



SYSTEMATIC REVIEW

Dexmedetomidine reduces postoperative cognitive and behavioral dysfunction in adults submitted to general anesthesia for non-cardiac surgery: meta-analysis of randomized clinical trials

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KEYWORDS

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Abstract Introduction and objectives Dexmedetomidine (DEX) have been associated with a decrease in postoperative cognitive and behavioral dysfunction in patients submitted to general anesthesia, whether inhalation or total intravenous anesthesia. Consequently, the DEX effects on postoperative agitation and delirium in patients submitted to general anesthesia for non-cardiac surgery have been investigated.

Method: We performed a meta-analysis of randomized and double-blind clinical trials assessing adults submitted to elective procedures under general anesthesia that received DEX or placebo. We searched articles published in English in the Pubmed and Web of Science databases using keywords such as dexmedetomidine, delirium, and agitation. We excluded duplicate publications, studies involving cardiac surgery or that used active control (other than saline solution). A random effects model was adopted using the DerSimonian-Laird method and estimate of Odds Ratio (OR) for dichotomous variables, and weighted mean difference for continuous variables, with their respective 95% Confidence Intervals (95% CI).

Results: Of the 484 articles identified, 15 were selected comprising 2,183 patients (1,079 and 1,104 patients in the DEX and control group, respectively). The administration of DEX was considered a protective factor for postoperative cognitive and behavioral dysfunction (OR = 0.36; 95% CI 0.23–0.57 and $p < 0.001$), regardless of the anesthesia technique used.

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Conclusion: Dexmedetomidine administration reduced by at least 43% the likelihood of postoperative cognitive and behavioral dysfunction in adult patients submitted to general anesthesia for non-cardiac surgery.

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Introduction

Delirium is an acute inability to sustain attention associated with cognitive dysfunction, impairment in mental status and in the sleep-wake cycle, as well as in behavior, which can lead the patient into a hypo or hyperactive state.^{1,2} It has risk factors such as older age, postoperative period, past comorbidities, previous neurological deficits and sensory impairments.^{1,3} As reported both in pivotal studies and in more updated publications, delirium is associated with longer hospital stay, functional reduction, less likelihood of regaining autonomy, and greater morbidity and mortality.⁴⁻⁶ It is estimated that approximately 20% of hospitalized patients over 65 years of age develop postoperative delirium.¹

Agitation is a mental state in which the patient is restless, uncooperative, and incoherent.⁷ It can be related to a paranoid ideation associated with time disorientation and misinterpretation of neurosensory stimuli, resulting from residual effect of anesthetic drugs.⁸ Postoperative agitation is associated with adverse events such as surgical site bleeding, accidental removal of drains or vascular catheters, and even damage to the surgery performed.⁹

Dexmedetomidine (DEX) is an α_2 adrenoceptor agonist, with selectivity ratio of 1600:1 ($\alpha_2:\alpha_1$). It acts on α_2 receptors of the locus coeruleus, promoting sedation, and on the spinal cord dorsal horn, decreasing the release of substance P and producing analgesia.¹⁰ DEX provides excellent sedation and analgesia, with minimal respiratory depression.^{11,12} DEX is also associated with reduction in delirium and postoperative stress, and increased patient satisfaction.¹³

Decreased postoperative agitation^{14,15} and delirium^{16,17} has been attributed to DEX, promoting a beneficial effect on morbidity and mortality associated with both conditions, which, in the present study, will be denominated postoperative cognitive and behavioral dysfunction. Therefore, the aim of the study was to evaluate the effects of dexmedetomidine on postoperative agitation and delirium in patients submitted to general anesthesia for non-cardiac surgery.

Method

We conducted a systematic review with meta-analysis of clinical trials on the effects of DEX on postoperative cognitive and behavioral dysfunction in adult patients submitted to general anesthesia for non-cardiac surgery. We complied with Prisma guidelines¹⁸ for the construction of a systematic review and meta-analysis of randomized clinical trials. We searched PubMed and Web of Science database English language articles published between January 2013 and March 2020. The search was performed using the key-

words "dexmedetomidine, delirium and agitation" or their synonyms, separated by AND and OR interlocutors with the following search strategy: (((((Deliri *) OR agitat *) AND dexmedetomidine))). To complement the search, we carried out a manual analysis of the references of the studies that complied with the inclusion criteria, aiming to detect original articles not recovered previously.

