

# A Comparison of Dexmedetomidine and Midazolam for the Prevention of Postoperative Nausea and Vomiting Caused by Hemabate in Cesarean Delivery: A Randomized Controlled Trial

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**Objective:** To compare the efficacy of dexmedetomidine and midazolam in the prevention of postoperative nausea and vomiting (PONV) caused by hemabate in postpartum hemorrhage during cesarean delivery.

**Methods:** One hundred and five parturients with American Society of Anesthesiology (ASA) physical status I and II, aged 20–40 years, undergoing elective cesarean delivery under epidural anesthesia were randomly allocated into dexmedetomidine group (group D, n=35), midazolam group (group M, n=35) and control group (group C, n=35). Patients received an intrauterine injection of 250 µg hemabate and continuous intravenous infusion of 5 units oxytocin immediately following the delivery of the infant. At the same time, patients in group D received 1 µg/kg intravenous dexmedetomidine, group M received 0.02 mg/kg intravenous midazolam and group C received 20 mL intravenous saline. Parameters such as the PONV, other adverse reactions (chest distress, flush, etc.) caused by hemabate, patient satisfaction, the sedation (OAA/S) scores, and the hemodynamic parameters were recorded in both groups.

**Results:** The PONV incidence in group D and group M was significantly lower compared with group C (6%, 17%, and 71% for group D, group M, and group C, respectively,  $P < 0.05$ ). The sedation (OAA/S) scores in group D and group M was significantly higher compared with group C ( $1.62 \pm 0.28$ ,  $1.75 \pm 0.31$ , and  $1.00 \pm 0.00$  for group D, group M, and group C, respectively,  $P < 0.05$ ). The patient satisfaction in group D and group M was significantly higher compared with group C (94%, 69%, and 46% for group D, group M, and group C, respectively,  $P < 0.05$ ). Furthermore, there were more patients satisfied with group D than group M (94% vs. 69%,  $P < 0.05$ ).

**Conclusion:** Intravenous dexmedetomidine (1 µg/kg) and midazolam (0.02 mg/kg) were equally effective in preventing PONV introduced by hemabate and dexmedetomidine is superior to midazolam in patient satisfaction.

**Keywords:** dexmedetomidine, midazolam, PONV, hemabate, cesarean delivery

## Introduction

### Background

Hemabate, a synthetic 15-methyl analog of prostaglandin F<sub>2α</sub>, has been discovered to be more powerful than oxytocin in preventing and reducing postpartum hemorrhage (PPH) in high-risk patients undergoing cesarean delivery.<sup>1</sup> However, due to the effect

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on gastrointestinal smooth muscle, hemabate may cause severe nausea and vomiting,<sup>2</sup> which may reduce patient satisfaction and delay discharge from hospital.

Dexmedetomidine is a highly selective  $\alpha_2$  adrenergic agonist that has several functions, including sedation, anti-anxiety, analgesia, cardiovascular stability, and less inhibition of respiration.<sup>3,4</sup> Recently, many studies have shown that it has antiemetic effect,<sup>5,6</sup> and Liu et al have shown that low dose dexmedetomidine can effectively prevent the adverse reactions induced by hemabate.<sup>7</sup> On the other hand, previous studies showed that midazolam was also effective in the reduction of PONV during cesarean delivery.<sup>8–10</sup> However, no studies have focused on comparing dexmedetomidine and midazolam for preventing the PONV induced by hemabate. In this trial, we will compare the efficacy of dexmedetomidine and midazolam in the prevention of PONV induced by hemabate in postpartum hemorrhage during cesarean delivery. To the best of our knowledge, this is the first trial that compared the efficacy and safety of dexmedetomidine and midazolam in the prevention of PONV induced by hemabate in postpartum hemorrhage during cesarean delivery.

## Methods

### Study Design

A total of 105 parturients with American Society of Anesthesiology (ASA) physical status I–II, aged 20–40 years, undergoing elective cesarean delivery under epidural anesthesia were randomly allocated into three groups: Group D (n=35), Group M (n=35) and Group C (n=35). Randomization was carried out by a computer-generated list of random numbers which were sealed in an envelope. Before anesthesia, an anesthesiologist who was blinded to the study opened the sealed envelope and performed the epidural anesthesia.

### Selection of Participants

Patients who had mental illnesses, neuromuscular sicknesses, reactive bronchial diseases, diabetes, body mass index (BMI > 30kg/m<sup>2</sup>), abnormal liver and renal function, the sensory block level was higher than that of T4, known allergies to any anesthetic agent, a history of PONV in previous surgery, or severe sinus bradycardia (<50 beats per min [bpm]) were excluded. Patients were also excluded from the study if they had a history of long-term opioid, NSAIDs or sedative utilization.

