Meta-Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(8) 1–13

DOI: 10.1177/03000605211039809
journals.sagepub.com/home/imr
SAGE

Effect of dexmedetomidine on hemodynamics in patients undergoing hysterectomy: a meta-analysis and systematic review

Zhaoqiu Li[1]*, Cuiping Li[2]* and Maoxian Zhang[3]

Abstract

Objective: We conducted a meta-analysis and systematic review to evaluate the effects of dexmedetomidine on the hemodynamics of patients undergoing hysterectomy.

Methods: We searched the Medline, Embase, and Cochrane Central Register of Controlled Trials databases for clinical randomized controlled trials (RCTs) that allowed direct or indirect comparisons of hemodynamic indicators. We also searched nine English-language databases up to April 2021 to identify relevant research. The Cochrane risk-of-bias tool for RCTs was applied to assess the methodological quality of the eligible studies. The meta-analysis was conducted using RevMan 5.4 software.

Results: Nine trials were included in this systematic review. The effect of dexmedetomidine on heart rate during surgery was significantly smaller than that of other sedatives. Intraoperative systolic and diastolic blood pressure and mean arterial pressure were more stable in the dexmedetomidine group compared with the control group. The postoperative modified Observer's Assessment of Alertness Score was also better in the dexmedetomidine compared with the control group.

Conclusions: Dexmedetomidine increases hemodynamic stability in patients undergoing hysterectomy, reduces the cardiovascular stress response during surgery, and effectively prevents postoperative adverse reactions, with good safety.

[1]Surgical Anesthesia Center, Sanya Maternal and Child Health Hospital, Sanya, Hainan, China
[2]Department of Anesthesiology, Dongguan Houjie Hospital, Dongguan, Guangdong, China
[3]Department of Anesthesiology, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, Ningxia, China

*These authors contributed equally to this work

Corresponding author:
Maoxian Zhang, Department of Anesthesiology, People's Hospital of Ningxia Hui Autonomous Region, 301 Zhengyuan North Street, Yinchuan, Ningxia 750001, China.
Email: nxyczmx8866@163.com

Keywords
Dexmedetomidine, hysterectomy, hemodynamics, meta-analysis, adverse reaction, cardiovascular stress

Date received: 14 May 2021; accepted: 28 July 2021

Introduction

Midazolam is one of the most commonly used sedative drugs during surgery, but it is accompanied by various adverse reactions such as hypotension, delirium, hallucinations, palpitations, skin rash, and hyperventilation. A previous study reported that dexmedetomidine may be a possible alternative to midazolam, with better sedative effects and safety.[1]

Dexmedetomidine is a highly selective α2 adrenergic receptor agonist[2] with sedative, analgesic, and opioid-preserving effects, which produces its analgesic action by inhibiting the sympathetic nervous system.[3] Moreover, its sedative effect is reversible; it induces a sleeplike state but patients can be easily aroused, and it can also reduce the stress response.[4]

Previous studies found that increasing anesthesia in the perioperative period may affect the quality of recovery from anesthesia, and that dexmedetomidine may improve anesthesia recovery.[5] However, although dexmedetomidine does not inhibit the respiratory system and rarely causes apnea, some studies found that it could lead to hypoxia and hypercapnia, and may have hemodynamic effects such as hypertension and hypotension.[6]

Reducing the stress response and maintaining hemodynamic stability are critical for ensuring a smooth operation in patients undergoing hysterectomy under general anesthesia. The current meta-analysis thus aimed to evaluate the intraoperative hemodynamic stability and safety of dexmedetomidine in patients undergoing hysterectomy. The effects of dexmedetomidine on intraoperative changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), Observer's Assessment of Alertness Score (OAA/S), and Visual Analogue Scale (VAS) were compared between patients receiving dexmedetomidine and other sedatives during hysterectomy. Based on these results, we suggest further studies to clarify the effectiveness and safety of dexmedetomidine results.

Methods

This systematic review was based on the Cochrane Handbook for Systematic Reviews of Interventions,[7] and the meta-analysis was conducted in accordance with the PRISMA guidelines.[8] Ethics approval and consent to participate were not required because this study was a meta-analysis.

Retrieval strategy

We conducted a comprehensive search of the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase databases, as well as ClinicalTrials.gov, the WHO ICTRP search portal, Web of Science, International HTA, LILACS, and OpenGrey databases. The following search terms were used: ((“Dexmedetomidine” [MeSH Terms] OR “Dexmedetomidine” [All Fields]) AND (“hysterectomy”[MeSH Terms] OR “hysterectomy”[All Fields])) AND ((“haemodynamic”[All Fields]) Fields] OR “hemodynamics”[MeSH Terms] OR “hemodynamics”[All Fields] OR

"hemodynamic"[All Fields]) AND random [All Fields]).