We included randomized, double-blind clinical trials with participants over 18-years of age, submitted to elective procedures under general anesthesia and receiving DEX or placebo. We excluded duplicate articles, studies comprising cardiac surgery patients or studies that used active control (other than saline solution).

Two independent investigators carried out a preliminary assessment of the titles/abstracts and extracted the data. After selecting the articles in conformity with the inclusion and exclusion criteria, there was full-text reading of the article. In case of disagreement, a third investigator made the final arbitration. Using a standardized form previously prepared by the authors, data were recorded on patient age, anesthesia technique, dosage and method administration of DEX, type of procedures and outcomes. For this study, the primary outcome was postoperative cognitive and behavioral dysfunction, comprising delirium and/or agitation (present or absent). Secondary outcomes included the interval in minutes for anesthesia awakening and tracheal extubation (awakening time and tracheal extubation time, respectively).

Sensitivity analysis was conducted to explore sources of heterogeneity among studies in the overall and in the subgroup analysis that evaluated cognitive outcome regarding patient age and the anesthesia technique. Statistical heterogeneity was calculated using the chi-square method (χ^2) and the Higgins test (I^2).¹⁹ The presence of heterogeneity was deemed to occur when $p < 0.05$ and $I^2 \geq 50\%$. The Odds Ratio (OR), with a 95% Confidence Interval (95% CI), was used to quantify the statistical difference between groups for dichotomous variables and Mean Difference (MD) for continuous variables (time in minutes). Following the qualitative analysis of the studies and statistical heterogeneity assessment, the random effects model was implemented using the DerSimonian-Laird²⁰ method, and the statistical analysis was performed using the Comprehensive Meta-analyses® software v.3.3. Assessment of potential publication bias was performed by visual analysis of the funnel plot and by using the Begg²¹ and Egger²² tests. The statistical significance adopted was 5%. To assess the impact of the study (Grading of Recommendations, Assessment, Development and Evaluations), we used the GRADEpro Guideline Development Tool (GRADEpro GDT®) software according to the methodological guidelines of the GRADE system provided by the Brazilian Ministry of Health.²³

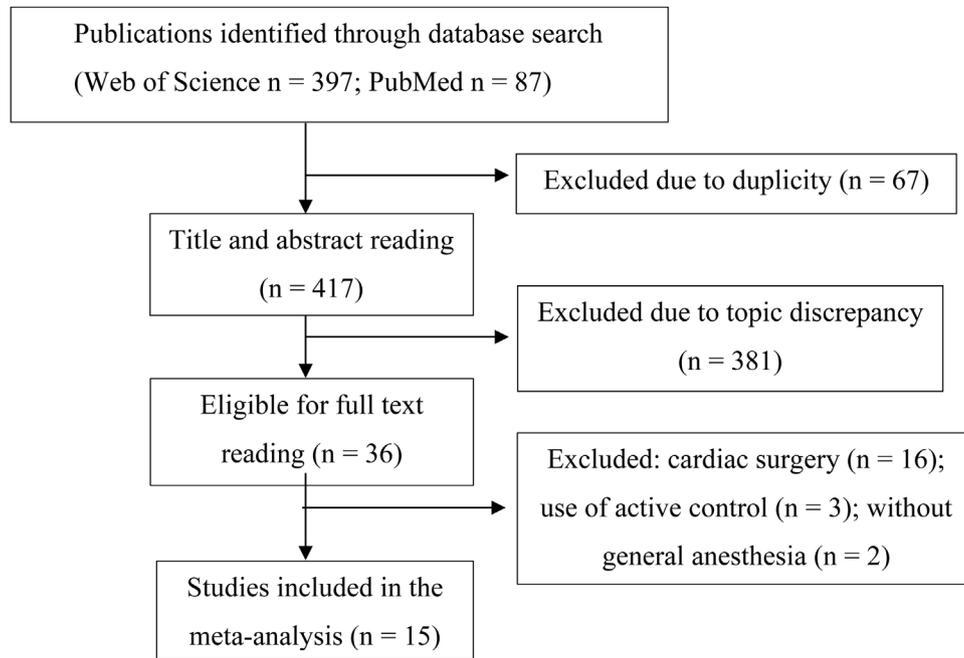


Figure 1 Flowchart of the selected studies.