## Ethics Issues

This study was conducted in accordance with the Declaration of Helsinki and approved by the Biological-Medical Ethical Committee of the Affiliated Hospital of Guizhou Medical University Hospital, Guiyang, Guizhou, China. Written informed consent was obtained from all patients. This study was also registered at [www.chictr.org](http://www.chictr.org) (identifier: ChiCTR-INR-17013500).

## Intervention

All parturients were maintained nil per os (nothing by mouth, NPO) 8 hours prior to anesthesia. Standard monitoring (the electrocardiography (ECG), noninvasive blood pressure (NIBP), and pulse oximetry saturation (SpO<sub>2</sub>)) were applied for each patient after they entered the operating room. All parturients were treated with lactated Ringer's solution (10 mL/kg) for 20–30 min to prevent hypotension. If the blood pressure decreased more than 20% from baseline pressure or systolic blood pressure decreased less than 90 mmHg, 10 mg of ephedrine was injected. A continuous epidural anesthesia (CEA) technique was performed for cesarean delivery procedures. The epidural anesthesia was performed at the L1–L2 interspace. As high as 0.75% ropivacaine 7–10 mL was infused. The vital signs of each parturient were monitored for every 5 min. Pinprick test was used to confirm adequate sensory block up to T4 level. Surgery was started when the sensory nerve block reached at T4–T6. Patients received an intrauterine injection of 250  $\mu$ g hemabate (Pharmacia & Upjohn Company, Kalamazoo, MI, USA) and continuous intravenous infusion of 5 units oxytocin during the cesarean delivery, immediately following the delivery of the infant. After hemabate injection, patients in group D received 1  $\mu$ g/kg intravenous dexmedetomidine (Jiang Su Heng Rui Medicine Co. Ltd, Jiangsu Province, China) diluted to 20 mL with physiological saline, group M received 0.02 mg/kg intravenous midazolam (Jiang Su Nhua Pharma. Co. Ltd, Jiangsu Province, China) diluted to 20 mL with physiological saline, and group C received 20 mL intravenous physiological saline. The infusion of above mentioned three group liquids were completed in 15 minutes. After surgery, the patient was transported to the PACU, and 1 h after the study medicine infusion, the parturient was transported to the ward. Patients got epidural analgesia with 0.1% ropivacaine+0.5  $\mu$ g/mL sufentanil (continuous, 8 mL/h; bolus, 2 mL; lockout interval, 15 min; 1-h limitation, 20 mL) in a patient-controlled analgesia device for the postoperative 48 h.

## Outcome Measures

Hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at the following time points: 1 min prior to hemabate administration (T0); 5 min (T1); 20 min (T2); 40 min (T3) and 60 min (T4) following hemabate injection. Parameters such as the adverse reactions caused by hemabate, the grade of patient satisfaction, the sedation (OAA/S) scores, and the hemodynamic parameters were recorded in both groups. The investigators, responsible anesthesiologists, surgeons, nurse, the patients, and the staff who registered patients and gathered study results were blinded to group allocation.

## Primary Outcome

The primary outcome was the incidence of PONV. Nausea was defined as an uneasy feeling in the stomach while vomiting refers to the forceful expulsion of gastric contents.<sup>11</sup> PONV was evaluated by means of Bellville scoring score (0: no symptoms, 1: nausea 2: retching 3: vomiting).<sup>12</sup> Patients were treated with 10 mg of metoclopramide in case of two or more emesis episodes.

## Secondary Outcomes

The secondary outcomes include the following: 1) Other adverse reactions induced by the hemabate, which include the following: (a) flush, (b) diarrhea, (c) headache, (d) elevated blood pressure, and (e) chest congestion; 2) the hemodynamic changes at each point; 3) the patient satisfaction: the patients completed a simple questionnaire (0, very satisfied; 1, satisfied; 2, not satisfied) while they leave the PACU. If the patient can not recall what happened during the procedure, then the sedation cannot be considered complete at the time of evaluation; 4) the sedation scores (Observer's Assessment of Alertness/Sedation (OAA/S) scale) (where 1 =awake/alert and 5 = deep sleep).<sup>13</sup>

## Statistical Analysis

The sample size was estimated based on the adverse reactions with a type I error of 0.05 and a power of 80%. Based on our pilot study, a sample size of 29 patients in each group was necessary. To allow for missing cases and dropouts due to various reasons, we calculated that we would need 35 patients for each group. Statistical analysis was conducted with SPSS for Windows version 22.0 (SPSS Inc, Chicago, IL, USA). Continuous data were presented as mean  $\pm$  standard deviation, and categorical data were presented as percentage. Normality

assessment of continuous data was performed with Kolmogorov-Smirnov and/or Shapiro-Wilk tests. Continuous data were compared with analysis of variance (ANOVA) for parametric data or Kruskal-Wallis test for non-parametric data. Post hoc comparisons among the repeated measures in each group were performed by the Tukey HSD and/or LSD method, if appropriate. Percentage data comparison was performed using the Chi-square test or Fisher's exact test. An analysis of ordinal data was performed using the Mann-Whitney *U*-test. Differences in the hemodynamic changes were compared by repeated-measures ANOVA. A *P* value less than 0.05 was considered statistically significant.

