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Clinical Research

Pharmacological strategies to prevent postoperative delirium: a systematic review and network meta-analysis

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Background: Postoperative delirium (POD) is a condition of cerebral dysfunction and a common complication after surgery. This study aimed to compare and determine the relative efficacy of pharmacological interventions for preventing POD using a network meta-analysis.

Methods: We performed a systematic and comprehensive search to identify and analyze all randomized controlled trials until June 29, 2020, comparing two or more pharmacological interventions, including placebo, to prevent or reduce POD. The primary outcome was the incidence of POD. We performed a network meta-analysis and used the surface under the cumulative ranking curve (SUCRA) values and rankograms to present the hierarchy of the pharmacological interventions evaluated.

Results: According to the SUCRA value, the incidence of POD decreased in the following order: the combination of propofol and acetaminophen (86.1%), combination of ketamine and dexmedetomidine (86.0%), combination of diazepam, flunitrazepam, and pethidine (84.8%), and olanzapine (75.6%) after all types of anesthesia; combination of propofol and acetaminophen (85.9%), combination of ketamine and dexmedetomidine (83.2%), gabapentin (82.2%), and combination of diazepam, flunitrazepam, and pethidine (79.7%) after general anesthesia; and ketamine (87.1%), combination of propofol and acetaminophen (86.0%), and combination of dexmedetomidine and acetaminophen (66.3%) after cardiac surgery. However, only the dexmedetomidine group showed a lower incidence of POD than the control group after all types of anesthesia and after general anesthesia.

Conclusions: Dexmedetomidine reduced POD compared with the control group. The combination of propofol and acetaminophen and the combination of ketamine and dexmedetomidine seemed to be effective in preventing POD. However, further studies are needed to determine the optimal pharmacological intervention to prevent POD.

Keywords: Delirium; Network meta-analysis; Pharmacology; Surgical procedures, operative.

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INTRODUCTION

Postoperative delirium (POD) is a condition of cerebral dysfunction and a common complication after surgery that occurs in 15–35% patients [1]. Old age, a history of stroke, use of narcotic analgesics, poor physical condition, alcoholism, preexisting cognitive impairment, and type of surgery are known risk factors for POD [2,3]. Especially patients undergoing major surgery, including cardiac surgery, are at increased risk of developing POD because of the complexity of the surgical procedure, the administration of intraoperative and postoperative anesthetic and other pharmacological agents. For this reason, POD is reported to affect up to 57% of cardiac-surgery patients [4].

POD is characterized by altered consciousness, disorientation, impaired memory, perceptual disturbance, altered psychomotor activity, and altered sleep-wake cycles after surgery. POD increases the rate of mortality, length of hospital stay, risk of placement to long-term care institutions, or functional disability, thus increasing hospitalization costs [2,5]. Therefore, appropriate prevention and treatment of POD is important for enhancing postoperative recovery and quality of life in elderly patients [6].

The treatment strategies for POD are well organized compared to the prevention strategies. The treatment for POD includes treating the underlying cause; correcting fluid and electrolyte imbalance or hypoxia; removing catheters if present, and treating patients who are restless, aggressive, agitative, and harm to themself or others with antipsychotics such as haloperidol, chlorpromazine, olanzapine, and risperidone [7,8].

However, it is unclear which strategies are effective for preventing POD. Therefore, various strategies to prevent POD, especially variable pharmacological interventions, such as dexmedetomidine, propofol, midazolam, ketamine, and acetaminophen, have been applied and compared. However, each study only compared two or three drugs and reported diverse results.

Recently, a few systematic reviews and meta-analyses have demonstrated and integrated the preventive effect of various interventions [9–14]. However, each study was limited to pair-wise meta-analysis and examined only two pharmacological interventions. No previous network meta-analysis (NMA) has compared the effectiveness of all available pharmacological interventions. Further, the aforementioned studies included studies conducted prior to 2017.

NMA complements traditional pair-wise meta-analysis by combining direct and indirect comparisons of treatments and provides objective ranking of various treatments based on the corresponding surface under the cumulative ranking curve (SUCRA) [15].

Thus, we reviewed all articles that investigated the effectiveness of pharmacological interventions to prevent POD and performed NMA to compare and quantify the rank order of the effectiveness of pharmacological interventions to prevent POD.

MATERIALS AND METHODS

Protocol and registration

We developed the protocol for this systematic review and NMA according to the preferred reporting requirements for systematic review and meta-analysis protocol (PRISMA-P) statement [16]. We registered the review protocol at the

International Prospective Register of Systematic Reviews (registration no. CRD42020189363; www.crd.york.ac.uk/prospero) on May 7, 2020.

This systematic review and NMA of pharmacological interventions for preventing POD were performed according to the protocol recommended by the Cochrane Collaboration [17] and reported according to the PRISMA extension for NMA guidelines [18].

Search strategy

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from inception to June 29, 2020 using the search terms related to pharmacological interventions for preventing POD. The search terms used for MEDLINE and EMBASE are presented in Supplementary Material. Two investigators (GJC and HK) screened the titles and abstracts of the retrieved articles. Reference lists were imported to Endnote software 8.1 (Thompson Reuters, USA), and duplicate articles were removed. Additionally, the references of articles obtained from the original search were reviewed to identify relevant articles.

Inclusion criteria and exclusion criteria

We included only randomized controlled trials (RCTs) that compared two or more pharmacological interventions

to prevent POD.

The PICO-SD information included the following:

1. Patients (P): all patients receiving surgery under general or regional anesthesia
2. Intervention (I): pharmacological interventions to prevent POD
3. Comparison (C): other pharmacological interventions to prevent POD, placebo, or no treatment
4. Outcome measurements (O): the incidence of POD
5. Study design (SD): RCTs
6. Subgroup analysis: general anesthesia and cardiac surgery

Exclusion criteria contained the following features:

1. Review articles, case reports, case-series, letters to the editor, commentaries, proceedings, laboratory science studies, and all other non-relevant studies
2. Studies that failed to report the outcomes of interest
3. Studies that investigated the effect of inhalational anesthetics or patient-controlled analgesia (PCA) regimens

There was on language limitations or date restrictions in our study.

Study selection

Two reviewers (JML and YJC) independently screened the titles and abstracts of the studies to identify trials that met the inclusion criteria outlined above. For articles determined to be eligible based on the title and/or abstract, the full paper was retrieved. Potentially relevant studies chosen by at least one author were retrieved, and the full text was evaluated. Full-text articles were assessed separately by two authors (JML and YJC), and any disagreements were resolved through discussion. In cases where agreement could not be reached, the dispute was resolved with the help of a third investigator (HK). To minimize data duplication owing to multiple reporting, articles from the same author, organization, or country were compared.

Data extraction

Using a standardized extraction form, the following data were extracted independently by two investigators (JML and YJC): 1) title, 2) name of the first author, 3) name of the journal, 4) year of publication, 5) study design, 6) type of pharmacological interventions, 7) dose of pharmacological agents, 8) country, 9) risk of bias, 10) inclusion criteria, 11) exclusion criteria, 12) age, 13) number of subjects, and 14) incidence of POD.

If the information was inadequate, attempts were made to contact the study authors, and additional information was requested. If unsuccessful, missing information was calculated from the available data, if possible, or was extracted from the figure using the open source software Plot Digitizer (version 2.6.8; http://plotdigitizer.sourceforge.net).

The reference lists were divided into two halves. Two investigators completed data extraction, one for each half of the reference list. Data extraction forms were cross-checked to verify the accuracy and consistency of the extracted data.

The degree of agreement between the two independent data extractors was computed using kappa statistics to measure the difference between the observed and expected agreements, i.e., whether they were random or by chance. Kappa values were interpreted as: 1) less than 0: less than chance agreement; 2) 0.01 to 0.20: slight agreement; 3) 0.21 to 0.40: fair agreement; 4) 0.41 to 0.60: moderate agreement; 5) 0.61 to 0.80: substantial agreement; and 6) 0.8 to 0.99: almost perfect agreement [19].

Risk of bias assessment

The quality of the studies was independently assessed by two investigators (JML and YJC) using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). Risk of bias judgment was assessed in the following domains: bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. Based on the results of risk of bias judgment, formal overall risk of bias judgment was categorized as "low risk of bias," "some concern," and "high risk of bias" [20].