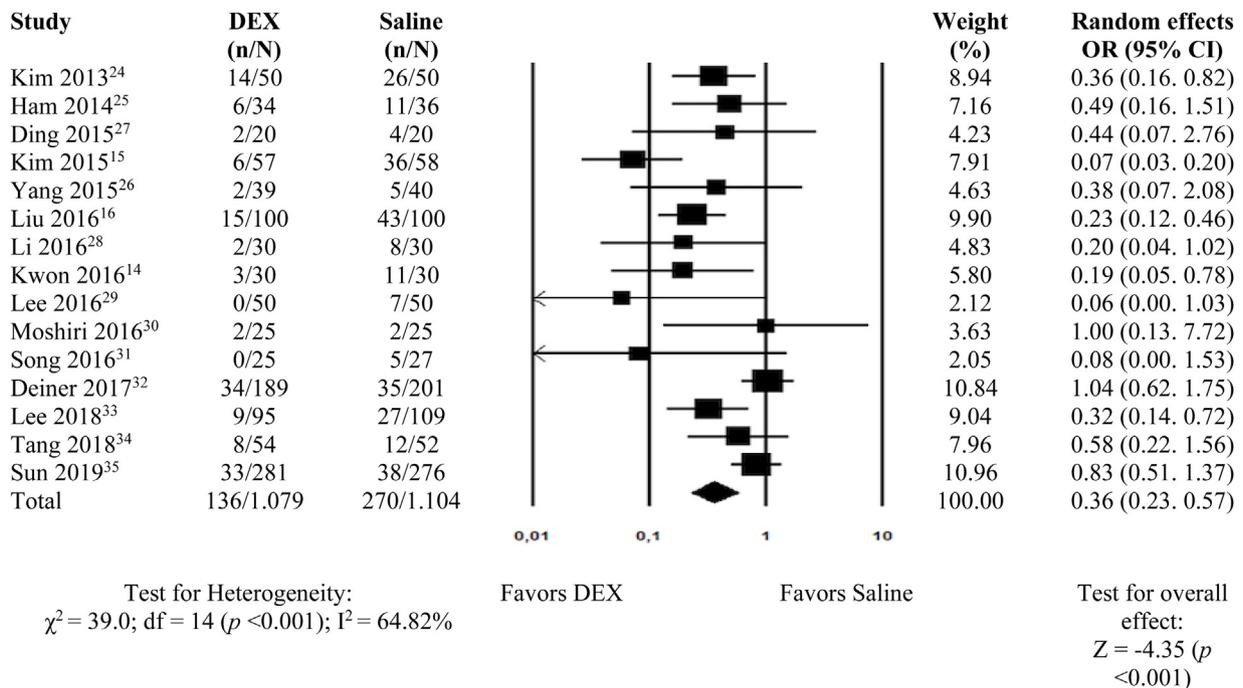


Figure 2 Meta-analysis of the effect of dexmedetomidine on postoperative cognitive and behavioral dysfunction in adults submitted to general anesthesia for non-cardiac surgery. df, Degrees of freedom.

Results

As depicted in Fig. 1, 484 studies (397 on Web of Science and 87 on PubMed) were identified, from which 15 were selected to constitute this meta-analysis.

Table 1 details the characteristics of the 15 trials selected.^{14–16,24–35} They comprised 2,183 patients (1,079 in

the intervention group and 1,104 in the control group). Seven studies were carried out in China, six in South Korea, one in the United States, and one in Iran.

Postoperative cognitive and behavioral dysfunctions were assessed in the 15 studies,^{14–16,24–35} and as shown in Fig. 2, the administration of DEX was considered a protective factor (OR=0.36; 95% CI 0.23–0.57 and $p < 0.001$). Postoperative delirium and agitation were separately evaluated,

Table 1 Description of the selected studies.