## Results

Of the 109 patients, 2 patients refused to participate and 2 patients did not meet inclusion criteria. The remaining 105 parturients completed the study (Figure 1). There were no significant differences between groups in demographic, clinical, and intraoperative characteristics (Table 1).

The PONV incidence in group D and group M was significantly lower compared with group C (6%, 17% and 71% for group D, group M, and group C, respectively,  $P < 0.05$ ), whereas the PONV incidence did not differ between group D and group M ( $P > 0.05$ ) (Table 2). The antiemetic agent metoclopramide was administered to 15 (43%) patients in group C, compared with 2 (6%) patients in group M and no patients in group D, which was statistically significant ( $P < 0.05$ ) (Table 2).

The incidence of chest distress in group D and group M was significantly lower compared with group C ( $P < 0.05$ ) (Table 3). Other side effects induced by hemabate such as flush, diarrhea, and headache did not differ between the groups.

No patients could not recall what happened during the operation, and all patients completed the satisfaction questionnaire assessment. The sedation (OAA/S) scores in group D and group M were significantly higher compared with group C ( $1.62 \pm 0.28$ ,  $1.75 \pm 0.31$ , and  $1.00 \pm 0.00$  for the group D, group M, and group C, respectively,  $P < 0.05$ ). The patient satisfaction score in group D and group M was significantly higher compared with group C (94%, 69%, and 46% for group D, group M, and group C, respectively,  $P < 0.05$ ). Furthermore, there were more patients satisfied with group D than group M (94% vs.69%,  $P < 0.05$ ) (Table 4). The hemodynamic changes did not differ between the three groups (Figure 2).

## Discussion

In this study, the high incidence of PONV caused by hemabate during cesarean delivery was confirmed similar to the previous

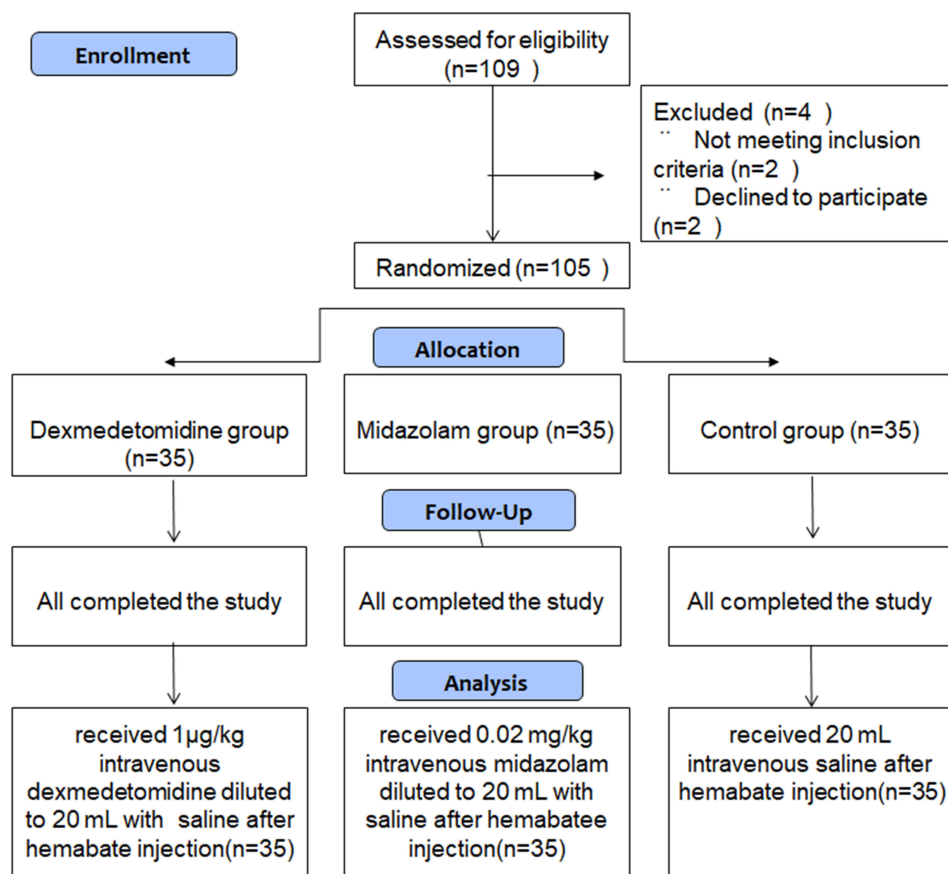


Figure 1 Flow diagram based on Consolidated Standards of Reporting Trials (CONSORT) statement.

studies.<sup>6</sup> In addition, the incidence of PONV in group D and group M were significantly lower compared with group C. To our knowledge, this is the first study comparing the effect of dexmedetomidine and midazolam for the prevention of PONV introduced by hemabate during cesarean delivery.