Statistical analysis

Ad-hoc tables were designed to summarize data from the included studies by showing their key characteristics and any important questions related to the review objectives. After extracting the data, the reviewers determined the feasibility of a meta-analysis.

A multiple treatment comparison NMA is a meta-analysis generalization method that includes both direct and in-

direct RCT comparison of treatments. A random-effects NMA based on a frequentist framework was performed using STATA software (version 15, StataCorp LP, USA) based on mvmeta with NMA graphical tools developed by Chaimani et al. [21].

Before conducting the NMA, we evaluated the transitivity assumption by examining the comparability of the risk of bias (all versus removing high risks of bias from the randomization process and overall risk of bias), demographics, and types of pharmacological interventions as potential treatment-effect modifiers across comparisons.

A network plot linking the included pharmacological interventions to prevent POD and their combination with other pharmacological agents was formed to indicate the types of agents, number of patients on different agents, and the level of pair-wise comparisons. The nodes show comparisons of pharmacological agents being compared, and the edges show the available direct comparisons among the pharmacological agents. The nodes and edges are weighed on the basis of the weights applied in NMA and the inverse of the standard error of effect.

We evaluated the consistency assumption for the entire network using the design-by-treatment interaction model. We also evaluated each closed loop in the network to evaluate local inconsistencies between the direct and indirect effect estimates for the same comparison. For each loop, we estimated the inconsistency factor (IF) as the absolute difference between the direct and indirect estimates and 95% confidence interval (CI) for each paired comparison in the loop [22]. When the IF value with 95% CI started at 0, it indicated that the direct evidence and the indirect evidence were consistent.

Mean summary effects with CI were presented together with their predictive intervals (PrIs) to facilitate interpretation of the results considering the magnitude of heterogeneity. PrIs provide an interval that is expected to encompass the estimate of a future study.

A rankogram and a cumulative ranking curve were drawn for each pharmacological intervention. Rankogram plots are the probabilities for treatments to assume a possible rank. We used surface under the cumulative ranking curve (SUCRA) values to present the hierarchy of pharmacological interventions to prevent the incidence of POD. The SUCRA is a relative ranking measure that accounts for the uncertainty in the treatment order, that is, accounts for both the location and the variance of all relative treatment effects. A higher SUCRA value is regarded as a more positive result for individual interventions [23].

We performed subgroup analysis based on all types of anesthesia, general anesthesia, and cardiac surgery, because the incidence of POD is expected to be different according to the type of anesthesia, and increase after cardiac surgery.

Quality of evidence

The evidence grade was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, which uses a sequential assessment of the evidence quality, followed by an assessment of the risk-benefit balance and a subsequent judgment on the strength of the recommendations [24].

RESULTS

Study selection

We initially retrieved 235 articles from MEDLINE, EMBASE, CENTRAL, and Google Scholar databases and 17 articles through a manual search. After adjusting for duplicates, 245 studies remained. Of these, 182 studies were discarded after reviewing the title and abstracts for the following reasons: related to other topics, designed as systematic reviews, reviews or retrospective studies, and conference abstracts. The full texts of the 63 remaining studies were reviewed in detail; 12 studies were excluded for the following reasons: three were study protocols [25–27], two were editorials [13,28], four were systematic reviews, [9–12] and three did not report the outcome of our interest (two compared an inhalational agent [13,29] and one was compared in the PCA regimen [30]). Thus, 51 studies with a total of 22,565 patients that included 18 different pharmacological interventions were included in this NMA (Fig. 1). The kappa value for the selected articles between the two reviewers was 0.844.

Characteristics of the included studies

The characteristics of the 51 studies are summarized in Table 1. All the studies were performed on adults with American Society of Anesthesiologists physical status classifications I, II, and III. The 51 studies were conducted in various countries, such as Australia [31,32], Canada [33,34], China [1,2,6,35–47], Denmark [48], Greece [49], India

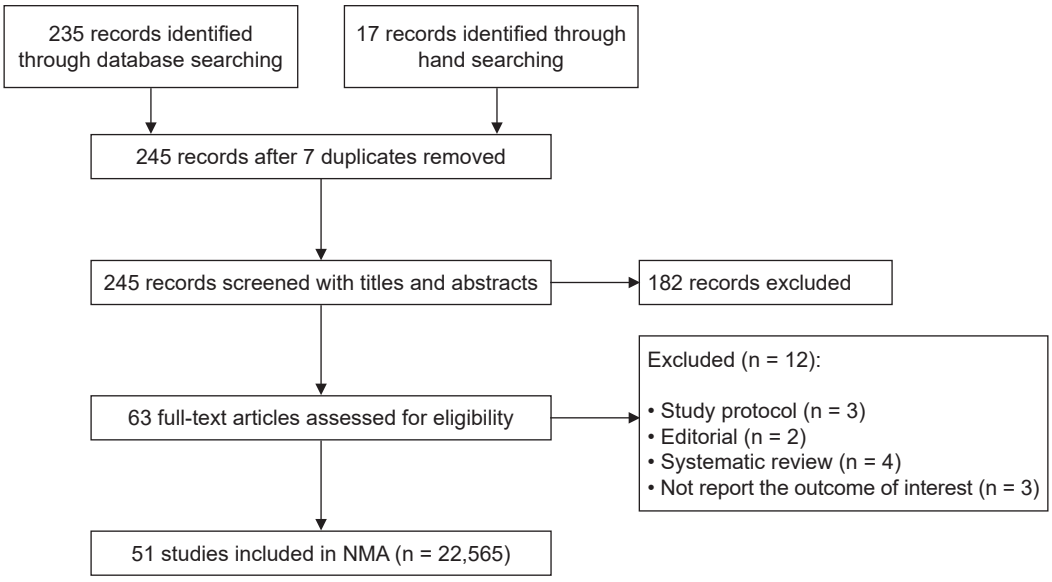

Fig. 1. PRISMA flowchart of included and excluded trials. PRISMA: preferred reporting requirements for systematic review and meta-analysis, NMA: network meta-analysis.

[50,51], Iran [52,53], Japan [54–57], the Netherlands [58–61], South Korea [62,63], Switzerland [64], Taiwan [65,66], Thailand [67], the United Kingdom [68], the United States of America [4,69–76], and Saudi arabia [77].

Twenty-seven types of pharmacological agents, including dexmedetomidine (Dexm) [2,4,6,31,33,35,36,38–45,47,50,51,62,63,65,66,69,70], propofol (Prop) [4,33,42–44,47,51,66,70], acetaminophen (AAP) [70], midazolam (Mida) [4,6,77], remifentanil (Remi) [62], morphine (Morp) [31], methylprednisolone (MPDL) [32,34,48], melatonin (Mela) [58,77], dexamethasone (Dexa) [52,59,61], haloperidol (Halo) [37,54,55,60], rivastigmine (Riva) [64], ketamine (Keta) [39,71], olanzapine (Olan) [72], gabapentin (Gaba) [73,76], nimodipine (Nimo) [1], cyproheptadine (Cypr) [53], ondansetron (Onda) [49], risperoidone (Risp) [67], L-tryptophan(L-tyr) [74], donepezil (Done) [68,75], Yokukansan (TJ-54) [56], diazepam (Diaz) [57], flunitrazepam (Flun) [57] and pethidine (Peth) [57], parecoxib (Pare) [46], and clonidine (Clon) [77] were evaluated.

The types of surgery investigated included cardiovascular surgery [4,31–35,42,43,47,50–52,59,61,62,64,67,70,71], orthopedic surgery [1,2,6,39,40,44,46,48,49,54,58,60,68,72,73,75–77], thoracoscopic and pulmonary surgery [41,56,65,74], abdominal and laparoscopic surgery [54–57,63,66], vascular and urology surgery [74], free flap [38], oral cancer surgery [45], and non-cardiac surgery [36,37,53,69]. The anesthesia method in the studies included only general anesthesia [1,2,4,6,31–35,38,39,41–43,45,47,49–52,55–57,59,61–67,69–71,76], general anesthesia + regional anesthesia [36,37,48,54,72-74], type of anesthesia were not decribed [40,53,58,60,68,75], and only regional anesthesia [44,46,77].

Study quality assessment

The risk of bias assessment in the included studies using the Cochrane tool is presented in Table 2.

All types of anesthesia

A total of 51 studies (22,565 patients) measured the incidence of POD. The pooled overall incidence of POD after all types of anesthesia was 18.5% (95% CI: 16.2% to 21.0%, $P_{chi}^2 < 0.001$, $I^2 = 92.0\%$). The network plot of all eligible comparisons for this endpoint is depicted in Fig. 2A.