Year of publication of the study	Details of the study	n	Age range (years)	Procedure
Kim 2013 ²⁴	DEX 0.4 mcg.kg ⁻¹ .h ⁻¹	50	20–58	Nose surgery
	Salina	50		
Ham 2014 ²⁵	DEX 0.1 mcg.kg ⁻¹	34	20–45	Orthognathic surgery
	Salina	36		
Kim 2015 ¹⁵	DEX 0.4 mcg.kg ⁻¹ .h ⁻¹	57	≥65	Orthopedic surgery
	Saline	58		
Yang 2015 ²⁶	DEX 0.5 mcg.kg ⁻¹ .h ⁻¹ and 0.2–0.7 mcg.kg ⁻¹ .h ⁻¹	39	18–80	Oral and maxillofacial surgery
	Salina	40		
Ding 2015 ²⁷	DEX 0.8 mcg.kg ⁻¹ .h ⁻¹	20	45–80	Cystectomy
	Salina	20		
Liu 2016 ¹⁶	DEX 0.2–0.4 mcg.kg ⁻¹ .h ⁻¹	100	65–80	Orthopedic surgery
	Salina	100		
Li 2016 ²⁸	DEX 0.6 mcg.kg ⁻¹ .h ⁻¹	30	18–65	Open gastrectomy
	Salina	30		
Lee 2016 ²⁹	DEX 0.1 mcg.kg ⁻¹ .h ⁻¹	50	≥20	Thoracoscopy
	Salina	50		
Kwon 2016 ¹⁴	DEX 0.5 mcg and 0.5 mcg.kg ⁻¹ .h ⁻¹	30	30–80	Transurethral resection of the prostate
	Salina	30		
Moshiri 2016 ³⁰	DEX 0.5 mcg.kg ⁻¹ .h ⁻¹	25	18–50	Electroconvulsive therapy
	Salina	25		
Song 2016 ³¹	DEX 0.5 mcg.kg ⁻¹ .h ⁻¹	25	18–60	Craniotomy
	Salina	27		
Deiner 2017 ³²	DEX 0.5 mcg.kg ⁻¹ .h ⁻¹	189	≥68	Non-cardiac elective surgery
	Salina	201		
Lee 2018 ³³	DEX 0.1 mcg.kg ⁻¹ and 0.2–0.7 mcg.kg ⁻¹ .h ⁻¹	95	≥65	Non-cardiac surgery
	Salina	109		
Tang 2018 ³⁴	DEX 0.1 mcg.kg ⁻¹ and 0.3 mcg.kg ⁻¹ .h ⁻¹	54	18–70	Neurosurgery
	Salina	52		
Sun 2019 ³⁵	DEX 0.1 mcg.kg ⁻¹ .h ⁻¹	281	≥65	Non-cardiac surgery
	Salina	276		
Total		2,183		

and DEX was effective in reducing both complications (6 studies^{16,27,32–35}; OR = 0.53; 95% CI 0.31–0.92 and $p = 0.023$; and 9 studies^{14,15,24–26,28–31}; OR = 0.24; 95% CI 0.13–0.42 and $p < 0.001$, respectively).

Fig. 3 depicts the age sub-group analysis (adults under 6-years vs. elderly above 60-years of age), and shows that administering DEX reduced the rate of postoperative cognitive and behavioral dysfunction in adults under 60-years of age (4 studies^{24,25,30,31}; OR = 0.40; 95% CI 0.22–0.75 and $p = 0.004$), and in the elderly (5 studies^{15,16,32,33,35}; OR = 0.52; 95% CI 0.39–0.69 and $p = 0.018$).

Regarding anesthesia technique sub-groups (intravenous vs. inhalational), two studies^{28,35} were excluded because they involved patients undergoing both techniques indistinctly. Conversely, one study¹⁵ was included in the sub-analysis of both techniques, as they were discriminated between groups. DEX was shown to be beneficial against postoperative cognitive and behavioral dysfunction in both procedures: intravenous anesthesia (5 studies^{15,16,28,30,31}; OR = 0.18; 95% CI 0.08–0.40 and $p < 0.001$) and inhalational anesthesia (9 studies^{14,15,24–27,29,33,34} OR = 0.28; 95% CI 0.17–0.47 and $p < 0.001$) (Fig. 3).

