Efficacy of dexmedetomidine on postoperative shivering: a meta-analysis of clinical trials

Efficacité de la dexmédétomidine pour contrôler les frissons postopératoires: une méta-analyse d'études cliniques

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Abstract

Purpose Shivering is a frequent complication in the postoperative period. The aim of the current meta-analysis was to assess the efficacy of dexmedetomidine on postoperative shivering.

Methods Two researchers independently searched PubMed, EMBASETM and the Cochrane Central Register of Controlled Trials for controlled clinical trials. The meta-analysis was performed by Review Manager.

Results Thirty-nine trials with 2,478 patients were included in this meta-analysis. Dexmedetomidine reduced postoperative shivering compared with placebo (risk ratio [RR] = 0.26; 95% confidence interval [CI]: 0.20 to 0.34),

with a minimum effective dose of $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ (RR = 0.36; 95% CI: 0.21 to 0.60). The anti-shivering effect can be achieved both intravenously and epidurally when administered within two hours prior to the end of surgery. The efficacy of dexmedetomidine was similar to widely used anti-shivering agents, such as fentanyl, meperidine, tramadol, clonidine and so on; however, dexmedetomidine may increase the incidence of sedation, hypotension, bradycardia and dry mouth.

Conclusions The present meta-analysis indicates that dexmedetomidine shows superiority over placebo, but not over other anti-shivering agents. Therefore, considering its high price and potential adverse events, dexmedetomidine may not be appropriate solely for the purpose of the prevention of postoperative shivering.

Author contributions Zhen-Xiu Liu, Feng-Ying Xu, Xiao Liang, and Zui Zou were involved in the study design. Feng-Ying Xu, Jian-Hua Xia, and Zui Zou were involved in the study conduct. Zhen-Xiu Liu, Feng-Ying Xu, Xiao Liang, Jing-Ru Wu, Miao Zhou, and Liang Wu were involved in data retrieval and analysis. Zhen-Xiu Liu, Feng-Ying Xu, and Zui Zou were involved in writing the paper.

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Résumé

Objectif Les frissons sont une complication fréquente en période postopératoire. L'objectif de cette méta-analyse était d'évaluer l'efficacité de la dexmédétomidine pour contrôler les frissons postopératoires.

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Méthode Deux chercheurs ont analysé de façon indépendante les bases de données PubMed, EMBASETM et le registre central d'études contrôlées Cochrane (Cochrane Central Register of Controlled Trials) pour en extraire les études cliniques contrôlées pertinentes. La méta-analyse a été réalisée avec Review Manager.

Résultats Trente-neuf études comportant un total de 2478 patients ont été incluses dans cette méta-analyse. La dexmédétomidine a réduit les frissons postopératoires par rapport au placebo (risque relatif [RR] = 0,26; intervalle de confiance [IC] 95 % : 0,20 à 0,34), avec une dose efficace minimum de 0,5 µg·kg⁻¹ (RR = 0,36; IC 95 % : 0,21 à 0,60). L'effet anti-frissons peut être obtenu par voie intraveineuse et péridurale lorsque l'agent est administré dans les deux heures précédant la fin de la chirurgie. L'efficacité de la dexmédétomidine était semblable à celle d'agents anti-frissons fréquemment utilisés tels que le fentanyl, la mépéridine, le tramadol et la clonidine; toutefois, la dexmédétomidine pourrait augmenter l'incidence de sédation, d'hypotension, de bradycardie et de sécheresse buccale.

Conclusion Cette méta-analyse indique que la dexmédétomidine démontre une supériorité par rapport au placebo, mais pas par rapport à d'autres agents anti-frissons. Par conséquent, au vu de son prix élevé et de ses effets secondaires néfastes potentiels, la dexmédétomidine peut ne pas être appropriée si le seul but est de prévenir les frissons postopératoires.