We aimed to retrieve randomized controlled trials (RCTs) of clinical subjects from which we could directly or indirectly extract data for comparison. We also checked the reference lists of selected studies to find additional studies for systematic review. There were no restrictions on the article language or type of publication. The last search was conducted in April 2021.

Inclusion and exclusion criteria

This meta-analysis was conducted according to the PICO (Patient/Problem/Population; Intervention/Exposure; Comparison and Outcomes) tool as follows: Population: adult patients undergoing hysterectomy under general anesthesia; Intervention: intraoperative use of dexmedetomidine; Comparison: comparison with non-use of dexmedetomidine during the operation; and Outcomes: hemodynamic changes after dexmedetomidine administration.

The primary outcome was increase in hemodynamic stability following use of dexmedetomidine compared with other sedatives in patients undergoing hysterectomy. Hemodynamic stability was indicated by intraoperative changes in HR, SBP, DBP, MBP, and MAP. The secondary outcome was changes in postoperative pain.

Study selection

Two researchers individually screened out eligible studies based on the title and abstract. Any disagreements were resolved through discussion. If the results of the reports were likely to be copied and published, only the report that analyzed the latest data was included in this study. In the event of missing or inconsistent data, the researcher attempted to contact the author(s) directly to obtain the missing data. Any further disagreements were resolved by a third researcher.

Data collection

The two researchers extracted data from the eligible studies using a data extraction and assessment form. Extracted data included author, year of publication, study population, intervention measures, comparison objects, and results. We calculated the mean and standard deviation (SD) for data expressed as the median and range for continuous data. The researcher contacted the author(s) to resolve any uncertainties.

Quality risk management and deviations

We assessed the risk of bias for RCTs using the Cochrane Collaboration tool. We evaluated random sequence generation, allocation concealment, provider, assessor-blinded clinical trial, incomplete data analysis, and selective outcome reporting based on the availability of the protocol and including all pre-specified results, and other sources of deviation, such as conflicts of interest and source funding. Disagreements were resolved by discussion between the two researchers, and studies were categorized as showing low, high, or unclear risk of bias.

Statistical analysis

Weighted mean difference (WMD) and associated 95% confidence intervals (CIs) for continuous variables were extracted or calculated from the included studies. For the meta-analysis, we merged the results and calculated the aggregate effect size using RevMan 5.4 (http: //training.cochrane.org). The Mantel–Haenszel method was adopted for the fixed effects model, and the inverse variance model was used for the fixed-effects model for continuous data.

Heterogeneity was assessed by I^2 and Q tests. $I^2 < 50\%$ indicated no significant

heterogeneity, and a fixed-effects model was applied. $I^2 \geq 50\%$ to $I^2 < 75\%$ indicated low heterogeneity and the random effects model was used to calculate the effect size. If $I^2 \geq 75\%$, a sensitivity analysis was performed to find the source of heterogeneity. If there was no methodological or clinical heterogeneity, a random-effects model was used for analysis. The overall effect was reported as a Z-score, with $P < 0.05$ considered significant. Symmetry was observed using funnel plots to assess publication bias.

Results

Characteristics of studies included in the meta-analysis

A total of 1038 studies were identified, of which 891 were excluded from further analysis because they were animal studies, irrelevant studies, non-original articles, reviews, or repetitions. A further 125 studies were excluded after reading the full text of the article. The remaining 22 studies were further evaluated for eligibility, and nine RCTs [9–17] that met all the criteria were finally included in the meta-analysis (Figure 1).

The characteristics of the selected studies are shown in Table 1. The total sample included 857 women who underwent hysterectomy, with laparoscopic hysterectomy being the most common type of surgery. Most of the women were middle-aged, with an average age of 45 years.