Although all 27 management modalities (nodes) were connected to the network, two comparisons (Control [Cont], Dexm) were compared directly to the other 25 nodes.

The evaluation of the network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency (χ^2 [8] =13.37, P = 0.100). Of the 14 closed loops in the network for the comparison of postoperative delirium, four loops (Dexm-Dexm + AAP-pro + AAP [01-04-05] [70], Dexm-Keta-Keta + Dexm [01-09-22] [39], Pro-Dexm + AAP-Prop + AAP [03-04-05] [70], Mida-Mela-Clon [06-11-25] [77]) were formed only by multi-arm trials. Thus, local inconsistency was evaluated in 10 loops. Although most loops showed no relevance in the local inconsistency between the direct and indirect point estimates,

Table 1. The Characteristics of the Including Studies

Study	Year	Country	Surgery	Anesthesia	Assessment tool	Assessor	Management	Administration time	No. of patients	Age (yr)	Sex, M/F (%)
Deiner et al. [69]	2017	USA	Noncardiac surgery	G/A	CAM, CAM-ICU, MMSE	Trained lay interviewers	Dexmedetomidine	Intraop	147	74	49/51
							Control		157	74	49/51
Djaiani et al. [33]	2016	Canada	Cardiac surgery	G/A	CAM, CAM-ICU	Tester	Dexmedetomidine	Postop	91	72.7	75/25
							Propofol		92	72.4	76/24
Susheela et al. [70]	2017	USA	Cardiac surgery	G/A	CAM, MMSE	Research members	Dexmedetomidine	Intraop & Postop	3	No described (> 60)	No described
							Dexmedetomidine + AAP		3		
							Propofol		3		
							Propofol + AAP		3		
Li et al. [35]	2017	China	Cardiac surgery	G/A	CAM, CAM-ICU	Research members	Dexmedetomidine	Periop	142	66	67/30
							Control		143	68	71/29
Maldonado et al. [4]	2009	USA	Cardiac surgery	G/A	CAM, CAM-ICU, DRS	Neuropsychiatrist	Dexmedetomidine	Postop	40	55	65/35
							Propofol		38	58	58/42
							Midazolam		40	60	68/32
Park et al. [62]	2014	South Korea	Cardiac surgery	G/A	CAM-ICU	Medical staff and non-psychiatrists	Dexmedetomidine	Postop	67	51	60/40
							Remifentanil		75	54	55/45
Shehabi et al. [31]	2009	Australia	Cardiac surgery	G/A	CAM-ICU	Nurse and the research team	Dexmedetomidine	No described	152	71	75/25
							Morphine		147	71	75/25
Su et al. [36]	2016	China	Noncardiac surgery	G/A, R/A	CAM-ICU	Research members	Dexmedetomidine	Periop	350	No described (> 65)	No described
							Control		350		
Wu et al. [65]	2018	Taiwan	Thoracoscopic surgery	G/A	No described	No described	Dexmedetomidine	Intraop	30	59	50/50
							Control		3	59	51/49
Clemmesen et al. [48]	2018	Denmark	Hip fracture surgery	G/A, R/A	CAM	Research members	Methylprednisolone	Preop	59	79	37/63
							Control		58	81	37/63
de Jonghe et al. [58]	2014	Netherland	Hip fracture surgery	No described	DSM-IV	Medical and nursing records	Melatonin	Periop	186	84	28/72
							Control		192	83	32/68
Dieleman et al. [59]	2012	Netherland	Cardiac surgery	G/A	No described	No described	Dexamethasone	Intraop	2,235	66	73/27
							Control		2,247	66	72/28
Fukata et al. [54]	2014	Japan	Abdominal, orthopedic surgery	G/A, R/A	NEECHAM	Research members	Haloperidol	Postop	59	81	50/50
							Control		60	80	50/50
Gamberini et al. [64]	2009	Switzerland	Cardiac surgery	G/A	CAM, MMSE, CDT	Research members	Rivastigmine	Periop	56	74	66/34
							Control		57	74	70/30
Hudetz et al. [71]	2009	USA	Cardiac surgery	G/A	ICDSC	Anesthesiologist	Ketamine	Intraop	29	68	No described
							Control		29	60	

(Continued to the next page)

Table 1. Continued

Study	Year	Country	Surgery	Anesthesia	Assessment tool	Assessor	Management	Administration time	No. of patients	Age (yr)	Sex, M/F (%)
Kalisvaart et al. [60]	2005	Netherland	Hip fracture surgery	No described	CAM, DSM-IV, MMSE, DRS-R-98	Treating surgeons	Haloperidol	Periop	212	79	19/81
							Control		218	80	21/79
Kaneko et al. [55]	1999	Japan	Gastrointestinal surgery	G/A	DSM	Medical and nursing records	Haloperidol	Postop	38	72	60/40
							Control		40	73	65/35
Larsen et al. [72]	2010	USA	Joint replacement surgery	G/A, R/A	CAM, DSM-IV, MMSE, DRS-R-98	Trained nurse	Olanzapine	Periop	196	73	52/48
							Control		204	74	40/60
Lee et al. [63]	2018	South Korea	Laparoscopic major surgery	G/A	CAM	Psychiatrist	Dexmedetomidine	Intra	236	73	45/55
							Control		118	74	43/57
Leung et al. [73]	2017	USA	Spine, joint replacement surgery	G/A, R/A	CAM	Research assistants	Gabapentin	Periop	350	73	45/55
							Control		347	73	55/45
Li et al. [1]	2017	China	Spine surgery	G/A	Nu-DESC	Nurse	Nimodipine	Periop	30	69	37/63
							Control		30	70	43/57
Liu et al. [2]	2016	China	Joint replacement surgery	G/A	CAM	No described	Dexmedetomidine	Intraop	60	71	43/57
							Control		58	73	50/50
Mardani and Bigdelian [52]	2013	Iran	Cardiac surgery	G/A	MMSE, DSM-IV	No described	Dexamethasone	Periop	43	65	84/16
							Control		50	60	88/12
Mohammadi et al. [53]	2016	Iran	Noncardiac surgery	No described	CAM-ICU	Anesthesiologist	Cyproheptadine	Postop	20	60	60/40
							Control		20	60	70/30
Papadopoulos et al. [49]	2014	Greece	Femoral, femur fracture surgery	G/A	CAM, MMSE	Research members	Ondansetron	Postop	51	72	No described
							Control		55	71	
Prakanrattana and Prapaitrakool [67]	2007	Thailand	Cardiac surgery	G/A	CAM, CAM-ICU	Anesthesiologist	Risperidone	Postop	63	61	57/43
							Control		63	61	60/40
Priye et al. [50]	2015	India	Cardiac surgery	G/A	No described	No described	Dexmedetomidine	Postop	32	45	51/49
							Control		32	41	50/50
Robinson et al. [74]	2014	USA	Vascular,urologic,thoracic surgery	G/A, R/A	CAM-ICU	Research members	L-tryptophan	Postop	152	69	99/1
							Control		149	69	97/3
Royse et al. [32]	2017	Australia Canada	Cardiac surgery	G/A	CAM-ICU	No described	Methylprednisolone	Intraop	250	73	63/37
							Control		248	74	66/34
Sampson et al. [68]	2007	UK	THR	No described	DSI	No described	Donepezil	Postop	19	70	58/42
							Control		14	65	43/57
Sheikh et al. [51]	2018	India	Cardiac surgery	G/A	No described	No described	Dexmedetomidine	Intraop	30	34	No described
							Propofol		30	36	