Shivering is a physiological response of the body for heat preservation through peripheral vasoconstriction and involuntary skeletal muscle contractions.¹ Despite the benefits from reducing heat loss, shivering increases the patients' oxygen consumption, carbon dioxide production, and energy expenditure,² and it may cause severe adverse effects during the recovery from general anesthesia, especially in patients with impaired cardiac and pulmonary reserves. Moreover, for awake patients, shivering is an uncomfortable experience, sometimes even worse than surgical pain.³ Effective prevention and treatment of shivering has become an essential step in increasing postoperative comfort and reducing shivering-related complications. Currently used anti-shivering agents are restricted by their side effects. For example, meperidine may induce nausea, vomiting, and respiratory depression,⁴ and patients receiving ketamine⁵ frequently experience hypertension and tachycardia.

Dexmedetomidine is a potent and highly selective α_2 -adrenoceptor agonist with sympatholytic, sedative, amnesic,⁶ and analgesic⁷ properties. Clinical researchers

have already studied the administration of dexmedetomidine to prevent shivering. Nevertheless, controversy about the effectiveness of dexmedetomidine for the prevention of shivering is still ongoing, with different results reported in associated literature. In our view, a quantitative analysis on a consolidation of the related data was needed, and therefore, we conducted the present meta-analysis in order to assess the relative merits regarding the anti-shivering effect of dexmedetomidine.

Methods

This meta-analysis of controlled trials evaluates the effect of intraoperative dexmedetomidine on postoperative shivering and was performed according to the recommendations of the PRISMA statement.

Search strategy

Two authors (L.Z.X and X.F.Y.) systematically searched PubMed, EMBASETM and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy comprised the following key words: (dexmedetomidine) and (shivering, shiver, tremor, shaking, or anti-shivering) and (postoperative, operation, surgery, anesthesia, or anaesthesia). The literature search was updated on August 30, 2014 with no language limitation. The reference lists of the reviews, original reports, and case reports (retrieved through the electronic searches) were checked to identify studies that had not yet been included in the computerized databases.

Study selection and data retrieval

The study selection criteria were pre-established. Inclusion criteria included: (1) controlled clinical trials; (2) intraoperative administration of dexmedetomidine; and (3) the reported presence or absence of shivering. Exclusion criteria included: (1) abstracts only; (2) patients with severe cerebrovascular disease or other contradictions for dexmedetomidine; (3) duplications; (4) missing data; and (5) incorrect statistical analysis performed in the report. The data retrieval included: name of the first author, publication year, funding, interventions, patients and operations, type of anesthesia, length of surgery, number of shivering cases and total patients, randomization, blinding, allocation concealment, withdrawal, body temperature, and side effects such as nausea, vomiting, and hypotension. Two authors (L.Z.X. and X.F.Y.) independently assessed the articles for compliance with the inclusion/exclusion criteria. Any

disagreement during the process of meta-analysis was resolved by discussion among all authors.

Qualitative assessment

Two authors (L.X. and Z.M.) independently evaluated the quality of the trials according to the guidelines recommended by the Cochrane Collaboration.⁸ Six categories were evaluated, with the first three considered as “key domains” (randomization and sequence generation, allocation concealment, blinding method, incomplete outcome data, selective outcome reporting, and other sources of bias). Each category was summarized into three levels: low risk, unclear risk, and high risk. The risk of bias of a particular study was assessed in relation to the three key domains: LOW (low risk of bias for all key domains); UNCLEAR (unclear risk of bias for one or more key domains); and HIGH (high risk of bias for one or more key domains).

Statistical analysis

The effect of dexmedetomidine on postoperative shivering compared with placebo or other anti-shivering drugs was estimated by calculating the pooled risk ratio (RR) and its 95% confidence intervals (CI) of the incidence of shivering. The overall effect was determined by a Z-test. All reported *P* values are two sided. A fixed effects model was used when $I^2 \leq 50\%$, otherwise a random effects model was adopted. Sensitivity analysis was performed to test the robustness of the results by re-analyzing the data after excluding the high-risk studies. Subgroup analyses were based on the types of anesthesia, the doses and routes administered, and the A-E interval (defined as the time interval from the last administration to the end of the operation. Two-hour duration was used as the cut-off point, because the half-life of dexmedetomidine is about two hours).⁹ Begg’s test was conducted to assess potential publication bias. Statistical analysis was performed with Review Manager (RevMan version 5.3; Cochrane Collaboration, Oxford, UK) and Stata[®] version 12.0 (Stata Corp, College Station, TX, USA).