Awakening time was assessed in five studies^{14,25,28,29,34} and there was no significant difference between the

groups (MD = 1.19; 95% CI –0.97–3.36; $p = 0.280$). Fig. 4 shows that tracheal extubation time was different between groups, with a lengthier duration for the DEX group (4 studies^{24,28,29,31}; MD = 1.43; 95% CI 0.76–2.11; $p < 0.001$).

The funnel plot analysis (Fig. 5) shows an asymmetry with absence of studies with small and medium samples to the right of the Summary of Findings, however the Begg ($p = 0.458$) and Egger ($p = 0.050$) tests refute the hypothesis of publication bias. The evaluation by the GRADE protocol demonstrated that, regarding search execution, the study has high safety.

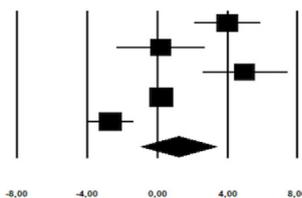
Discussion

This meta-analysis included 15 randomized clinical trials published between 2013 and 2019, evaluating the effect of DEX on cognitive and behavioral dysfunction in the post-operative period of adult patients submitted to general anesthesia.

We observed variation in the dosage and method administration of DEX, with studies administering DEX throughout the intraoperative period, while others used it only at anesthetic induction, and others that maintained the drug

Awakening time

Study	DEX		Saline		<i>p</i> value	Weight (%)	Random effects MD (95%CI)
	Mean (min)	N	Mean (min)	N			
Ham 2014 ²⁵	11.0	34	7.0	36	0.000	19.73	4.00 (2.10, 5.90)
Li 2016 ²⁸	6.3	30	6.1	30	0.877	17.67	0.20 (-2.32, 2.72)
Lee 2016 ²⁹	15.4	50	10.4	50	0.000	18.03	5.00 (2.58, 7.42)
Kwon 2016 ¹⁴	7.4	30	7.2	30	0.161	23.15	0.20 (-0.08, 0.48)
Tang 2018 ³⁴	7.7	54	10.4	52	0.000	21.42	-2.70 (-4.01, -1.39)
Total		198		198		100.00	1.19 (-0.97, 3.36)

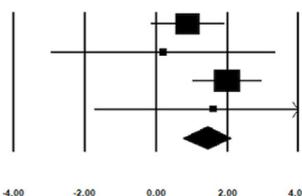


Test for Heterogeneity:
 $\chi^2 = 49.47$; $df = 4$ ($p < 0.001$); $I^2 = 91.92\%$

Test for overall effect:
 $Z = 1.080$ ($p = 0.280$)

Tracheal extubation time

Study	DEX		Saline		<i>p</i> value	Weight (%)	Random effects MD (95% CI)
	Mean (min)	N	Mean (min)	N			
Kim 2013 ²⁴	8.7	50	7.8	50	0.092	42.45	0.90 (-0.14, 1.94)
Li 2016 ²⁸	7.3	30	7.1	30	0.902	4.54	0.20 (-2.97, 3.37)
Lee 2016 ²⁹	20.0	50	18.0	50	0.000	48.86	2.00 (1.03, 2.97)
Song 2016 ³¹	38.4	25	36.8	27	0.349	4.15	1.60 (-1.72, 4.92)
Total		155		157		100.00	1.43 (0.76, 2.11)



Test for Heterogeneity:
 $\chi^2 = 2.93$; $df = 3$ ($p = 0.403$); $I^2 = 0\%$

Favors Saline Favors DEX

Test for overall effect:
 $Z = 4.163$ ($p < 0.001$)

Figure 3 Meta-analysis of the effect of dexmedetomidine on postoperative cognitive and behavioral dysfunction according to age sub-groups and type of anesthesia in adults submitted to general anesthesia for non-cardiac surgery. *df*, Degrees of freedom.

postoperatively. Such studies have achieved similar results regarding the rate of postoperative cognitive and behavioral dysfunction, suggesting there is no recommended time for the administration of DEX regarding its beneficial effect against such events.