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Table 1. Continued

Study	Year	Country	Surgery	Anesthesia	Assessment tool	Assessor	Management	Administration time	No. of patients	Age (yr)	Sex, M/F (%)
Sugano et al. [56]	2017	Japan	GI, lung cancer surgery	G/A	DSM-IV	Physicians	TJ-54	Periop	93	76	65/35
							Control		93	77	65/35
Wang et al. [37]	2012	China	Noncardiac surgery	G/A, R/A	CAM-ICU	Research members	Haloperidol	Postop	229	74	63/37
							Control		228	74	63/37
Whitlock et al. [34]	2015	Canada	Cardiac surgery	G/A	CAM	Outcome adjudicators	Methylprednisolone	Intraop	3,755	68	60/40
							Control		3,752	67	61/39
Yang et al. [38]	2015	China	Free flap surgery	G/A	CAM-ICU	Investigator	Dexmedetomidine	Periop	39	50	50/50
							Control		40	50	50/50
He et al. [6]	2018	China	Vertebral osteotomy	G/A	CAM	No described	Dexmedetomidine	Periop	30	83	53/47
							Midazolam		30	82	63/37
							Control		30	83	56/44
Ma et al. [39]	2013	China	Orthopedic surgery	G/A	CAM	Research members	Ketamine	Periop	30	66	53/47
							Dexmedetomidine		30	69	34/66
							Ketamine + Dexemetomidine		30	66	40/60
							Control		30	68	60/40
Xuan et al. [40]	2018	China	Joint replacement surgery	No described	CAM, CAM-ICU	Research members	Dexmedetomidine	Postop	227	67	42/58
							Control		226	67	45/55
Sauër et al. [61]	2014	Netherland	Cardiac surgery	G/A	CAM, CAM-ICU	Research nurse	Dexamethasone	Intraop	367	67	70/30
							Control		370	66	69/31
Huyan et al. [41]	2019	China	Radical pulmonary resection	G/A	ICDSC	No described	Dexmedetomidine	Periop	173	71	51/49
							Control		173	72	54/46
Shi et al. [42]	2019	China	Cardiac surgery	G/A	CAM	Research members	Dexmedetomidine	Intraop	84	75	75/25
							Propofol		80	74	70/30
Liu et al. [43]	2016	China	Cardiac surgery	G/A	CAM	No described	Dexmedetomidine	Postop	44	53	52/48
							Propofol		44	57	68/32
Mei et al. [44]	2018	China	Hip arthroplasty	R/A	CAM	Research members	Dexmedetomidine	Intraop	148	76	43/57
							Propofol		148	74	48/52
Guo et al. [45]	2015	China	Oral cancer surgery	G/A	CAM-ICU	No described	Dexmedetomidine	Postop	78	72	53/47
							Control		78	71	50/50
Aizawa et al. [57]	2002	Japan	GI surgery	G/A	DSM-IV	Psychiatrist	Diazepam + Flunitrazepam + Pethidine (DFP)	Postop	20	76	75/25
							Control		20	76	55/45
Mu et al. [46]	2017	China	Joint replacement surgery	R/A	CAM, CAM-ICU	Research members	Parecoxib	No described	310	70	26/74
							Control		310	71	27/73

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Table 1. Continued

Study	Year	Country	Surgery	Anesthesia	Assessment tool	Assessor	Management	Administration time	No. of patients	Age (yr)	Sex, M/F (%)
Sultan [77]	2010	Saudi Arabia	Hip arthroplasty	R/A	AMT	Resident anesthetist	Melatonin	Preop	53	70	45/55
							Midazolam		50	70	52/48
							Clonidine		51	72	53/47
							Control		49	72	45/55
Liptzin et al. [75]	2005	USA	Joint replacement surgery	No described	CAM, DSM-IV, DSI	Research members	Donepezil	Periop	39	67	36/64
							Control		41	68	49/51
Leung et al. [76]	2006	USA	Spine surgery	G/A	CAM	Research members	Gabapentin	Periop	9	57	44/56
							Control		12	61	58/42
Liu et al. [47]	2016	China	Cardiac surgery	G/A	CAM	No described	Dexmedetomidine	Periop	29	53	34/66
							Propofol		32	55	47/53
Chang et al. [66]	2018	Taiwan	GI surgery	G/A	CAM	No described	Dexmedetomidine	Periop	31	71	61/39
							Propofol		29	70	55/45

CAM: confusion assessment method, CAM-ICU: confusion assessment method for intensive care unit, MMSE: mini-mental state examination, DRS: delirium rating scale, DSM-IV: diagnostic and statistical manual of mental disorders-IV, NEECHAM: neelon and champagne confusion scale, CDT: clock drawing test, ICDSC: intensive care delirium screening checklist, DRS-R-98: delirium rating scale-revised-98, Nu-DESC: nursing delirium screening score, DSI: delirium symptom interview, AMT: appreviated mental test, Intraop: intra-operative, Periop: peri-operative, Preop: pre-operative, G/A: general anesthesia, R/A: regional anesthesia, THR: total hip replacement, GI: gastro-intestinal.

Table 2. Risk of Bias Assessment

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias judgement
Deiner et al., 2017 [69]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Djaiani et al., 2016 [33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Susheela et al., 2017 [70]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Li et al., 2017 [35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Maldonado et al., 2009 [4]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Park et al., 2014 [62]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Shehabi et al., 2009 [31]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Su et al., 2016 [36]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wu et al., 2018 [65]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Clemmesen et al., 2018 [48]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
de Jonghe et al., 2014 [58]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Dieleman et al., 2012 [59]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fukata et al., 2014 [54]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Gamberini et al., 2009 [64]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Hudetz et al., 2009 [71]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

(Continued to the next page)

Table 2. Continued

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias judgement
Kalisvaart et al., 2005 [60]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kaneko et al., 1999 [55]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Larsen et al., 2010 [72]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lee et al., 2018 [63]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Leung et al., 2017 [73]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Li et al., 2017 [1]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Liu et al., 2016 [2]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Mardani and Bigdelian, 2013 [52]	Some concerns	Some concerns	Some concerns	Low risk	Low risk	High risk
Mohammadi et al., 2016 [53]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Papadopoulos et al., 2014 [49]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Prakanrattana and Prapaitrakool, 2007 [67]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Priye et al., 2015 [50]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Robinson et al., 2014 [74]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Royse et al., 2017 [32]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Sampson et al., 2007 [68]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sheikh et al., 2018 [51]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sugano et al., 2017 [56]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Wang et al., 2012 [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Whitlock et al., 2015 [34]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Yang et al., 2015 [38]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
He et al., 2018 [6]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Ma et al., 2013 [39]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Xuan et al., 2018 [40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sauër et al., 2014 [61]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Huyan et al., 2019 [41]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Shi et al., 2019 [42]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Liu et al., 2016 [43]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Mei et al., 2018 [44]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Guo et al., 2015 [45]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Aizawa et al., 2002 [57]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Mu et al., 2017 [46]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sultan, 2010 [77]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Liptzin et al., 2005 [75]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Leung et al., 2006 [76]	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Liu et al., 2016 [47]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Chang et al., 2018 [66]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

