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REVIEW ARTICLE

Effect of dexmedetomidine in children undergoing general anesthesia with sevoflurane: a meta-analysis

Marco Aurélio Soares Amorim[a,*], **Catia Sousa Govêia**[b,c,d], **Edno Magalhães**[c,e,f], **Luís Cláudio Araújo Ladeira**[g], **Larissa Govêia Moreira**[h], **Denismar Borges de Miranda**[i,j]

[a] *Centro de Ensino e Treinamento José Quinan, Goiânia, GO, Brazil*
[b] *Universidade de Brasília (UnB), Centro de Ensino e Treinamento, Brasília, DF, Brazil*
[c] *Sociedade Brasileira de Anestesiologia, Rio de Janeiro, RJ, Brazil*
[d] *Universidade de Brasília (UnB), Faculdade de Ciências Médicas, Brasília, DF, Brazil*
[e] *Universidade de Brasília (UnB), Brasília, DF, Brazil*
[f] *Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil*
[g] *Hospital Universitário de Brasília, Brasília, DF, Brazil*
[h] *Secretaria de Saúde do Distrito Federal, Brasília, DF, Brazil*
[i] *Pontifícia Universidade Católica de Goiás (PUC-GO), Goiânia, GO, Brazil*
[j] *Universidade Federal de Goiás (UFG), Instituto de Medicina Tropical e Saúde Pública, Goiânia, GO, Brazil*

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Abstract
Background and objectives: Sevoflurane is often used in pediatric anesthesia and is associated with high incidence of psychomotor agitation. In such cases, dexmedetomidine (DEX) has been used, but its benefit and implications remain uncertain. We assessed the effects of DEX on agitation in children undergoing general anesthesia with sevoflurane.
Method: Meta-analysis of randomized clinical and double-blind studies, with children undergoing elective procedures under general anesthesia with sevoflurane, using DEX or placebo. We sought articles in English in PubMed database using the following terms: Dexmedetomidine, sevoflurane (Methyl Ethers/sevoflurante), and agitation (Psychomotor Agitation). Duplicate articles with children who received premedication and used active control were excluded. It was adopted random effects model with DerSimonian–Laird testing and odds ratio (OR) calculation for dichotomous variables, and standardized mean difference for continuous variables, with their respective 95% confidence interval (CI).
Results: Of 146 studies identified, 10 were selected totaling 558 patients (282 in DEX group and 276 controls). The use of DEX was considered a protective factor for psychomotor agitation (OR = 0.17; 95% CI 0.13–0.23; $p < 0.0001$) and nausea and vomiting in PACU (OR = 0.49; 95% CI 0.35–0.68; $p < 0.0001$). Wake-up time and PACU discharge time were higher in the dexmedetomidine group. There was no difference between groups for extubation time and duration of anesthesia.

* Corresponding author.
E-mail: marcomc18@hotmail.com (M.A. Amorim).

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Conclusion: Dexmedetomidine reduces psychomotor agitation during wake-up time of children undergoing general anesthesia with sevoflurane.

PALAVRAS-CHAVE
Anestesia geral;
Anestésicos inalatórios;
Dexmedetomidina;
Agitação psicomotora;
Metanálise

Efeito da dexmedetomidina em crianças submetidas à anestesia geral com sevoflurano: uma metanálise

Resumo
Justificativa e objetivos: Sevoflurano é frequentemente usado em anestesia pediátrica e está associado à alta incidência de agitação psicomotora ao despertar. Nesses casos a dexmedetomidina (dex) tem sido usada, porém permanecem incertos seus benefícios e suas implicações. Foram avaliados os efeitos da dex sobre a agitação no despertar de crianças submetidas à anestesia geral com sevoflurano.
Método: Metanálise de ensaios clínicos randomizados e duplamente encobertos, com crianças submetidas a procedimentos eletivos sob anestesia geral com sevoflurano, que usaram dex ou placebo. Buscaram-se artigos em língua inglesa na base de dados Pubmed com termos como *Dexmedetomidine, sevoflurane (Methyl Ethers/sevoflurane) e agitation (Psychomotor Agitation)*. Artigos duplicados, com crianças que receberam medicação pré-anestésica e que usaram controle ativo foram excluídos. Adotou-se modelo de efeitos aleatórios com testes de DerSimonian-Laird e cálculo de *odds ratio* (OR) para variáveis dicotômicas e diferença de média padronizada para variáveis contínuas, com seus respectivos intervalos de confiança de 95% (IC).
Resultados: Dos 146 estudos identificados, 10 foram selecionados, com 558 pacientes (282 no grupo dex e 276 controles). O uso da dex foi considerado fator de proteção para agitação psicomotora (OR = 0,17; 95% IC 0,13-0,23; p < 0,0001) e para náuseas e vômitos na SRPA (OR = 0,49; 95% IC 0,35-0,68; p < 0,0001). Tempo para despertar e para alta da SRPA foram maiores no grupo dexmedetomidina. Não houve diferença entre os grupos para tempo de extubação e duração da anestesia.
Conclusão: A dexmedetomidina reduz a agitação psicomotora no despertar de crianças submetidas à anestesia geral com sevoflurano.