Study bias

We evaluated all the included RCTs for random sequence generation, allocation

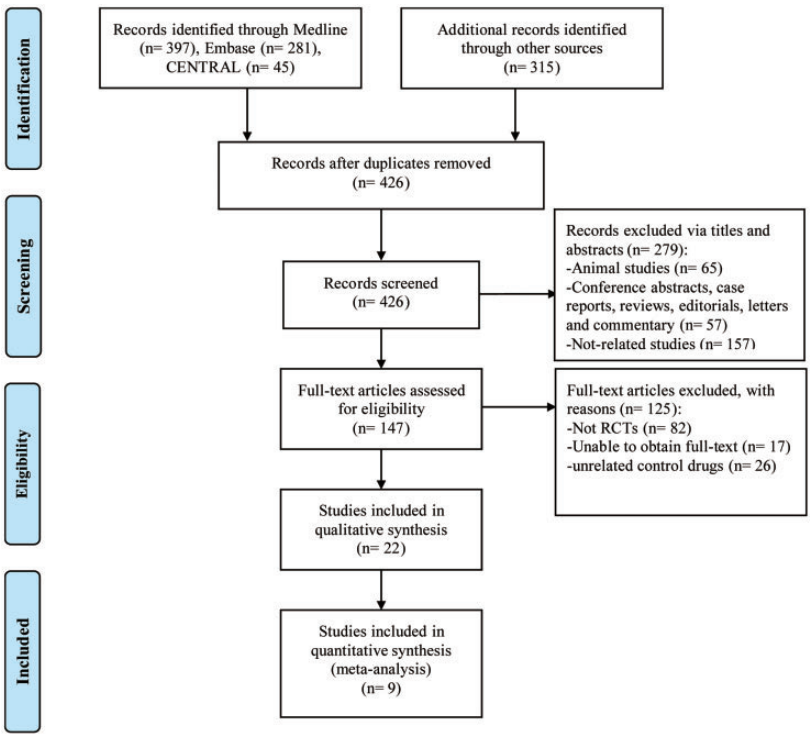

Figure 1. Flow diagram of the study selection.
RCT, randomized controlled trial.

Table 1. Study characteristics.

Author name	Publication year	Sample size (Dex/control)	Type of surgery	Intervention		Age		Outcomes
				Dex group	Control group	Dex group	Control group	
Lin et al.[9]	2009	50/48	Total hysterectomy	Dex + morphine	Morphine	43.5 (25–29)	43.5 (25-57)	HR/MBP
Jung et al.[10]	2011	25/25	Total laparoscopic hysterectomy	Dex + ketorolac	Remifentanil + ketorolac	46.3 ± 3.7	45.4 ± 4.2	HR/(MOAA/S)/VAS/DBP/SBP
Seo et al.[11]	2014	90/30	Laparoscopic total hysterectomy	Dex	0.9% Normal saline	45.9 ± 5.5	45.6 ± 5.3	HR/DBP/SBP
Sezen et al.[12]	2014	59/60	Hysterectomies	Dex	Midazolam	47.5 ± 5.5	47.0 ± 6.0	HR/DBP/SBP/MBP
Choi et al.[13]	2016	30/60	Total laparoscopic hysterectomy	Dex	Remifentanil + fentanyl	45.1 ± 3.9	48.2 ± 4.1	HR/(MOAA/S)/VAS/DBP/SBP
Megalla et al.[14]	2016	25/50	Vaginal hysterectomy	Dex	Nalbuphine + 0.9% normal saline	53.25 ± 15.91	53.7 ± 12.5	HR/MBP
Thada et al.[15]	2017	32/32	Total abdominal hysterectomy	5 μg Dex + 0.5% hyperbaric bupivacaine	2.5 ml 0.5% Hyperbaric bupivacaine + 25 μg (0.5 ml) fentanyl	41.5 ± 5.2	40.7 ± 5.2	HR/MAP
Du et al.[16]	2018	41/40	Total laparoscopic hysterectomy	Dex	0.9% Normal saline	47.2 ± 10.3	46.5± 9.2	HR/VAS/MBP
Xu et al.[17]	2021	80/80	Laparoscopic hysterectomy	Dex + lidocaine	Lidocaine + 0.9% normal saline	47.6 ± 5.7	47.5 ± 52	HR/VAS/MBP/MAP

HR, heart rate; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; MOAA/S, Modified Observer's Assessment of Alertness Score; VAS, Visual Analogue Scale; Dex, dexmedetomidine.

concealment, outcome evaluation, and adopted double-blind methods, and for complete outcome data without selective outcome reporting. Comprehensive assessment indicated a low risk of bias (Figure 2).

Meta-analysis

Heart rate. Meta-analysis of nine trials[9–17] indicated that dexmedetomidine had a significantly smaller effect on patient HR during surgery than other sedatives (WMD = −5.20, 95% CI: −7.97 to −2.44, $P < 0.05$; $I^2 = 53\%$, $Z = 3.69$, $P < 0.05$, Figure 3).

Systolic blood pressure. Meta-analysis of four trials[10–13] showed that dexmedetomidine had less effect on intraoperative SBP than other sedatives (WMD = −18.16, 95% CI: −27.71 to 8.60, $P < 0.05$; $I^2 = 0\%$, $Z = 3.73$, $P > 0.05$, Figure 4a).

Diastolic blood pressure. Meta-analysis of four trials[10–13] suggested that dexmedetomidine also had a smaller effect on DBP in patients undergoing surgery compared with the control group (WMD = −13.18, 95% CI: −18.95 to −7.42, $P < 0.05$; $I^2 = 40\%$, $Z = 4.48$, $P > 0.05$, Figure 4b).