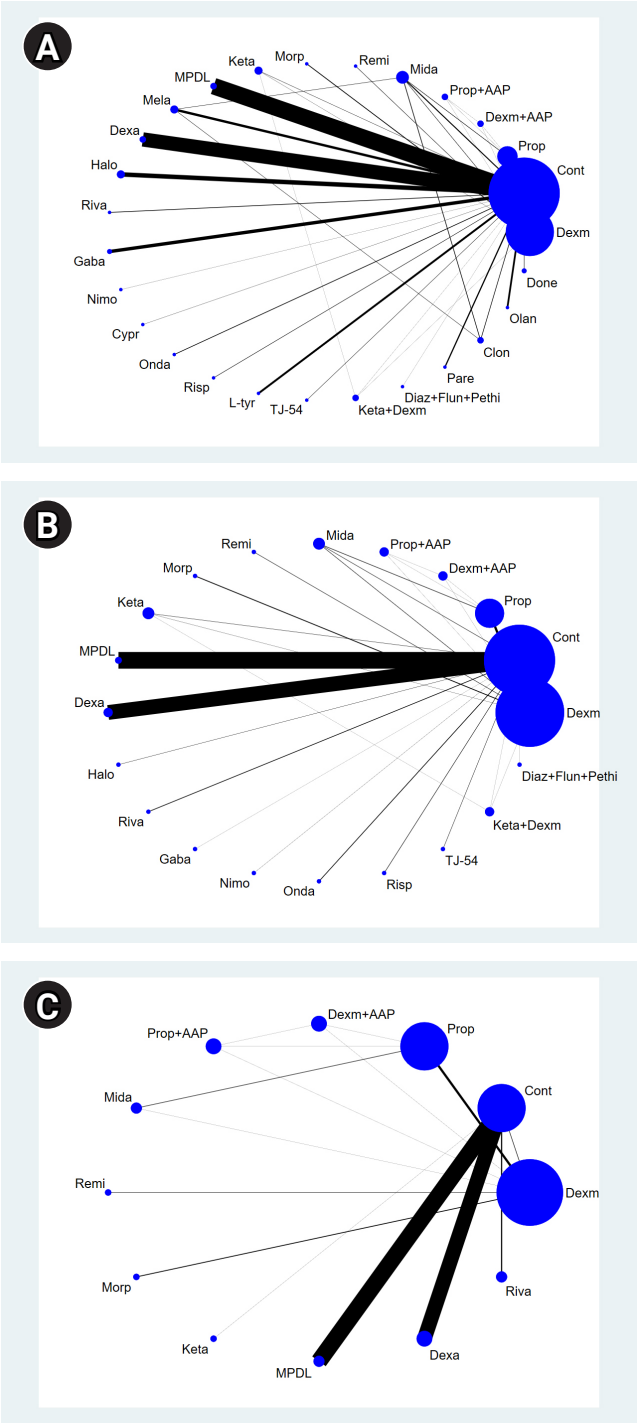


Fig. 2. Network plot of included studies comparing different pharmacological interventions. The nodes show a comparison of pharmacological interventions to prevent postoperative delirium, and the edges show the available direct comparisons among the pharmacological interventions. The nodes and edges are weighed on the basis of the weights applied in the network meta-analysis and the inverse of the standard error of effect. (A) All types of anesthesia, (B) general anesthesia, (C) cardiac surgery.

inconsistencies were observed between the direct and indirect point estimates in the Cont-Mela-Clon (02-11-25) and Cont-Mida-Mela (02-06-11) loops (Fig. 3A).

Dexm showed a lower incidence of POD than Cont only in terms of 95% CI. Olan showed marginal significance compared with Cont in terms of 95% CI (Fig. 4A). Insignificance in the 95% PrIs suggests that any future RCT could change the significance of the effectiveness of these comparisons.

The rankograms showed that Prop+AAP and Keta+Dexm had the lowest incidence of POD (Fig. 5A). The cumulative ranking plot was drawn, and the SUCRA probabilities of the different pharmacological agents for POD were calculated (Fig. 6A). The expected mean rankings and SUCRA values of each pharmacological intervention are presented in Fig. 7A. According to the SUCRA value, the incidence of POD was lower in the order of the Prop + AAP (86.1%), followed by Keta + Dexm (86.0%), Diaz + Flun + Pethi (84.8%), and Olan (75.6%). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which suggested a less likely publication bias (Fig. 8A).

General anesthesia

A total of 35 studies (17,241 patients) were analyzed. The pooled overall incidence of POD after general anesthesia was 16.5% (95% CI: 14.2% to 19.2%, $P_{chi}^2 < 0.001$, $I^2 = 89.3\%$).

The network plot of all eligible comparisons for this endpoint is depicted in Fig. 2B. Although all 20 management modalities (nodes) were connected to the network, two comparisons (Cont, Dexm) were directly compared to the other 18 nodes.

The evaluation of the network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency (χ^2 [6] = 11.50, P = 0.074). Of the 10 closed loops in the network for the comparison of postoperative delirium, three loops (Dexm-Dexm + AAP-Prop + AAP [01-04-05] [70], Pro-Dexm + AAP-Prop + AAP [01-09-19] [70], Dexm-Keta-Dexm + Keta [03-04-05] [39]) were formed only by multi-arm trials. Thus, local inconsistency was evaluated in seven loops. There was no significance in the local inconsistency between the direct and indirect point estimates (Fig. 3B).

Dexm showed a lower incidence of POD than Cont only in terms of 95% CI (Fig. 4B). Insignificance in the 95% PrIs suggests that any future RCT could change the significance

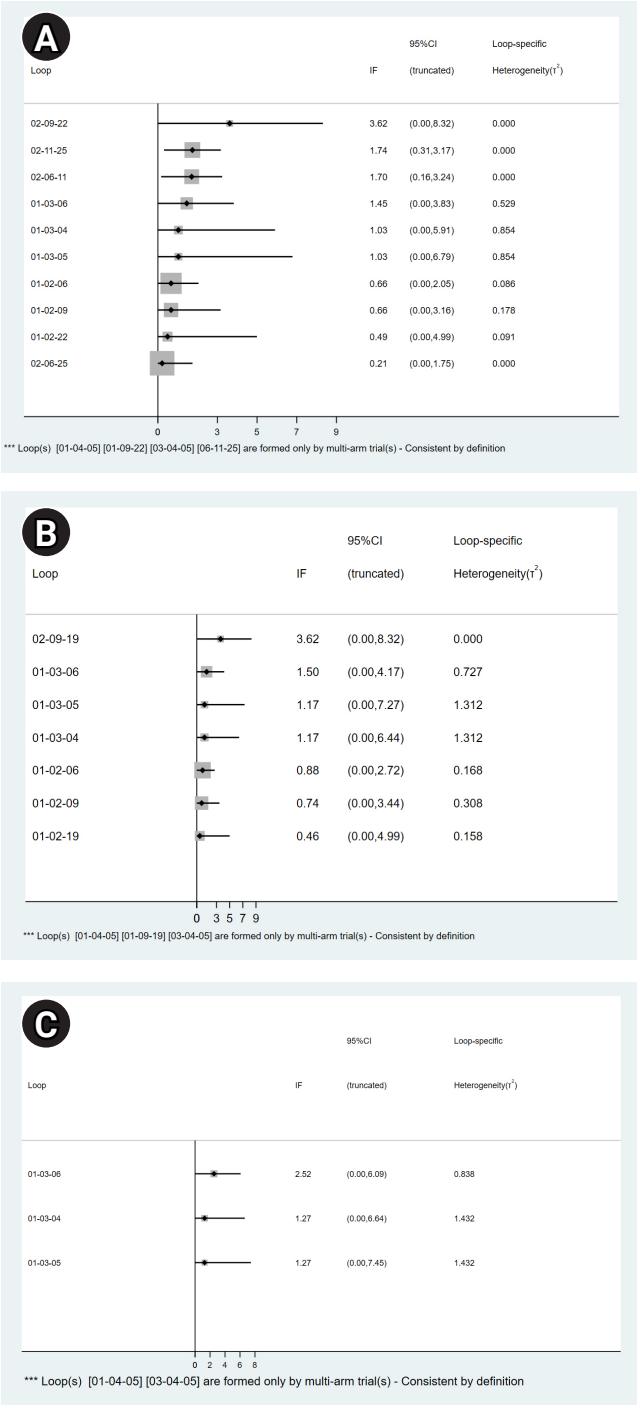


Fig. 3. Inconsistency plot between the direct and indirect effect estimates for the same comparison. Inconsistency factor (IF) as the absolute difference with 95% confidence interval (CI) between the direct and indirect estimates for each paired comparison is presented. IF values close to 0 indicate that the two sources are in agreement. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.