Results

Study selection

As shown in the flow diagram (Fig. 1), the search of PubMed, EMBASE, CENTRAL, and the reference lists yielded 237 articles. Initially, 166 trials were discarded because they were not controlled trials according to the titles, and after reviewing the abstracts, an additional 21

trials were excluded as they were not relevant to our study. We could not retrieve the full texts of three^{10–12} of the remaining 50 papers despite attempting electronic retrieval interlibrary loan or contacting the authors. After carefully reading 47 papers, we excluded eight with no related endpoints. Finally, 39 trials^{3,9,13–49} met the selection criteria and were included in the meta-analysis.

Study characteristic

Twenty-two of the included studies explored the efficacy of intraoperative dexmedetomidine compared with placebo.^{3,9,13–32} Other control agents included fentanyl,^{33–36} remifentanyl,^{37,38} meperidine,¹⁵ midazolam,^{39–41} propofol,^{43,44} ketamine,^{45,46} tramadol,^{24,47} clonidine,⁴² propacetamol,⁴⁸ and buprenorphine⁴⁹ (Table 1). Twenty studies reported the side effects, including sedation,^{4,13,22,28,31} nausea,^{9,14,20,22,23,27,29,30} vomiting,^{14,22,23} bradycardia,^{17,20,23,26–28,30–32} hypotension^{20,23,26–28,30,32} and dry mouth.^{14,22,23} Only eight of the included articles clearly mentioned the funding status, five of which^{3,21,22,35,37} were supported by an institutional foundation, and three studies^{23,44,47} declared no financial support.

The methodological quality of the included studies

Thirty^{3,13,14,16,19–21,23,24,26–33,35–38,40–44,46–49} of the 39 included trials provided a detailed description of randomization. Odd/even admission number was used in the process of randomization in three trials.^{9,25,45} Twenty-nine trials^{3,9,13,14,16,19,21,23,27–31,33–38,41–44,47–49} reported allocation concealment, and 27 studies^{3,9,13,14,16,19,24,25,27–35,37–42,44,47–49} were double-blinded. No incomplete outcomes (attrition bias)⁸ were reported in the 39 included trials, and all studies reported every endpoint mentioned in the Methods section (reporting bias).⁸ however, some bias⁸ may exist in of the two trials,^{27,32} as the length of surgery was not clear. An overview of the risk of bias is summarized in Fig. 2.

Results of the meta-analysis

Dexmedetomidine versus placebo

Twenty-two trials^{3,9,13–32} including 1,415 patients investigated the anti-shivering efficacy of dexmedetomidine compared with placebo. The incidence of postoperative shivering in the dexmedetomidine group was significantly lower than in the placebo group (34.2% vs 8.6%, respectively; pooled RR = 0.26; 95% CI: 0.20 to 0.34) (Fig. 3). Begg’s test suggested no significant publication bias (*P* = 0.128) in this comparison between dexmedetomidine and placebo.

Furthermore, dexmedetomidine can significantly reduce postoperative nausea and vomiting (PONV) compared with

Fig. 1 Flow diagram of the inclusion and exclusion process

placebo (data not shown). Nevertheless, compared with placebo, dexmedetomidine increased the probability of sedation (pooled RR of five trials: 2.94; 95% CI: 2.18 to 3.98), bradycardia (pooled RR of nine trials: 2.39; 95% CI: 1.54 to 3.72), hypotension (pooled RR of seven trials: 1.35; 95% CI: 1.04 to 1.75), and dry mouth (pooled RR of three trials: 7.33; 95% CI: 2.28 to 23.58) (Table 2).

Subgroup analyses were carried out to evaluate the factors that affected postoperative shivering.