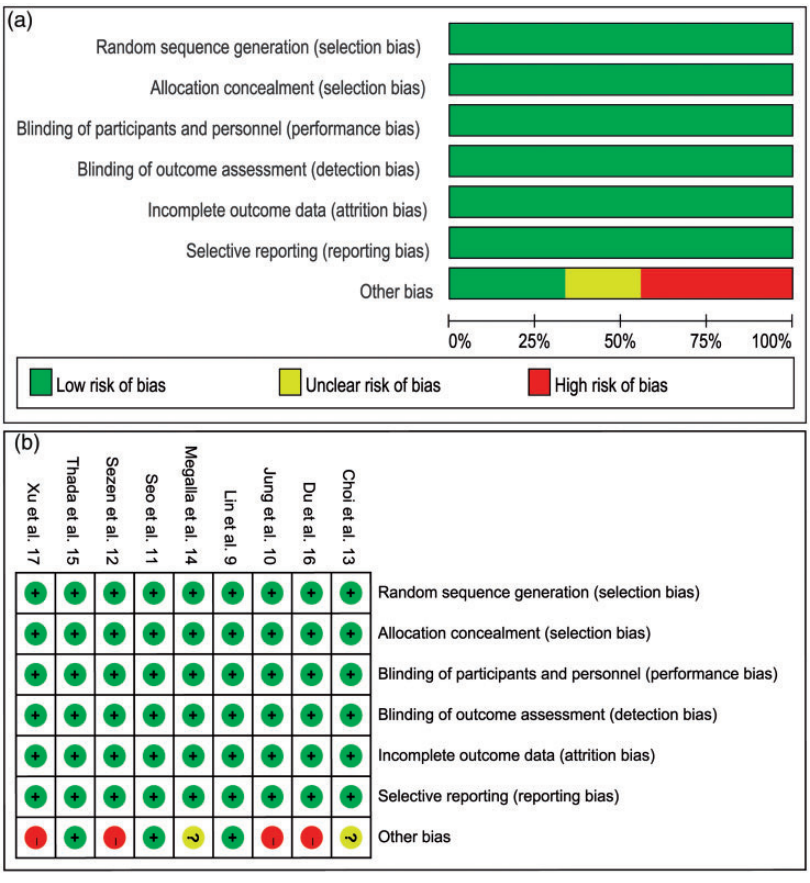

Figure 2. Risk of bias assessment. Risk of bias graph (a) and summary (b).

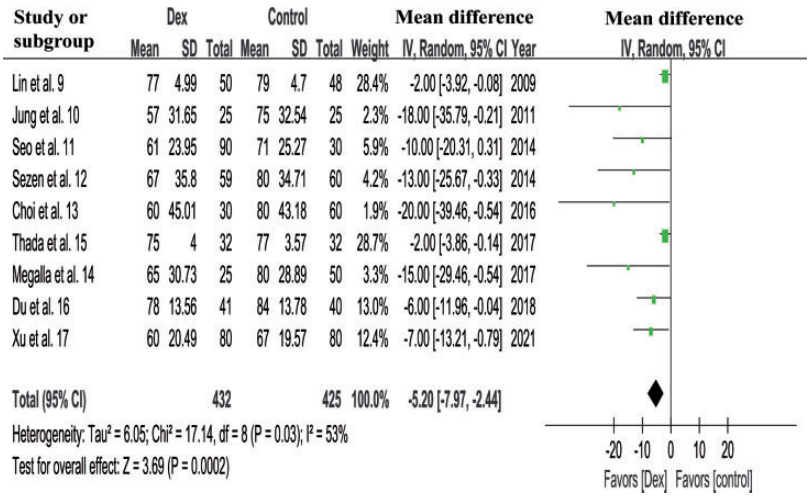

Figure 3. Effect of dexmedetomidine on intraoperative heart rate. SD, standard deviation; IV, inverse variance; CI, confidence interval.

Mean blood pressure. Meta-analysis of data from five trials[9,12,14,16,17] indicated that dexmedetomidine had a similar effect on intraoperative MBP to other sedatives (WMD = −1.39, 95% CI: −3.58 to 0.80; $I^2 = 68\%$, Z = 1.25, $P < 0.05$, Figure 4c).

Mean arterial pressure. Meta-analysis of two trials[15,17] showed that MAP was significantly lower in the dexmedetomidine group compared with the control group (WMD = −1.97, 95% CI: −3.19 to −0.75, $P < 0.05$; $I^2 = 0\%$, Z = 3.17, $P > 0.05$, Figure 4d).

Modified Observer's Assessment of Alertness Score. Meta-analysis of data from two trials[10,13] suggested that intraoperative use of dexmedetomidine had significantly less impact on postoperative modified OAA/S compared with the control group (WMD = −0.23, 95% CI: −0.39 to −0.08, $P < 0.05$; $I^2 = 0\%$, Z = 2.91, $P > 0.05$, Figure 5a).

Visual Analogue Scale. A meta-analysis of four trials[10,13,16,17] indicated that postoperative VAS reduction was similar in patients treated with dexmedetomidine and other sedatives (WMD = −0.10, 95% CI: −0.75 to 0.54; $I^2 = 90\%$, Z = 0.31, $P < 0.05$, Figure 5b).