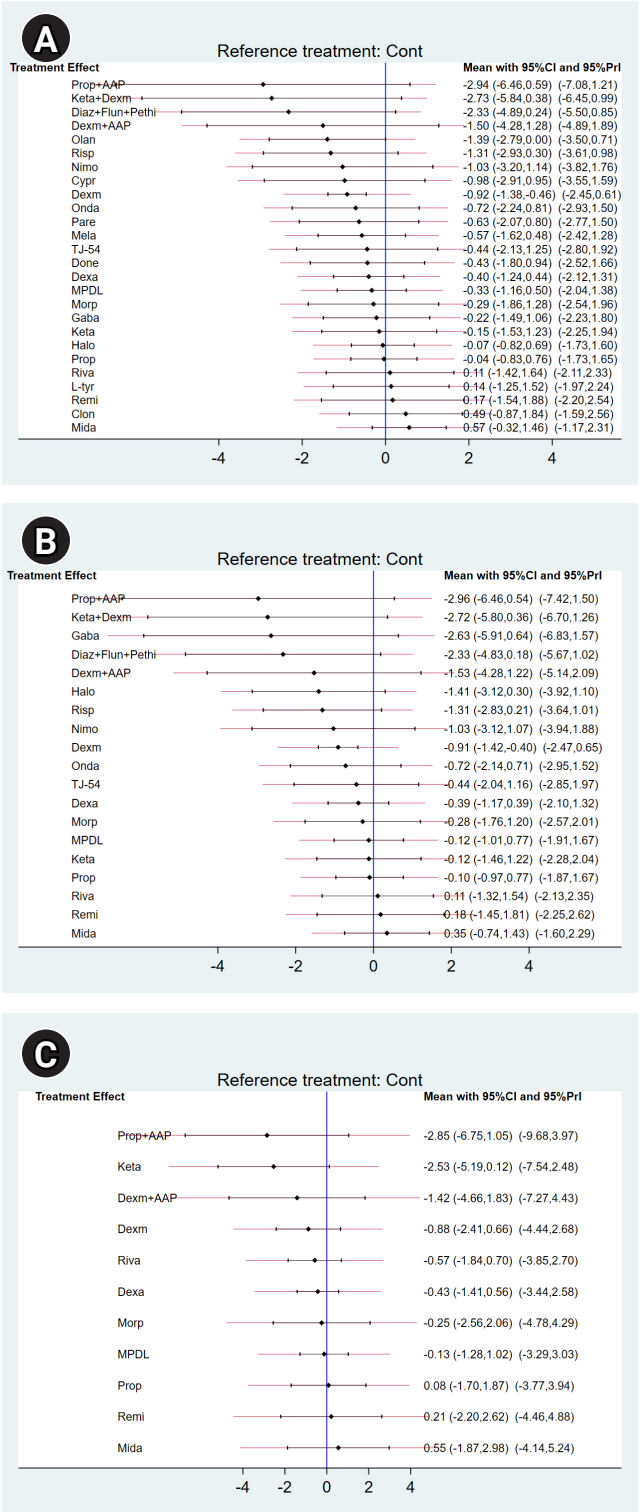
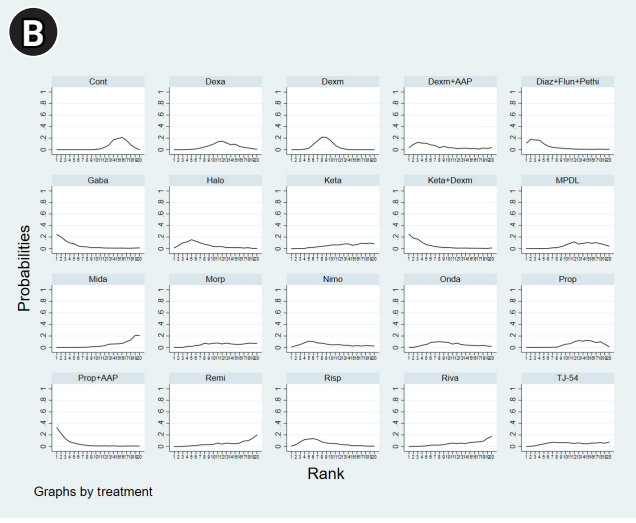


Fig. 4. Predictive interval plots between each management modality and placebo group. Diamond shape represents the mean summary effects. Black line represents the 95% confidence interval (CI), and red line represents the predictive interval (PrI). PrIs provide an interval that is expected to encompass the estimate of a future study. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.



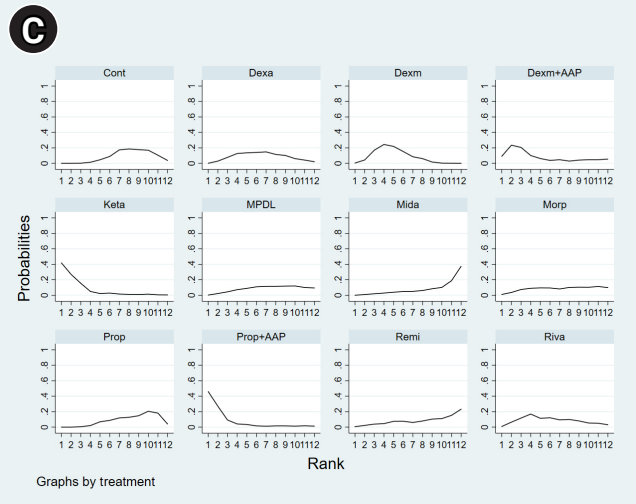
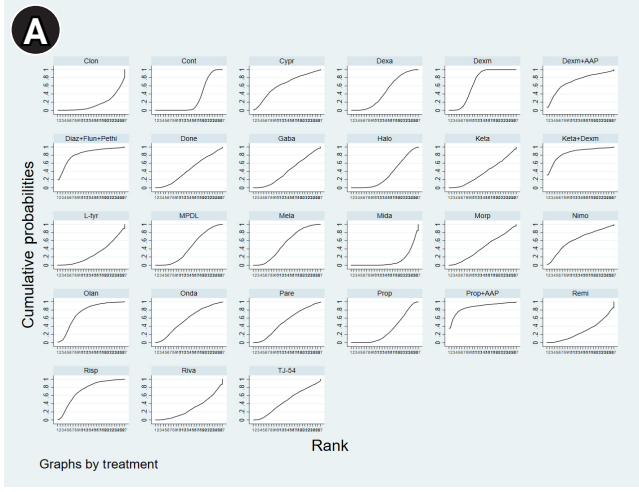
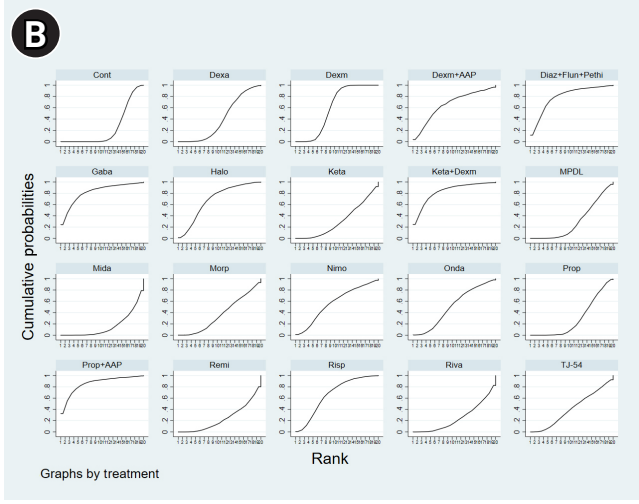


Fig. 5. Rankogram. Profiles indicate the probabilities for treatments to assume any of the possible ranks. It is the probability that a given treatment ranks first, second, third, and so on, among all of the treatments evaluated in the NMA. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery. NMA: network meta-analysis.





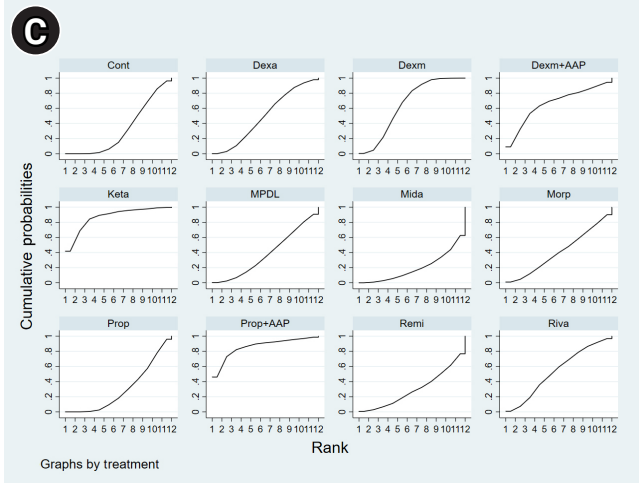


Fig. 6. Cumulative ranking curve plot. The profile indicates the sum of the probabilities from those ranked first, second, third, and so on. A higher cumulative ranking curve (surface of under cumulative ranking curve [SUCRA]) value is regarded as an improved result for an individual's intervention. When ranking treatments, the closer the SUCRA value is to 100%, the higher the treatment ranking is relative to all other treatments. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.