Types of anesthesia Dexmedetomidine significantly reduced the incidence of shivering in general anesthesia (pooled RR of 12 trials: 0.26; 95% CI: 0.20 to 0.34) and regional anesthesia (pooled RR of ten trials: 0.27; 95% CI: 0.16 to 0.45) (Fig. 3). The most common dexmedetomidine dosage was $1.0 \mu\text{g}\cdot\text{kg}^{-1}$, so we chose this group in one trial.¹

The A-E interval The incidence of shivering in groups with an A-E interval less than two hours was reduced by dexmedetomidine (pooled RR of 18 trials: 0.24; 95% CI: 0.19 to 0.32) compared with placebo (Fig. 4); however, only one trial³⁰ was conducted with an A-E interval more than two hours in which no statistical difference in the incidence of shivering could be found between dexmedetomidine and placebo ($P = 0.64$).

Dose of dexmedetomidine Subgroup analysis suggested a beneficial effect of a single-dose bolus of $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine compared with placebo (pooled RR of three trials: 0.36; 95% CI: 0.21 to 0.60). A sensitivity analysis to remove a high-risk study²¹ (high risk of bias for one or more key domains, refer to Methods section) showed a similar result favouring dexmedetomidine (pooled RR = 0.52; 95% CI: 0.31 to 0.87) and decreased heterogeneity (I^2 from 73% to 42%). One trial¹⁹ presented that $0.75 \mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine reduced the incidence of shivering with a reported P value of 0.002. A subgroup of dexmedetomidine $1.0 \mu\text{g}\cdot\text{kg}^{-1}$ also reduced the incidence of shivering (pooled RR of six trials: 0.24; 95% CI: 0.16 to 0.37) (Fig. 5).

Routes of administration Dexmedetomidine injected intravenously (pooled RR of 17 trials: 0.24; 95% CI: 0.18 to 0.31) or into the epidural space (pooled RR of three trials: 0.28; 95% CI: 0.11 to 0.72) lowered the incidence of shivering; however, two trials evaluating dexmedetomidine injected into the subarachnoid space showed no difference compared with placebo (pooled RR = 1.57; 95% CI: 0.45 to 5.54) (Fig. 6). Sensitivity analysis was performed excluding the article³⁰ with an A-E interval more than two hours (no difference from placebo) to minimize heterogeneity. A similar result favouring dexmedetomidine was found (pooled RR = 0.13; 95% CI: 0.03 to 0.52) with almost no heterogeneity across studies ($I^2 = 0\%$).

Table 1 Characteristics of the included trials

Study	Year	patients	Type of anesthesia	Time	Comparisons	Total	Event	Mean or median of surgery time (min.)	Mean temperature of the end of surgery (°C)	Funding
Aldehayat ¹³	2011	adults	GA	E	dexmedetomidine 1.0 µg·kg ⁻¹ iv placebo iv	35 35	4 16	152 140	- -	-
Bajwa ¹⁴	2012	adults	GA	M	dexmedetomidine 1.0 µg·kg ⁻¹ iv placebo iv	40 40	2 17	59 58	36.4 36.2	-
Bicer ¹⁵	2006	adults	GA	E	dexmedetomidine 1.0 µg·kg ⁻¹ iv meperidine 0.5 mg·kg ⁻¹ iv placebo iv	40 40 40	6 4 22	115 102 98	35.7 35.8 35.8	-
Elvan ¹⁶	2008	adults	GA	L+M	dexmedetomidine iv placebo iv	40 40	7 21	78 82	35.8 36	-
Gao ¹⁷	2012	adults	GA	L+M	dexmedetomidine iv no treatment	24 24	0 6	- -	- -	-
Jalonen ¹⁸	1997	adults	GA	L+M	dexmedetomidine iv placebo iv	40 40	13 23	180 185	- -	-
Karaman ³	2013	adults	GA	L+M	dexmedetomidine iv placebo iv	30 30	3 14	62 66	35.3 35.3	①
Kim ¹⁹	2013	adults	GA	E	dexmedetomidine 0.5 µg·kg ⁻¹ iv dexmedetomidine 0.75 µg·kg ⁻¹ iv dexmedetomidine 1.0 µg·kg ⁻¹ iv placebo iv	30 30 30 30	12 4 5 19	111 106 105 109	35.7 35.8 35.9 36	-
Lee ²⁰	2013	adults	GA	L+M	dexmedetomidine iv placebo iv	28 29	2 17	141 141.6	36.1 36.1	-
Li ²¹	2011	adults	GA	P	dexmedetomidine 0.5 µg·kg ⁻¹ iv placebo iv	40 40	0 12	- -	- -	②
Wu ²²	2013	adults	GA	P	dexmedetomidine 1.0 µg·kg ⁻¹ iv placebo iv	40 40	3 15	96 92	- -	③
Yildiz ²³	2006	adults	GA	P	dexmedetomidine 1.0 µg·kg ⁻¹ iv placebo iv	25 25	2 2	59 61	- -	No
Bozgeyik ²⁴	2014	adults	SA	P	tramadol 100 mg iv dexmedetomidine 0.5 µg·kg ⁻¹ iv placebo iv	30 30 30	3 1 6	45 44 42	36.44 36.33 36.58	-
Coskuner ²⁵	2007	adults	EA	L+M	dexmedetomidine iv placebo iv	30 30	0 4	81 86	- -	-