Sensitivity analysis

Heterogeneity was unaffected by eliminating the included studies one by one and switching to different effect models, indicating that the results were relatively robust and reliable.

Assessment of publication bias

Funnel plots of HRs were used to assess publication bias. The distribution symmetry of each point was poor, suggesting possible publication bias (Figure 6).

Adverse events

Lin et al.[9] reported adverse reactions such as nausea and vomiting, and noted significantly fewer adverse reactions in the dexmedetomidine group compared with the control group (34% vs 56.3%, $P < 0.05$). Thada et al.[15] reported one case of

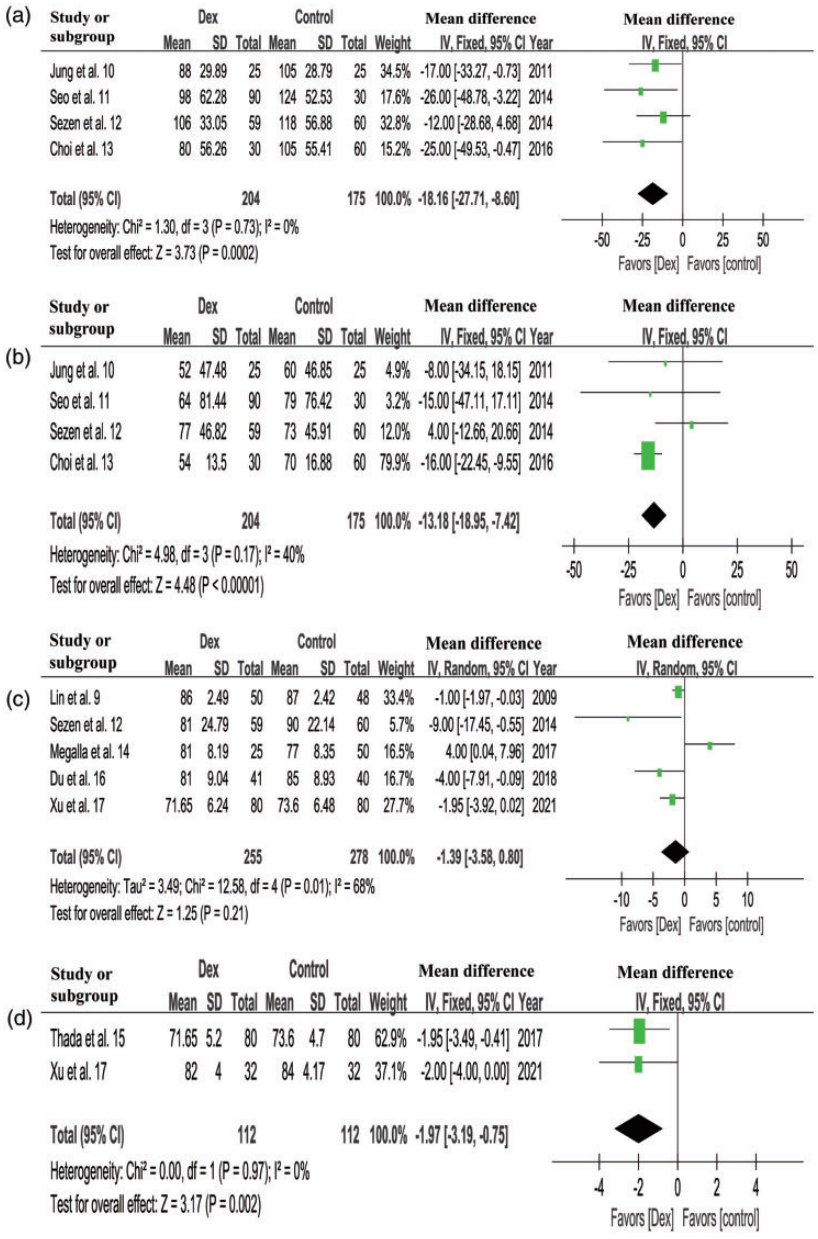

Figure 4. Effects of dexmedetomidine on intraoperative hemodynamics parameters. Effects of dexmedetomidine on intraoperative (a) systolic blood pressure, (b) diastolic blood pressure, (c) mean blood pressure, and (d) mean arterial pressure.
SD, standard deviation; IV, inverse variance; CI, confidence interval.