Delirium is a multifactor event and the most effective prevention strategies comprise pharmacological and non-pharmacological approaches.^{1–3} Among the pharmacological options, DEX was effective in reducing the delirium rate when compared to placebo.^{16,33}

This meta-analysis shows DEX as a protective factor against delirium and postoperative agitation in adults submitted to general anesthesia for non-cardiac surgery and a similar result has been found by other authors.^{15,24,26,28} Although the actual mechanism for this effect remains unknown, the analgesic and sedative effects of DEX are thought to be contributing factors.^{13,36} Studies have suggested a perioperative anti-inflammatory activity of DEX as they reported a decrease in plasma concentration of interleukin 6 and the tumor necrosis factor alpha.³⁷ There is also evidence that DEX decreases plasma concentration of neuron-specific enolase and S100 β protein, both neural injury biomarkers perioperatively, and promotes neuroprotective effect.³⁴ Therefore, one should consider that DEX, additionally to its known action at the locus coeruleus, has inherent neurocytological protection activity,^{28,34,37} reducing postoperative agitation and delirium and thus

contributing to preservation of preoperative neurological status.³²

Elderly people are more prone to delusions and to cognitive dysfunction postoperatively, nonetheless DEX acted as a beneficial anesthetic adjunct agent as it prevented these events in both age sub-groups analyzed, adults below 60-years and the elderly sub-group. This result was also found elsewhere, however, when trials assessed the DEX effect in patients submitted to cardiac and non-cardiac surgery.³⁸ Thus, DEX effectiveness in preventing cognitive and behavioral dysfunction revealed to be age independent.

Regarding the analysis by subgroup of anesthetic technique, we observed that DEX was a protective factor for cognitive and behavioral dysfunction in both intravenous and inhalation general anesthesia. This finding underlines the concepts that lessening the endocrine-metabolic stress and providing analgesia play a more prominent role than choosing the anesthetic technique itself.³⁹

This study revealed no difference in awakening time with administration of DEX, conflicting with the literature.^{25,29} Due to its elimination half-life of 2 to 2.5 hours and upward context-sensitive half-life, DEX sustains sedative activity through its sympatholytic properties.⁴⁰ Additionally, due to DEX capability of intensifying the effects of other analgesics simultaneously administered,⁴¹ there is the likelihood of extending anesthesia effects and thus prolonging awakening time. Conversely, a significant difference was found in tracheal extubation time, but with irrelevant clinical sig-