Introduction

Sevoflurane is widely used in pediatric anesthesia for its pharmacological profile, which allows rapid inhalational induction and awakening from anesthesia, low hepatotoxicity and hemodynamic stability.[1] However, the occurrence of agitation is a common phenomenon in children undergoing general anesthesia with sevoflurane.[1]

Emergence agitation in children was first described in the early 1960s and is characterized by a dissociated state of consciousness in which the child becomes inconsolable, irritable, uncooperative, and sometimes aggressive. Although temporary, it is an extremely distressing event for children, parents, and health professionals.[2]

Prevalence of agitation varies from 25% to 80% in the literature, depending on the definition and criteria used by the authors.[1,3] It is influenced by the technique and anesthetic agents.[4] Different drugs such as opioids, ketamine, benzodiazepines, and α_2-agonists,[2] have been used in the prevention and treatment of agitation, but with varying success, which contributes to the development of studies to improve perioperative care delivered to children.

Dexmedetomidine (Dex), dextrorotatory enantiomer of medetomidine, is a highly selective α_2-adrenergic, with an α_2:α_1 receptor ratio of 1,600:1, and important sedative and analgesic effects.[5] Its sedative effect occurs through interaction with postsynaptic α_2-receptors in the *locus coeruleus*, reduces noradrenalin release, and facilitates the action of inhibitory neurons, particularly gamma-aminobutyric acid system. The analgesic effect is promoted by the action of α_2-receptors on dorsal horn and supraspinal cord and decreased release of substance P.[6]

Dexmedetomidine has been used to reduce psychomotor agitation, although the actual benefits and implications in anesthetic practice are still uncertain. Thus, the aim of this meta-analysis was to evaluate the effects of dexmedetomidine on emergence agitation in children undergoing general anesthesia with sevoflurane, including the incidence of postoperative nausea and vomiting (PONV), emergence time, extubation time, duration of anesthesia, and time of discharge from the post-anesthesia recovery room (PACU).

Methods

This is a meta-analysis of clinical trials evaluating the use of dexmedetomidine to prevent emergence agitation in children undergoing general anesthesia with sevoflurane. PRISMA guidelines[7] were followed to perform a systematic review and meta-analysis of randomized controlled trials. Articles in English (2000–2014) were selected in the Pubmed database with keywords such as Dexmedetomidine, sevoflurane (Methyl Ethers/sevoflurante) and agitation (Psychomotor Agitation), or its synonyms separated by AND/OR interlocutors with the following search strategy: *(dexmedetomidine[MeSH Terms]) OR adrenergic alpha agonists[MeSH Terms]) OR dexmedetomidine[Title/Abstract]) OR dexmedetomidine) OR adrenergic alpha agonists) AND anesthetics, intravenous[MeSH Terms]) OR anesthetics, intravenous[Title/Abstract]) AND (hypnotics and sedatives[MeSH Terms])) OR (hypnotics and sedatives[Title/Abstract])) AND sevoflurane) OR sevoflurane[Title/Abstract]) OR sevoflurane[Supplementary Concept])) AND children[MeSH Terms])) AND agitation, psychomotor[MeSH Terms]*. In addition to the search, we reviewed manually the references of studies meeting the inclusion criteria, in order to identify original studies that were not previously found.

Randomized, double-blind, controlled studies, with children (under 10 years old) undergoing elective procedures under general anesthesia with sevoflurane, using dexmedetomidine or placebo were included. Duplicate articles or with children using premedication, involving only sedation and using active control were excluded.

Two independent researchers (MA and CG) conducted a preliminary assessment of the titles/abstracts and data extraction. Selected studies were read in full considering the inclusion and exclusion criteria. In case of disagreement, a third researcher (LC) made the final evaluation. Data regarding patient's age, anesthesia (Dex dose), type of procedure, and outcomes were recorded on a standardized form developed by the authors. For this study, the following outcomes were considered: emergence agitation (defined by each paper according to the scale used: Paediatric Anaesthesia Emergence Delirium – PAED,[8] Watcha,[9] and five-point scale)[10]; PONV (present or absent); and times for extubation, emergence, PACU discharge, and duration of anesthesia (time interval described by articles in minutes).