Table 1 continued

Study	Year	patients	Type of anesthesia	Time	Comparisons	Total	Event	Mean or median of surgery time (min.)	Mean temperature of the end of surgery (°C)	Funding
Dinesh ²⁶	2014	adults	SA	L+M	dexmedetomidine <i>iv</i>	50	0	-	-	-
Gupta ²⁷	2011	adults	SA	I	placebo <i>iv</i>	50	5	-	-	-
					dexmedetomidine SA 5 µg	30	0	-	-	-
Hanoura ²⁸	2014	adults	SA	I	placebo SA	30	1	-	-	-
					dexmedetomidine EA 1.0 µg·kg ⁻¹	25	1	49	-	-
Jain ²⁹	2012	adults	SA	I	placebo EA	25	8	48	-	-
					dexmedetomidine EA 2.0 µg·kg ⁻¹	30	1	81	-	-
Salgado ³⁰	2008	adults	EA	I	placebo EA	30	8	79	-	-
					dexmedetomidine EA 1.0 µg·kg ⁻¹	20	3	213	-	-
Tekin ⁹	2007	adults	SA	L+M	placebo EA	20	2	208	-	-
					dexmedetomidine <i>iv</i>	30	0	71	-	-
					placebo <i>iv</i>	30	5	73	-	-
Usta ³¹	2011	adults	SA	L+M	dexmedetomidine <i>iv</i>	30	3	65	36	-
					placebo <i>iv</i>	30	17	68	36.2	-
Yektas ³²	2014	adults	SA	I	dexmedetomidine SA 2 µg	20	4	-	-	-
					dexmedetomidine SA 4 µg	20	5	-	-	-
					placebo SA	20	2	-	-	-
Aksu ³³	2009	adults	GA	E	dexmedetomidine 0.5 µg·kg ⁻¹ <i>iv</i>	20	0	175	-	-
					fentanyl 1.0 µg·kg ⁻¹ <i>iv</i>	20	1	179	-	-
Bajwa ³⁴	2011	adults	EA	I	dexmedetomidine EA 1.0 µg·kg ⁻¹	50	1	-	-	-
					fentanyl EA 1.0 µg·kg ⁻¹	50	2	-	-	-
Techanivate ³⁵	2012	adults	GA	I	dexmedetomidine 0.5 µg·kg ⁻¹ <i>iv</i>	20	1	35	-	④
					fentanyl 0.5 µg·kg ⁻¹ <i>iv</i>	20	2	35	-	-
Turgut ³⁶	2008	adults	GA	L+M	dexmedetomidine <i>iv</i>	25	6	216	-	-
					fentanyl <i>iv</i>	25	11	229	-	-
Jung ³⁷	2011	adults	GA	L+M	dexmedetomidine <i>iv</i>	25	3	98	-	⑤
					remifentanyl <i>iv</i>	25	0	97	-	-
Turgut ³⁸	2009	adults	GA	L+M	dexmedetomidine <i>iv</i>	25	7	216	-	-
					remifentanyl <i>iv</i>	25	13	229	-	-
Erkola ³⁹	1994	adults	GA	P	dexmedetomidine 2.5 µg·kg ⁻¹ <i>im</i>	60	6	-	-	-
					midazolam 0.08 µg·kg ⁻¹ <i>im</i>	61	31	-	-	-
Koruk ⁴⁰	2010	children	GA	I	dexmedetomidine <i>iv</i>	21	0	16.1	-	-
					midazolam <i>iv</i>	25	4	17	-	-