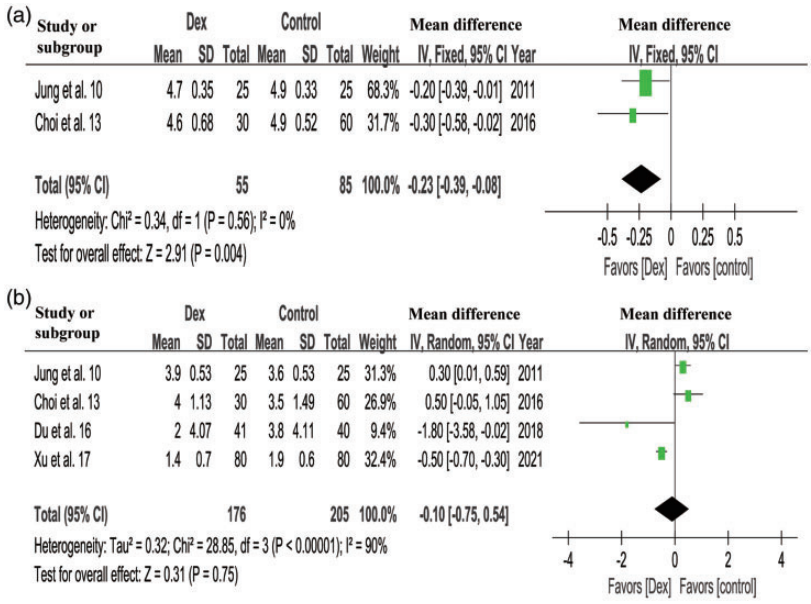

Figure 5. Effects of dexmedetomidine on alertness and pain scores. (a) Modified Observer's Assessment of Alertness Score and (b) postoperative Visual Analogue Scale score.
SD, standard deviation; IV, inverse variance; CI, confidence interval.

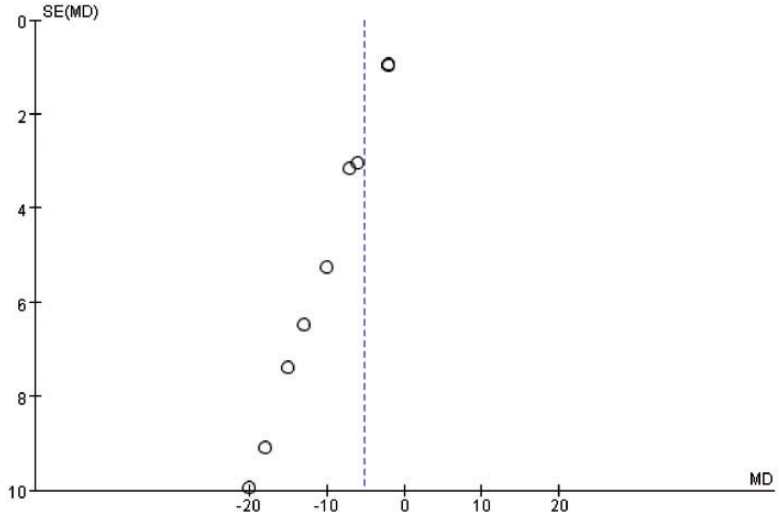

Figure 6. Funnel plot for publication bias assessment.
SE, standard error; MD, mean difference.

bradycardia and Choi et al.[13] reported three cases of xerostomia. Three studies[14,16,17] did not report any serious adverse reactions, and the remaining three studies[10–12] did not mention any adverse events.

Discussion

We conducted a meta-analysis of nine high-quality studies, which indicated that intraoperative use of dexmedetomidine could avoid drastic fluctuations in HR, SBP, DBP, and MAP, and reduce the stress response in women undergoing hysterectomy. Patients receiving intraoperative dexmedetomidine had lower postoperative modified OAA/S scores, conducive to postoperative resuscitation and arousal. However, there was no significant difference in MBP between patients receiving dexmedetomidine and other sedatives. This result may be related to extra-clinical factors, and further research is required to clarify this issue. There was also no significant difference in postoperative VAS between the two groups, possibly related to the sample size and dose, and further studies are needed to test this. Only one study reported SpO_2[14] and found no difference between the two groups. This meta-analysis clearly showed that dexmedetomidine increased hemodynamic stability during hysterectomy, with a relatively high quality of evidence.

Patients undergoing hysterectomy are prone to anxiety and tension as a result of worry about the operation, which can lead to increased sympathetic excitability. Various factors associated with general anesthesia can also cause a stress response, with increases in catecholamine and blood sugar levels, carbon dioxide partial pressure, and oxygen consumption, and reduced venous return and cardiac output. A smooth operation may thus be hindered by secretion disorders stimulated by the sympathetic nervous system, together with increased blood pressure and heart rate.[1,12]