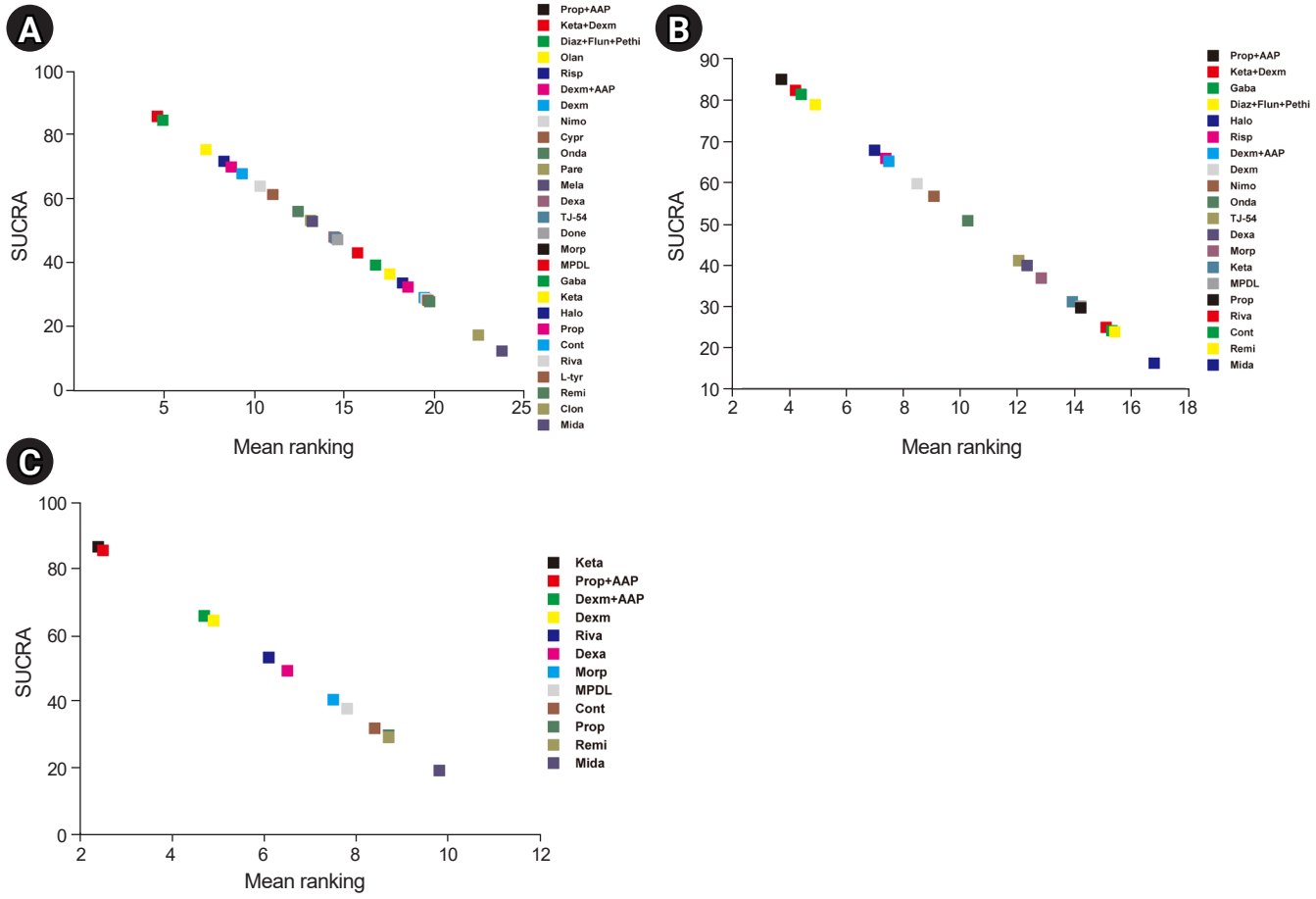


Fig. 7. Expected mean ranking and surface of under cumulative ranking curve (SUCRA) values. X-axis corresponds to expected mean ranking based on SUCRA value, and Y-axis corresponds to SUCRA value. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.

of the effectiveness of these comparisons.

The rankogram showed that Prop + AAP, Keta + Dexm, and Gaba had the lowest incidence of POD (Fig. 5B). The cumulative ranking plot was drawn, and the SUCRA probabilities of the different pharmacological agents for the POD were calculated (Fig. 6B). The expected mean rankings and SUCRA values of each pharmacological agent are presented in Fig. 7B. According to the SUCRA value, the incidence of POD was lower in the order of the Prop + AAP (85.9%), followed by Keta + Dexm (83.2%), Gaba (82.2%), and Diaz + Flun + Pethi (79.7%).

Cardiac surgery

A total of 19 studies (15,090 patients) were analyzed. The pooled overall incidence of POD after cardiac surgery was 15.4% (95% CI: 12.8% to 18.4%, $P_{chi}^2 < 0.001$, $I^2 = 89.8\%$).

The network plot of all eligible comparisons for this endpoint is depicted in Fig. 2C.

Although all 13 management modalities (nodes) were connected to the network, three comparisons (Cont, Dexm, Prop) were compared directly to the other 10 nodes.

The evaluation of the network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency (χ^2 [2] = 4.12, P = 0.128). Of the five closed loops in the network of the comparison of postoperative delirium, two loops (Dexm-Dexm + AAP-Prop + AAP [01-04-05] [70] and Pro-Dexm + AAP-Prop + AAP [03-04-05] [70]) were formed only by multi-arm trials. Thus, local inconsistency was evaluated in three loops. There was no significance in the local inconsistency between the direct and indirect point estimates (Fig. 3C).

None of the regimens showed a lower incidence of POD than Cont only in terms of both 95% CI and 95% PrIs (Fig. 4C). The rankogram showed that Prop + AAP and Keta had the lowest incidence of POD (Fig. 5C). The cumulative ranking plot was drawn, and the SUCRA probabilities of the different pharmacological interventions for the POD were calculated (Fig. 6C). The expected mean rankings and SUCRA values of each pharmacological intervention are

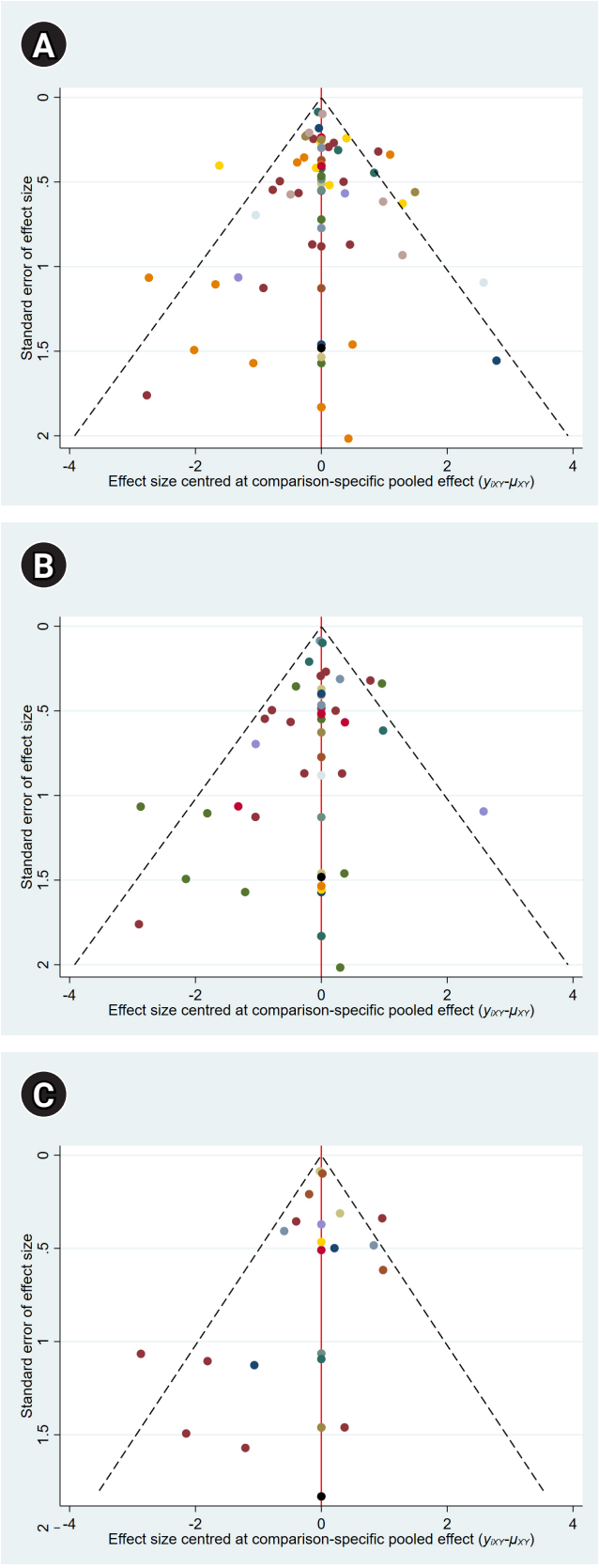


Fig. 8. Comparison-adjusted funnel plot.

presented in Fig. 7C. According to the SUCRA value, the incidence of POD was lower in the order of Keta (87.1%), Prop + AAP (86.0%), followed by Dexm + AAP (66.3%). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which suggested a less likely publication bias (Fig. 8C).