Table 1 continued

Study	Year	patients	Type of anesthesia	Time	Comparisons	Total	Event	Mean or median of surgery time (min.)	Mean temperature of the end of surgery (°C)	Funding
Sheta ⁴¹	2014	children	GA	P	dexmedetomidine IN 1.0 µg·kg ⁻¹	36	9	112	-	-
Bajwa ⁴²	2011	adults	EA	I	midazolam IN 0.2 µg·kg ⁻¹	36	3	108	-	-
					dexmedetomidine EA 1.5 µg·kg ⁻¹	25	2	96	-	-
Tosun ⁴³	2006	children	GA	L+M	clonidine EA 2.0 µg·kg ⁻¹	25	1	100	-	-
					dexmedetomidine <i>iv</i>	22	0	40	-	-
					propofol <i>iv</i>	22	1	45	-	-
Mousa ⁴⁴	2013	adults	GA	L+M	dexmedetomidine <i>iv</i>	20	3	216	-	No
					propofol <i>iv</i>	20	9	214	-	-
Koruk ⁴⁵	2010	children	GA	I	dexmedetomidine 1.0 µg·kg ⁻¹ <i>iv</i>	9	1	57	-	-
					ketamine 0.5 mg·kg ⁻¹ <i>iv</i>	9	0	48	-	-
Shanreai ⁴⁶	2012	adults	GA	L+M	dexmedetomidine <i>iv</i>	30	1	-	-	-
					ketamine <i>iv</i>	30	0	-	-	-
Mittal ⁴⁷	2014	adults	SA	E	dexmedetomidine 0.5 µg·kg ⁻¹ <i>iv</i>	25	1	-	-	No
					tramadol 0.5 mg·kg ⁻¹ <i>iv</i>	25	2	-	-	-
Gomez-Vazquez ⁴⁸	2007	adults	EA	L+M	dexmedetomidine <i>iv</i>	15	0	55	-	-
					propacetamol <i>iv</i>	15	4	50	-	-
Gupta ⁴⁹	2014	adults	SA	I	dexmedetomidine SA 5 µg	30	5	95	-	-
					buprenorphine SA 60 µg	30	2	92	-	-

GA = general anesthesia; SA = spinal anesthesia; EA = epidural anesthesia; IM = intramuscular; IN = intranasal; P = preoperative; I = induction; E = end; L + M = loading and maintenance

①The institutional and/or departmental sources

② Natural Science Foundation of Heilongjiang Province (D200857)

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Fig. 2 Summary of the risk of bias of the included studies

Dexmedetomidine vs other anti-shivering agents

Nineteen studies,^{15,24,33-45,47-49} involving 1,063 patients, compared the efficacy of dexmedetomidine with other drugs on postoperative shivering. No significant difference could be found between dexmedetomidine and other agents, including fentanyl, remifentanyl, meperidine, midazolam, ketamine, tramadol, clonidine, buprenorphine, or propacetamol, except propofol (pooled RR = 0.33; 95% CI: 0.11 to 0.98) (Table 3). Nevertheless, one of the articles comparing dexmedetomidine with propofol was assessed and had a high risk of bias. Therefore, the superiority of dexmedetomidine over propofol was not reliably assessed.

Our systematic review showed that dexmedetomidine not only has an anti-shivering effect, but it may also increase hemodynamic stability during a sudden increase in stress (e.g., intubation, skin incision, extubation), provide a deeper level of sedation, decrease PONV, and prolong postoperative analgesia compared with different agents (Table 4). Of importance, however, recovery and orientation time (patients' response to questions regarding time, place, and person) after tracheal extubation was prolonged with dexmedetomidine when compared with certain other agents (Table 4).