Dexmedetomidine has the advantages of alleviating pain, reducing the stress response, and stabilizing hemodynamics, with no respiratory depression, making it widely used as an adjuvant in clinical anesthesia.[18] HR, SBP, DBP, and SpO_2 are important indicators that can comprehensively reflect changes in hemodynamics in patients during anesthesia induction.[19] Dexmedetomidine has sedative, amnestic, sympathetic neurolytic, and analgesic effects. It mainly acts on $\alpha 2$ receptors in the spinal cord and locus coeruleus to inhibit neuronal discharge and sympathetic outflow and reduce sympathetic nerve activity, leading to a reduced perioperative stress response and consequent sedative and analgesic effects.[20] When dexmedetomidine enters the body, it binds to $\alpha 2$ receptors, reducing sympathetic tone and strengthening vagus nerve activity, while inhibiting adenylate cyclase activity and adenosine cyclophosphate synthesis, and reducing the influx of calcium ions to the nerves. The release of transmitters thus reduces hyperpolarization of the presynaptic and postsynaptic membranes, thereby contributing to sedation and the anti-stress response.[4,20]

Dexmedetomidine thus exerts several sedative mechanisms, including (1) inhibiting adenylate cyclase activity and reducing cyclic adenosine production in the cell; (2) directly stimulating central postsynaptic membrane $\alpha 2$ receptors in the hypothalamus and cerebellum, and reducing central sympathetic nerve impulses and inhibiting peripheral sympathetic nerve activity; (3) stimulating peripheral sympathetic nerve presynaptic membrane $\alpha 2$ receptors to enhance its negative feedback effect; and (4) reducing norepinephrine release from peripheral nerves and reducing peripheral vascular resistance, thereby inhibiting hemodynamic fluctuations caused by tracheal intubation.[21,22]

Dexmedetomidine has also been shown to exert a significant anti-inflammatory effect, regulate the inflammatory response, and significantly reduce tumor necrosis factor-α and interleukin-6 levels in a dose- and time-dependent manner, thus aiding postoperative recovery and reducing the inflammatory response.[23,24] In addition, dexmedetomidine has demonstrated a protective effect on the brain, protecting cells from damage, reducing organ ischemia–reperfusion injury, increasing cerebral blood flow, preventing brain tissue edema, and improving behavioral disorders, including aggression and cognitive impairment.[25] Dexmedetomidine could thus be used to alleviate adverse reactions caused by general anesthesia.[26]

This study indicated that dexmedetomidine did not affect postoperative recovery in patients following hysterectomy, possibly related to its antisympathetic, sedative, and analgesic effects, and it also had no significant effect on normal breathing.[5] In accordance with the current results, Silva-Jr et al.[27] reported that dexmedetomidine had a better sedative effect compared with benzodiazepines, which reduced restlessness in surgical patients during the recovery period and was conducive to postoperative recovery.

This study had some limitations. First, the sample size was small and the patient ages were relatively homogeneous, suggesting that the results may not be applicable to the whole population. In addition, the study was subject to the inherent limitations of meta-analyses, including heterogeneity due to the different designs of the original studies, and differences in patient control measures, type of surgery, method of anesthesia, and dexmedetomidine dose, with the optimal dose still being unclear. Moreover, the RCTs included in this meta-analysis covered a long time span, and the surgical methods and equipment used may have differed from those currently used. Furthermore, the funnel plot showed poor symmetry, indicating a high possibility of publication bias. These factors may have caused a certain degree of bias, and the differences mean that future studies including more recent clinical studies may produce different results. Therefore, although the included trials were high quality, the conclusions regarding the hemodynamic effects of dexmedetomidine should be interpreted with caution.

In conclusion, the available data suggest that dexmedetomidine increases the hemodynamic stability of patients undergoing hysterectomy, avoids drastic fluctuations in HR, SBP, DBP, and MAP, reduces cardiovascular stress during surgery, and effectively prevents postoperative adverse reactions. Dexmedetomidine is relatively safe, with a low incidence of adverse reactions and few side effects. However, more studies are needed to confirm these findings and further experiments are required to draw more reliable conclusions.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Maoxian Zhang https://orcid.org/0000-0003-2621-1925

Supplemental material

Supplemental material for this article is available online.