Sensitivity analysis was planned to explore sources of heterogeneity between studies, when present. Statistical heterogeneity was calculated using the chi-square method (χ^2) and Higgins' test (I^2).[11] Presence of heterogeneity was considered at $p < 0.05$ and $I^2 \geq 50\%$. Odds ratio (OR) with 95% confidence interval (CI) was used to quantify the statistical difference between groups for dichotomous variables and standardized mean difference (SMD) for continuous variables (time in minutes). After assessing the quality and statistical heterogeneity of studies, we adopted the random effects model using the DerSimonian–Laird[12] method and statistical analysis using the BioEstat® 5.0 software.[13] The assessment of potential for publication bias was made by visual analysis of funnel plots and Begg's[14] and Egger's[15] tests, with statistical significance level set at 5%.

Results

Initially, 146 studies were identified (116 studies in Pubmed and 30 manually searched), of which 10 were selected to compose this meta-analysis, as shown in Fig. 1.

The 10 studies included 558 patients, 282 in the intervention group, and 276 in the control group (Table 1). Three studies were conducted in Turkey,[17–19] three studies in China,[21–23] and others studies in Chile,[1] United States,[16] Japan,[20] and South Korea.[24]

Emergence agitation was assessed in 10 studies, and the use of dexmedetomidine was considered a protection factor (OR = 0.17; 95% CI 0.13–0.23; $p < 0.0001$), as shown in Fig. 2. Surgery subgroup analysis showed no effect change (urogenital[1,24] with OR = 0.14; 95% 0.04–0.44; $p = 0.0008$; ophthalmic[21,23] with OR = 0.06; 95% CI 0.01–0.45; $p = 0.0067$, ENT,[17,19] with OR = 0.20; 95% CI 0.14–0.30; $p < 0.0001$).

The use of dexmedetomidine reduces the incidence of PONV (Fig. 3), with OR = 0.49 (95% CI 0.35–0.68 and $p < 0.0001$).

Emergence time was assessed in seven studies,[17–19,21–23] (SMD = 1.78; 95% CI 1.12–2.44; $p = 0.0001$) and PACU discharge in four studies[1,16,18,23] (SMD = 8.54; 95% CI 6.62–10.44; $p < 0.0001$), higher in dexmedetomidine group.

There was no difference between groups regarding extubation time (SMD = 0.70; 95% CI 0.33–1.06; $p = 0.0002$), assessed in eight studies,[1,16–19,21–23] and duration of anesthesia (SMD = 3.19; 95% CI −0.79–7.14; $p = 0.11$), assessed in seven studies.[1,16,18–20,23,24]

Based on the funnel plot analysis (Fig. 4), there is an asymmetry with no small sample studies to the right of the summary effect, which supports a potential for publication bias confirmed by Begg's ($p = 0.02$) and Egger's ($p = 0.03$) tests.

Discussion

This meta-analysis consists of 10 randomized controlled trials published between 2004 and 2014, which assessed the effect of dexmedetomidine on emergence agitation in children undergoing general anesthesia with sevoflurane.

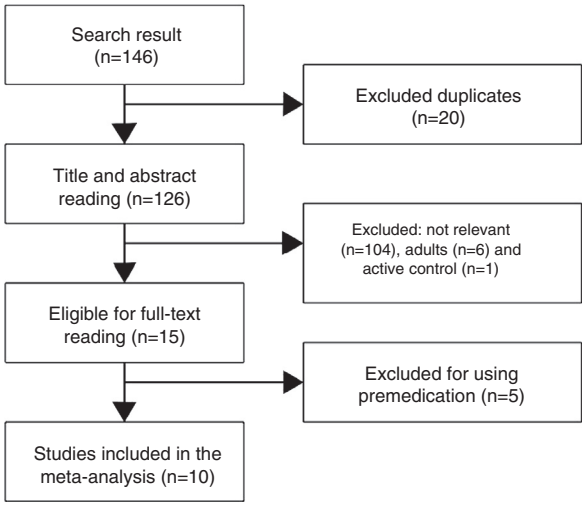

Figure 1 Diagram of study selection.

Table 1 Description of selected studies.