Discussion

Postoperative shivering frequently causes uncomfortable feelings and is complicated by such complications as tachycardia, hypertension, and cardiac ischemia, which can lead to severe consequences. There is still an urgent need to find an effective way to prevent or control postoperative shivering.

The present meta-analysis was undertaken to evaluate the efficacy of dexmedetomidine in the prevention of postoperative shivering. The main findings are as follows: (1) Dexmedetomidine shows superiority over placebo in the prevention of postoperative shivering, but not over other anti-shivering agents. (2) The beneficial effect can be achieved through both intravenous and epidural injection. Nevertheless, the time interval between the last administration and the end of surgery should be less than two hours, which is about the half-life of dexmedetomidine. (3) While a $1.0 \mu\text{g}\cdot\text{kg}^{-1}$ bolus dose is the most commonly used in the published articles, a $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ bolus infusion can still have a preventive effect. (4) Physicians should be cautious about the side effects of dexmedetomidine, such as sedation, bradycardia, hypotension, and dry mouth.

The anti-shivering effect of dexmedetomidine may be mediated primarily by the α_{2b} -drenoceptor, in the hypothalamus. Dexmedetomidine suppresses the spontaneous firing rate of neurons, decreases the central thermosensitivity,¹⁴

Fig. 3 Results of subgroup analysis of the incidence of postoperative shivering by anesthesia types

Table 2 Incidence of various side effects of dexmedetomidine vs placebo

Side effects	Number of studies	Number shivering/total number of patients		RR (95%CI)	References
		Dexmedetomidine	Placebo		
Sedation	5	104/170	35/170	2.94 (2.18 to 3.98)	13,14,22,28,31
Bradycardia	9	52/252	21/253	2.39 (1.54 to 3.72)	17,20,23,26-28,30-32
Hypotension	7	70/198	52/199	1.35 (1.04 to 1.75)	20,23,26-28,30,32
Dry mouth	3	21/105	2/105	7.33 (2.28 to 23.58)	14,22,23

CI = confidence interval; RR = risk ratio

and finally reduces the vasoconstriction and shivering thresholds.⁵⁰

Several elements for the clinical use of dexmedetomidine should be considered. Kim *et al.*¹⁹ recommended the minimum effective dose of $0.75 \mu\text{g}\cdot\text{kg}^{-1}$ for adults. Furthermore, Bozgeyik *et al.*²⁴ did not find any difference

between $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine and placebo; however, this investigation was hampered by a relatively small sample size (30 patients per group). Based on the data of relevant trials, we found that $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine was sufficiently effective to prevent postoperative shivering. Our finding that epidural dexmedetomidine, not spinal, is an

Fig. 4 Results of subgroup analysis of the incidence of postoperative shivering by the A-E intervals (defined as the time interval from the last administration to the end of the operation)

Fig. 5 Results of subgroup analysis of the incidence of postoperative shivering by doses of intravenous dexmedetomidine

available option for anti-shivering might cause confusion, since subarachnoid administration has always been considered a faster and more effective approach compared with the epidural route. We speculate that the injected dose

may be responsible. Spinal administration of 4–5 μg of dexmedetomidine compared with epidural administration of 1.0 $\mu\text{g}\cdot\text{kg}^{-1}$ may not be enough to activate the receptors inhibiting shivering.²⁸

Fig. 6 Results of subgroup analysis of the incidence of postoperative shivering by routes of dexmedetomidine administration

Despite its analgesic, sedative, antiemetic, and anti-shivering properties, dexmedetomidine increased the risk of these side effects. Somnolence, one of the most dangerous complications, although rare, has been reported resulting from an overdose of dexmedetomidine.⁵¹ Moreover, the price of dexmedetomidine is considerably higher than other drugs. Consequently, we do not recommend the use of dexmedetomidine solely for the purpose of preventing postoperative shivering.

A previous meta-analysis¹ suggested an inferior role of dexmedetomidine compared with some “more efficacious agents” like meperidine, tramadol and nefopam. Nevertheless, the results of the analysis are inconclusive, as there were only two trials involving dexmedetomidine with just 160 patients, and there was no direct comparison

between dexmedetomidine and the other agents. In contrast, we included 39 articles, adopted a wide range of clinically relevant outcome variables, and focused on direct comparison in order to reach a solid conclusion.