Quality of evidence

Three outcomes were evaluated using the GRADE system. For each outcome, the qualities of inconsistency, indirectness, imprecision and publication bias were assessed as not serious, but qualities of risk of bias were assessed as serious. Thus, the overall quality of evidence for each outcome was downgraded and rated as moderate (Table 3).

DISCUSSION

There are various pharmacological interventions to prevent POD. We performed a network meta-analysis to compare the effectiveness of reported pharmacological interventions. In our study, the incidence of POD was decreased in the following order: Prop + AAP, Keta + Dexm, Gaba, and Diaz + Flun + Pethi after all types of anesthesia; Prop + AAP, Keta +Dexm, Gaba, and Diaz + Flun + Pethi after general anesthesia; and Keta, Prop + AAP, and Dexm + AAP after cardiac surgery. However, only the Dexm group showed a statistically lower incidence of POD compared with the control group after all types of anesthesia and after general anesthesia.

In our study, there was a synergistic effect when Prop was added to AAP. Although Prop + AAP failed to show statistical significance, Prop + AAP was ranked the most effective pharmacological intervention with a low incidence of POD after all types of anesthesia and after general anesthesia. Prop is a short-acting, intravenous sedative-hypnotic agent commonly used for general anesthesia and sedation. It has also been used to control other conditions such as chemotherapy-induced emesis, as an antipruritic in patients with intractable pruritus due to liver disease, as an adjuvant in alcohol withdrawal syndrome, and to treat status epilepticus and severe refractory delirium. Prop has been recently shown to have a long-term neuroprotective effect and CNS inhibition effect [78–80]. AAP is commonly used as an adjuvant analgesic. Some prior studies have indicated that AAP reduces opioid consumption and inflammation. Recently, AAP has been shown to confer central

Table 3. The GRADE Evidence Quality for Post-operative Delirium

Type	No. of studies	Quality assessment					Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
All type of anesthesia	51	Serious	Not serious	Not serious	Serious	None	⊕⊕⊕○ Moderate
General Anesthesia	35	Serious	Not serious	Not serious	Serious	None	⊕⊕⊕○ Moderate
Cardiac surgery	19	Serious	Not serious	Not serious	Serious	None	⊕⊕⊕○ Moderate

GRADE: grading of recommendations, assessment, development, and evaluation.

analgesic properties. This makes it likely that AAP would reduce delirium. Despite these properties, IV AAP has not been studied in the context of delirium prevention [81,82]. In our study, a synergistic effect occurred as the neuroprotective effect of Prop was added to the POD prevention effect of AAP.

Dexm, a selective α_2-adrenergic agonist, has a strong modulating effect on the activity of the sympathetic system and is increasingly used as a sedative and an adjuvant anesthetic during surgery. Dexm binds to α_2-receptors present in both the central and peripheral nervous systems [83–86]. Meanwhile, Dexm inhibits the release of norepinephrine and sympathetic activity. In our study, Dexm reduced POD after all types of anesthesia and after general anesthesia compared with the control group. These results are in close agreement with a previous report by Al Tmimi et al. [13] and Shen et al. [14] in which the risks of POD were decreased in elderly patients after non-cardiac surgery.

Several mechanisms have been suggested to explain how Dexm reduces the incidence of POD after surgery and anesthesia. First, because of its highly selective and specific α_2-adrenergic agonistic characteristics, Dexm reduces the amount of other sedatives and opioids used during surgery, which may cause POD development and prolongation [40,51]. Second, Dexm attenuates the immune cascade and inflammatory mediators, consequently relieving inflammatory response [87], which is associated with POD. Third, Dexm induces a near-natural sleep-like sedative pattern, which might help to reduce the risk of delirium significantly. In addition, Dexm has been suggested as a neuroprotectant during mechanical ventilation by reducing cerebral blood and cerebral perfusion pressure [88–90].

Keta, which is ineffective with monotherapy, when combined with Dexm becomes the most effective modality. Several reports in the past few years have evaluated Keta for the treatment of hyperactive delirium. Keta offers a potential option for treating difficult to manage hyperactive delirium [91]. Moreover, Keta is an NMDA receptor antagonist, which reduces post-ischemic neuronal cell loss in the cortex and improves neurological outcome after cerebral ischemia [92,93]. Thus, Keta may produce a prolonged effect on postoperative neurocognitive function by causing a "preconditioning-like" effect through the temporary inactivation of NMDA receptors, thereby rendering these receptors less susceptible to subsequent activation by ischemia and reperfusion injury. However, this intriguing hypothesis has not been formally tested. Keta may also confer neuroprotection by suppressing the inflammatory response after surgery [71,94].

For quality of life, which has recently attracted attention, postoperative complications of surgical patients should be prevented and treated appropriately. Among complications, POD can directly or indirectly increase postoperative morbidity and mortality in elderly patients. Delirium is not always a transient disorder; in some cases, it may be accompanied by subtle structural brain damage, leading to permanent cognitive impairment. Therefore, there is growing interest in proper preventive methods [62,68].

In our study, we focused on the incidence of POD, preventive effect of interventions, and collected pharmacological intervention data. There have been a number of preventative methods introduced in other studies, but their efficacy has not been properly compared. To compensate for this, our NMA including various pharmacological interventions. Throughout this study, we attempted to identify the most effective prevention of POD.

There are several limitations in this study. First, as with all meta-analyses, there were clinical and methodological heterogeneities regarding administration timing (for example, preoperative or intraoperative or postoperative), method (for example, bolus or continuous infusion) and dose spectrum of pharmacological interventions, and assessor of POD and assessment tool of POD. Second, in our study,

incidence of POD was used as an indicator of prevention. However, to reduce morbidity and mortality associated with POD, it is also important to reduce the severity and duration of POD. Therefore, further studies should be conducted to evaluate the effects on the severity and duration of POD. Third, the most efficacious modalities determined in the current NMA were documented to be effective in a limited number of clinical trials. Further, as our NMA was based on various single-center small-scale trials, a risk of overestimation or underestimation of true treatment effects or lack of power to discriminate the effectiveness of pharmacological interventions may be present. Therefore, further large-scale RCTs with the qualified protocol should be conducted in the future to encompass different pharmacological interventions and substantiate our findings.

Despite these limitations, the current NMA has several strengths compared to previous NMAs. First, a rigorous methodology based on a published, pre-planned protocol to provide evidence of pharmacological interventions to prevent POD was used. Second, inconsistencies among the enrolled studies were not significant, and publication bias of the enrolled studies was minimal. Third, most enrolled studies exhibited a low risk of bias, except for bias from the randomization process and bias due to deviations from intended intervention domains.

In conclusion, the NMA performed in this study has strength and meaning for comparing pharmacological interventions in the clinical efficacy of preventing POD. Dexm showed a significant decrease in the incidence of POD compared with the control group. The combination of Prop and AAP and the combination of Keta and Dexm seemed to be effective in preventing POD. However, further studies are needed to determine the optimal pharmacological intervention to prevent POD.

SUPPLEMENTARY MATERIALS

Supplementary data including search terms used for MEDLINE and EMBASE can be found online at https://doi.org/10.17085/apm.20079

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: Jun Mo Lee, Eun Jin Ahn, Geun Joo Choi, Hyun Kang. Data curation: Jun Mo Lee, Hyun Kang. Formal analysis: Ye Jin Cho, Hyun Kang. Funding acquisition: Hyun Kang. Methodology: Geun Joo Choi, Hyun Kang. Project administration: Jun Mo Lee, Ye Jin Cho, Hyun Kang. Visualization: Ye Jin Cho, Geun Joo Choi, Hyun Kang. Writing - original draft: Jun Mo Lee, Ye Jin Cho, Geun Joo Choi, Hyun Kang. Writing - review & editing: Jun Mo Lee, Eun Jin Ahn, Hyun Kang. Investigation: Jun Mo Lee, Ye Jin Cho, Eun Jin Ahn, Hyun Kang. Resources: Jun Mo Lee, Hyun Kang. Software: Hyun Kang. Supervision: Eun Jin Ahn, Geun Joo Choi, Hyun Kang. Validation: Jun Mo Lee, Ye Jin Cho, Eun Jin Ahn, Hyun Kang.

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