Study	Year of publication	Study details	*n*	Age	Procedure type
Ibacache[1]	2004	Dex 0.3 mcg kg^{-1}	30	1–10	Inguinal hernia repair, orchidopexy and circumcision
		Saline solution	30		
Shukry[16]	2005	Dex 0.2 mcg kg^{-1}	23	1–10	Elective surgeries
		Saline solution	23		
Guler[17]	2005	Dex 0.5 mcg kg^{-1}	30	3–7	Adenotonsillectomy
		Saline solution	30		
Isik[18]	2006	Dex 1 mcg kg^{-1}	21	1–10	Magnetic resonance imaging
		Saline solution	21		
Erdil[19]	2009	Dex 0.5 mcg kg^{-1}	30	2–7	Adenoidectomy with or without myringotomy
		Saline solution	30		
Sato[20]	2010	Dex 0.3 mcg kg^{-1}	39	1–9	Outpatient surgery
		Saline solution	42		
Lili[21]	2012	Dex 0.5 mcg kg^{-1}	30	3–7	Vitrectomy
		Saline solution	30		
He[22]	2013	Dex 1 mcg kg^{-1}	32	3–7	Small superficial surgeries
		Saline solution	26		
Chen[23]	2013	Dex 1 mcg kg^{-1}	27	2–7	Strabismus
		Saline solution	24		
Kim[24]	2014	Dex 1 mcg kg^{-1}	20	1–5	Hernioplasty or orchidopexy
		Saline solution	20		

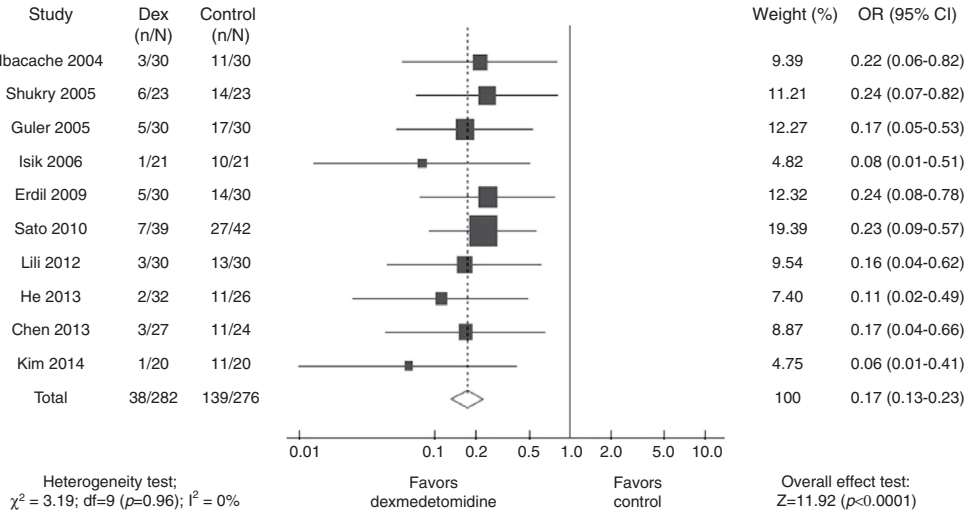

Figure 2 Meta-analysis of dexmedetomidine effect on emergence agitation in children undergoing general anesthesia with sevoflurane.

There was variation in dexmedetomidine dosage (0.2–1.0 mcg kg^{-1}), as well as in administration technique. One used continuous infusion of dexmedetomidine[16] and the others used it for a short period, ranging from 5 to 10 min. Regarding the time of administration, only one study administered the drug at the end of the procedure[17] and all others after induction of anesthesia, with similar results regarding emergence agitation, which confirms that there is no ideal time for dexmedetomidine administration.

The causes of emergence agitation following general anesthesia are multifactorial; it may involve pain, anxiety, and disorientation on rapid awakening.[25] In an attempt to minimize this event, numerous drugs have been used, such as opioids, ketamine, benzodiazepines, and α_2-agonists, but with uncertain results.[2] This meta-analysis presents dexmedetomidine as a protective factor for emergence agitation in children undergoing general anesthesia with sevoflurane, similar result already described by other authors.[2] Although the actual mechanism for this effect remains unknown, it is believed that the analgesic and sedative effects of dexmedetomidine contribute to this phenomenon, as postoperative analgesic consumption was lower.[2]

Sevoflurane has been associated with high incidence of emergence agitation in children undergoing general anesthesia,[1,17] even without surgery.[18] This fact is not yet fully understood. It has been hypothesized that sevoflurane can exert an irritating effect on the central nervous