References

1. Gulla KM, Sankar J, Jat KR, et al. Dexmedetomidine vs midazolam for sedation in mechanically ventilated children: a randomized controlled trial. *Indian Pediatr* 2021; 58: 117–122.
2. Lin N, Vutskits L, Bebawy JF, et al. Perspectives on dexmedetomidine use for neurosurgical patients. *J Neurosurg Anesthesiol* 2019; 31: 366–377.
3. Keating GM. Dexmedetomidine: a review of its use for sedation in the intensive care setting. *Drugs* 2015; 75: 1119–1130.
4. Ng KT, Shubash CJ and Chong JS. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* 2019; 74: 380–392.
5. Hedenqvist P, Jensen-Waern M, Fahlman Å, et al. Intravenous sufentanil-midazolam versus sevoflurane anaesthesia in medetomidine pre-medicated Himalayan rabbits undergoing ovariohysterectomy. *Vet Anaesth Analg* 2015; 42: 377–385.
6. Barends CR, Absalom A, Van Minnen B, et al. Dexmedetomidine versus midazolam in procedural sedation. A systematic review of efficacy and safety. *PLoS One* 2017; 12: e0169525.
7. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
9. Lin TF, Yeh YC, Lin FS, et al. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* 2009; 102: 117–122.
10. Jung HS, Joo JD, Jeon YS, et al. Comparison of an intraoperative infusion of dexmedetomidine or remifentanil on perioperative haemodynamics, hypnosis and sedation, and postoperative pain control. *J Int Med Res* 2011; 39: 1890–1899.
11. Seo KH, Kim YI and Kim YS. Optimal dose of dexmedetomidine for attenuating cardiovascular response during emergence in patients undergoing total laparoscopic hysterectomy. *J Int Med Res* 2014; 42: 1139–1149.
12. Sezen G, Demiraran Y, Seker IS, et al. Does premedication with dexmedetomidine provide perioperative hemodynamic stability in hypertensive patients? *BMC Anesthesiol* 2014; 14: 113.
13. Choi JW, Joo JD, Kim DW, et al. Comparison of an intraoperative infusion of dexmedetomidine, fentanyl, and remifentanil on perioperative hemodynamics, sedation quality, and postoperative pain control. *J Korean Med Sci* 2016; 31: 1485–1490.
14. Megalla SA and Mansour HS. Dexmedetomidine versus Nalbuphine for treatment of postspinal shivering in patients undergoing vaginal hysterectomy: A randomized, double blind, controlled study. *Egypt J Anaesth* 2016; 33: 47–52.
15. Thada B, Khare A, Sethi SK, et al. Comparison of dexmedetomidine and fentanyl as intrathecal adjuvants to 0.5% hyperbaric bupivacaine for total abdominal hysterectomy under subarachnoid block: a prospective randomized double blind study. *Anaesthesia, Pain and Intensive Care* 2017; 21: 65–78.
16. Du J, Li JW, Jin J, et al. Intraoperative and postoperative infusion of dexmedetomidine combined with intravenous butorphanol patient-controlled analgesia following total hysterectomy under laparoscopy. *Exp Ther Med* 2018; 16: 4063–4069.
17. Xu S, Hu S, Ju X, et al. Effects of intravenous lidocaine, dexmedetomidine, and their combination on IL-1, IL-6 and TNF-α in patients undergoing laparoscopic hysterectomy: a prospective, randomized controlled trial. *BMC Anesthesiol* 2021; 21: 3.
18. Afonso J and Reis F. Dexmedetomidine: current role in anesthesia and intensive care. *Rev Bras Anestesiol* 2012; 62: 118–133.
19. Kanaya N, Hirata N, Kurosawa S, et al. Differential effects of propofol and sevoflurane on heart rate variability. *Anesthesiology* 2003; 98: 34–40.

20. Salim B, Rashid S, Ali MA, et al. Effect of pharmacological agents administered for attenuating the extubation response on the quality of extubation: a systematic review. *Cureus* 2019; 11: e6427.
21. Shaikh SI, Revur LR and Mallappa M. Comparison of epidural clonidine and dexmedetomidine for perioperative analgesia in combined spinal epidural anesthesia with intrathecal levobupivacaine: a randomized controlled double-blind study. *Anesth Essays Res* 2017; 11: 503–507.
22. Zhang X, Wang D, Shi M, et al. Efficacy and safety of dexmedetomidine as an adjuvant in epidural analgesia and anesthesia: a systematic review and meta-analysis of randomized controlled trials. *Clin Drug Investig* 2017; 37: 343–354.
23. Taniguchi T, Kurita A, Kobayashi K, et al. Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. *J Anesth* 2008; 22: 221–228.
24. Wu Y, Liu Y, Huang H, et al. Dexmedetomidine inhibits inflammatory reaction in lung tissues of septic rats by suppressing TLR4/NF-κB pathway. *Mediators Inflamm* 2013; 2013: 562154.
25. Ding L, Zhang H, Mi W, et al. [Effects of dexmedetomidine on recovery period of anesthesia and postoperative cognitive function after robot-assisted laparoscopicradical prostatectomy in the elderly people]. *Zhong Nan Da Xue Bao Yi Xue Ban* 2015; 40: 129–135.
26. Laflam A, Joshi B, Brady K, et al. Shoulder surgery in the beach chair position is associated with diminished cerebral autoregulation but no differences in postoperative cognition or brain injury biomarker levels compared with supine positioning: the anesthesia patient safety foundation beach chair study. *Anesth Analg* 2015; 120: 176–185.
27. Silva-Jr JM, Katayama HT, Nogueira FAM, et al. Comparison of dexmedetomidine and benzodiazepine for intraoperative sedation in elderly patients: a randomized clinical trial. *Reg Anesth Pain Med* 2019; 44: 319–324.