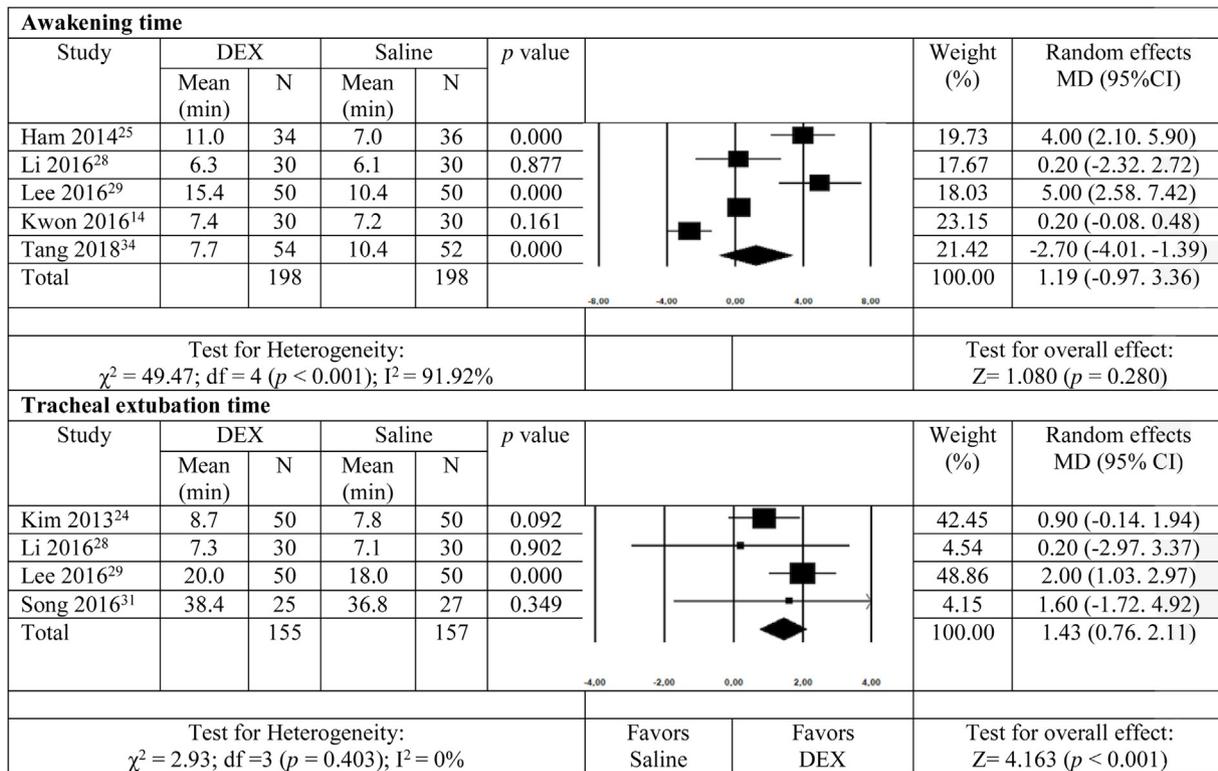


Figure 4 Meta-analysis of the effect of dexmedetomidine on awakening and tracheal extubation time in adults submitted to general anesthesia for non-cardiac surgery. df, Degrees of freedom.

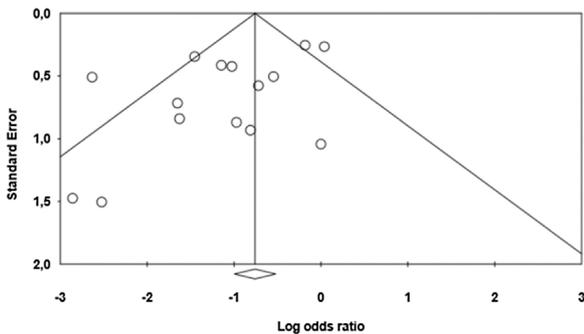


Figure 5 Funnel plot of the effect of dexmedetomidine on cognitive and behavioral dysfunction in adults submitted to general anesthesia for non-cardiac surgery.

nificance, or less than two minutes. This effect coincides with the literature.³⁸ The reason for not observing a greater difference may lie in the heterogeneity of the methods and timing of drug administration in the primary studies included here.

The quality of the meta-analysis depends on the selection of relevant studies, heterogeneity, and detection bias.¹⁸ Despite the different strategies adopted in this study to minimize possible biases, they cannot be ruled out. A search was performed using two important databases, complemented by manual search, and the selected works were submitted to the appreciation of two independent investigators. We included only clinical, double-blind, randomized tri-

als. The present study adds an important contribution in demonstrating the protective effect of DEX against cognitive and behavioral dysfunction in patients submitted to non-cardiac surgery. Additional systematic reviews with meta-analysis can be found in the literature, however, they include patients admitted in intensive care units, undergoing cardiac surgery or only elderly patients.^{38,42,43}

The authors of this meta-analysis considered that the studies were heterogeneous, due to the variation of DEX dose between groups, and the type of surgery the patients were submitted to. Nonetheless, the heterogeneity was tested and confirmed with a high χ^2 value and an I^2 greater than 64%, which indicate medium heterogeneity.

As they followed the GRADE protocol,²³ the authors considered that the study has no significant publication bias, because the search was conducted using two important databases and was complemented by manual analysis of the references. The GRADE outcome indicates that the study has a considerable impact and high consistency concerning the DEX protection effect on postoperative cognitive and behavioral dysfunction.

DEX provides reliable hemodynamic stability and has been increasingly administered in anesthetic practice due to its straightforward use in the pre-anesthetic, intraoperative and even postoperative period, as well as its wide range of dosage formulations.¹¹ In addition to the beneficial effects on cognitive and behavioral dysfunction evaluated in this study, there is a reported sparing effect on the use of volatile agents and opioids.³¹

Conclusion

This systematic review with meta-analysis reveals that the administration of dexmedetomidine reduced from 43% to 77% the likelihood of cognitive and behavioral dysfunction in the postoperative period of adult patients submitted to general anesthesia for non-cardiac surgery.

Conflicts of interest

The authors declare no conflicts of interest.

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