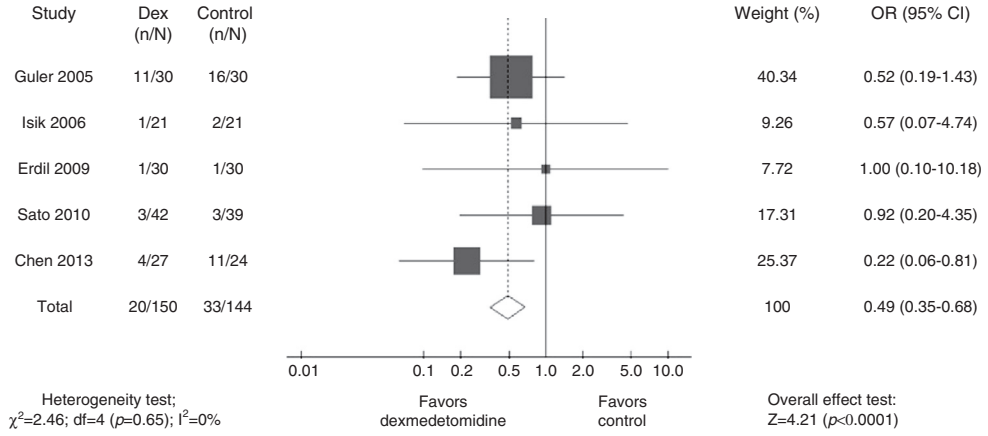

Figure 3 Meta-analysis of dexmedetomidine effect on nausea and vomiting incidence in children undergoing general anesthesia with sevoflurane.

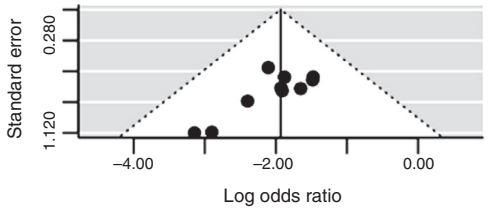

Figure 4 Funnel plot of dexmedetomidine effect on emergence agitation in children undergoing general anesthesia with sevoflurane.

system.[26] The decrease in emergence agitation provided by dexmedetomidine may also be justified by the lower consumption of sevoflurane.[27]

PONV are common complications in children undergoing general anesthesia with sevoflurane.[18] Studies have shown conflicting results on the effect of dexmedetomidine for this complication.[20,23] In the present study, the use of dexmedetomidine appeared as a protective factor for the incidence of nausea and vomiting. The use of dexmedetomidine has been associated with reduced need for postoperative opioid analgesics, which implies a lower incidence of nausea and vomiting induced by opioid.[28] Moreover, dexmedetomidine has been used successfully in the treatment of cyclical vomiting syndrome in children, by yet-unknown mechanisms.[29]

In this study, the times of emergence and PACU discharge were considered statistically higher in dexmedetomidine group, justified by its sedative effect,[5] but without clinical repercussions.[17–19,22]

Regarding the time of extubation and duration of anesthesia, this meta-analysis found no statistically significant difference between dexmedetomidine and control groups. This result disagrees with some individual studies, by finding a longer extubation time and duration of anesthesia in dexmedetomidine group.[17,18]

It is noteworthy that the studies used different scales to assess agitation. One study[23] used the PAED scale[8], four studies[1,16,21,24] used the Watcha scale,[9] and five studies[17–20,22] used the five-point scale.[10] Although only the PAED scale has been validated,[8] the others are widely used in clinical researches.

The meta-analysis quality depends on the selection of relevant studies, heterogeneity, and detection bias.[2] Despite the different strategies used in this study to minimize possible biases, it may not be discarded. A search was conducted in an important database and selected works were submitted to two independent evaluators. Double-blind randomized clinical trials were included. The use of random effects model is justified by the observation of clinical heterogeneity identified in studies: different doses and times of dexmedetomidine administration, procedures, and emergence assessment scales. Another limitation of this study refers to the use of only one database for search, which confirms the occurrence of publication bias, as identified in this meta-analysis.

Due to its good hemodynamic stability, dexmedetomidine has been used as an adjuvant anesthetic and may be used as pre-anesthetic medication, during anesthesia, or even postoperatively, and provides sedation and analgesia[5] without respiratory depression.[17,18,20,30] Its use entails benefits, such as lower consumption of inhalational anesthetics,[21] less need for postoperative analgesic and opioid drugs,[2,28] and lower oxygen consumption.[31]

In conclusion, this meta-analysis highlights the use of dexmedetomidine in reducing emergence agitation in children undergoing general anesthesia with sevoflurane.

Conflicts of interest

The authors declare no conflicts of interest.

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