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

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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.

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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 agonist2 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]) OR “hemodynamics”[MeSH Terms] OR “hemodynamics”[All Fields] OR...
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 I² and Q tests. I² < 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...
Table 1. Study characteristics.

| Author name   | Publication year | Sample size (Dex/control) | Type of surgery               | Intervention                        | Age          | Outcomes                  |
|---------------|------------------|---------------------------|--------------------------------|-------------------------------------|--------------|---------------------------|
| Lin et al.    | 2009             | 50/48                     | Total hysterectomy             | Dex + morphine                      | 43.5 (25–29) | HR/MBP                    |
| Jung et al.   | 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.    | 2014             | 90/30                     | Laparoscopic total hysterectomy | Dex 0.9% Normal saline              | 45.9 ± 5.5  | 45.6 ± 5.3 HR/DBP/MBP     |
| Sezen et al.  | 2014             | 59/60                     | Hysterectomies                 | Dex Midazolam                       | 47.5 ± 5.5  | 47.0 ± 6.0 HR/DBP/MBP     |
| Choi et al.   | 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.| 2016             | 25/50                     | Vaginal hysterectomy           | Dex Nalbuphine 0.9% normal saline   | 53.25 ± 15.91 | 53.7 ± 12.5 HR/MBP       |
| Thada et al.  | 2017             | 32/32                     | Total abdominal hysterectomy   | 5 μg Dex + 0.5% Hyperbaric bupivacaine + 25 μg (0.5 ml) fentanyl | 41.5 ± 5.2  | 40.7 ± 5.2 HR/MAP         |
| Du et al.     | 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.     | 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 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 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 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).](image-url)
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.

| Study or subgroup | Dex  | Control | Mean difference | Mean difference |
|------------------|------|---------|-----------------|----------------|
|                   | Mean | SD     | Total Mean | SD Total | Mean | SD Total | Weight | IV, Fixed | 95% CI Year | Mean difference |
| Jung et al. 10    | 4.7  | 0.35   | 25         | 4.9  | 0.33 | 25     | 68.3%  | 4.58 | 0.02 | 2011       | -0.20 [0.35, -0.01] |
| Choi et al. 13    | 4.6  | 0.68   | 30         | 4.9  | 0.52 | 60     | 31.7%  | 6.74 | 0.02 | 2016       | -0.30 [0.58, -0.02] |
| Total (95% CI)    | 55   |         | 85         |          | 100.0% | -0.23 [0.09, -0.38] |
| Funnel plot for publication bias assessment.

**Figure 6.** Funnel plot for publication bias assessment. SE, standard error; MD, mean difference.
bradycardia and Choi et al.\textsuperscript{13} reported three cases of xerostomia. Three studies\textsuperscript{14,16,17} did not report any serious adverse reactions, and the remaining three studies\textsuperscript{10–12} did not mention any adverse events.

**Discussion**

We conducted a meta-analysis of nine high-quality studies, which indicated that intra-operative 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 post-operative 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\textsubscript{2}\textsuperscript{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\textsuperscript{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\textsuperscript{18}. HR, SBP, DBP, and SpO\textsubscript{2} are important indicators that can comprehensively reflect changes in hemodynamics in patients during anesthesia induction\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{21,22}.
Dexmedetomidine has also been shown to exert a significant anti-inflammatory effect, regulate the inflammatory response, and significantly reduce tumor necrosis factor-\( \alpha \) 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.

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