This is a novel meta-analysis regarding the use of dexmedetomidine for anti-shivering and an evaluation of the factors that might influence its effectiveness. Most of the included trials were well designed and reported with low risk of bias. Moreover, we compared dexmedetomidine directly with other anti-shivering agents and excluded studies with a high risk of bias through sensitivity analysis. All of these strategies enhanced the reliability of our conclusion. Nevertheless, this meta-analysis has several limitations. First, only eight trials^{3,21-23,35,37,44,47} reported the source of their funding; and therefore, we did not know

Table 3 Incidence of postoperative shivering with dexmedetomidine compared with other anti-shivering drugs

Drugs	Number of studies	Number shivering/total number of patients		RR (95%CI)	References
		Dexmedetomidine	Control		
Fentanyl	4	8/115	16/115	0.52 (0.25 to 1.07)	33-36
Remifentanyl	2	10/50	14/50	0.93 (0.19 to 4.64)	37,38
Meperidine	1	6/40	4/40	1.50 (0.46 to 4.91)	15
Midazolam	3	15/120	13/121	1.10 (0.29 to 4.17)	39-41
Propofol	2	3/42	10/42	0.33 (0.11 to 0.98)	43,44
Ketamine	2	2/39	0/39	3.00 (0.33 to 27.23)	45,46
Tramadol	2	2/55	5/55	0.40 (0.08 to 2.01)	24,47
Clonidine	1	1/25	2/25	0.50 (0.05 to 5.17)	42
Buprenorphine	1	5/30	2/30	2.5 (0.53 to 11.89)	49
Propacetamol	1	0/15	4/15	0.11 (0.01 to 1.90)	48

CI = confidence interval; RR = risk ratio.

Table 4 Incidence of various side effects of dexmedetomidine vs other anti-shivering drugs ($P < 0.05$)

Drugs	Hemodynamics*	Sedation	Nausea and vomiting	Postoperative analgesia and consumption of analgesic	Recovery time	Orientation time	Heart rate
Fentanyl	Unstable ^{33,36}	Lower ³⁴	Higher ³⁴	Shorter and more ³⁴⁻³⁶	No difference ^{33,35}	-	-
Remifentanyl	Unstable ³⁷	Lower ³⁸	-	Shorter and more ³⁸	-	-	-
Meperidine	-	Lower ¹⁵	-	-	-	Shorter ¹⁵	-
Midazolam	Unstable ³⁹	Lower ⁴¹	Higher ⁴⁰	-	Longer ⁴⁰	-	-
Propofol	-	-	-	-	Shorter ⁴³	-	-
Ketamine	Unstable ⁴⁵	-	-	-	Longer ^{45,46}	-	Quicker ^{45,46}
Tramadol	-	Lower ²⁴	Higher ⁴⁷	-	-	-	-
Clonidine	-	Lower ⁴²	-	-	-	-	-
Buprenorphine	-	-	-	Shorter and more ⁴⁹	-	-	-
Propacetamol	-	Lower ⁴⁸	-	-	-	-	-

*Hemodynamics were recorded when patients experienced tracheal intubation, skin incision, tracheal extubation, or other sudden increase in stress

whether the other trials were supported by industry, which could make the design prone to show the drug in its best light. Second, body temperature was detected by various techniques throughout the literature and we failed to include this as an evaluation item.

In conclusion, the present meta-analysis indicated that the administration of dexmedetomidine may prevent the incidence of postoperative shivering, although there was no difference compared with other anti-shivering drugs, such as fentanyl, meperidine, tramadol, and clonidine. Our results provided evidence to extend the clinical value of dexmedetomidine beyond its routine usage for sedation and analgesia. Nevertheless, due to its relatively high price and potential side effects, we do not recommend that anesthesiologists or perioperative medical staff use dexmedetomidine solely for the purpose of preventing postoperative shivering.

Declaration of conflict of interest The authors declare no financial interests relating to patents or shareholdings in corporations involved in the medical market.

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