCD is limited. Further RCTs with adequate power and methodology are warranted, especially those examining P-NCD.

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Conflicts of interest

There are no conflicts of interest.

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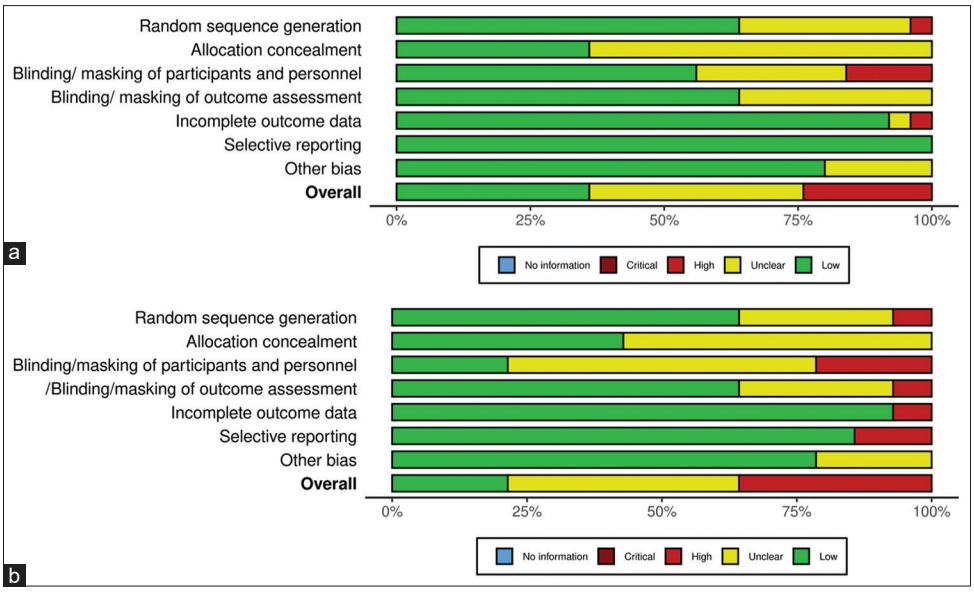

S-Figure 1: Risk of bias summary plots for studies. (a) Summary plot for studies in anesthetic techniques and approaches. (b) Summary plot for studies in other pharmacological and non-pharmacological approaches

Supplementary file

Perioperative Approaches to Prevent Delayed Neurocognitive Recovery and Postoperative Neurocognitive Disorder in Older Surgical Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

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