The overall incidence of PONV during regional anesthesia for cesarean delivery is estimated to 21–79%.<sup>14</sup> PONV can increase the potential risk of aspiration, reduce patient satisfaction, and prolong hospitalization.<sup>15</sup> In addition, PONV may

increase procedure time and inadvertent surgery trauma, causing electrolyte imbalance and aggravate bleeding.<sup>16</sup> Hemabate has a strong and lasting contractile effect on uterine smooth muscle, which can effectively prevent and reduce PPH during cesarean deliver. However, one of the most distressing side effects after its administration is severe nausea and vomiting.<sup>7</sup> Therefore, PONV should be prevented as soon as possible to enhance recovery after surgery according to the guidelines,<sup>14</sup> especially for those who receive hemabate. The common

Table 1 Patients Demographic Data

Variables	Group D (n=35)	Group M (n=35)	Group C (n=35)
Age (years)	31.3±4.6	33.7±3.7	32.9±4.4
Height (cm)	159.5±5.3	160.1±4.2	162.0±4.8
Weight (kg)	68.5±8.0	69.3±8.1	70.1±6.8
BMI (kg/m <sup>2</sup> )	27.6±2.5	27.1±2.3	26.8±3.0
Gestational period (weeks)	38.3±0.9	38.0±0.6	38.5±1.1
Duration of surgery (min)	72.2±8.7	70.3±8.5	68.7±7.6

Note: Data are shown as means ± SD.

Abbreviations: BMI, body mass index; Group D, dexmedetomidine group; Group M, midazolam group; Group C, control group.

Table 2 Incidence of PONV in 3 Groups

Variables	Group D (n=35)	Group M (n=35)	Group C (n=35)
Nausea-Vomiting	2 (6%)*	6 (17%)*	25 (71%)
Nausea	2 (6%)*	4 (11%)	10 (29%)
Retching	0 (0%)	1 (3%)	7 (20%)
Vomiting	0 (0%)	1 (3%)	8 (23%)
Use of antiemetics	0 (0%)*	2 (6%)*	15 (43%)

Notes: Data are shown as number (%). \*Significance difference in comparison with control group (P<0.05).

Abbreviations: Group D, dexmedetomidine group; Group M, midazolam group; Group C, control group.

**Table 3** Incidence of Other Adverse Reactions in 3 Groups

Variables	Group D (n=35)	Group M (n=35)	Group C (n=35)
Flush	0 (0%)	3 (9%)	5 (14%)
Chest distress	1 (3%)*	0 (0%)*	9 (26%)
Elevated blood pressure	0 (0%)	0 (0%)	1 (3%)
Diarrhea	0 (0%)	0 (0%)	2 (6%)
Headache	0 (0%)	0 (0%)	1 (3%)

**Notes:** Data are shown as number (%). \*Significance difference in comparison with control group ( $P<0.05$ ).

**Abbreviations:** Group D, dexmedetomidine group; Group M, midazolam group; Group C, control group.

**Table 4** Patient Satisfaction and OAA/S in 3 Groups

	Group D (n=35)	Group M (n=35)	Group C (n=35)
Very satisfied	23 (66%)*#	13 (37%)*	5 (14%)
Satisfied	10 (31%)	11 (32%)	11 (32%)
Not satisfied	2 (6%)*#	11 (32%)*	19 (54%)
OAA/S	1.62±0.28*	1.75±0.31*	1.00±0.00

**Notes:** Data are shown as number (%) or means ± SD. \*Significance difference in comparison with control group ( $P<0.05$ ). #Significance difference in comparison with control group ( $P<0.05$ ).

**Abbreviations:** OAA/S, Observer's Assessment of Alertness/Sedation scale; Group D, dexmedetomidine group; Group M, midazolam group; Group C, control group.

causes of PONV during cesarean delivery including age, surgical procedure, anesthetic technique, opioid administration, and hypotension.<sup>14</sup> In this study, all patients and groups were identical regarding the operation and their anesthetic management.

The incidence of PONV can be lowered with some sedatives such as dexmedetomidine and midazolam. As a highly selective  $\alpha_2$  adrenergic receptor agonist, dexmedetomidine exhibits sedative, analgesic, and sympatholytic properties.<sup>17</sup> Recently, the incidence of PONV induced by dexmedetomidine has caused extensive concern. A recent meta-analysis indicated that dexmedetomidine significantly reduced the occurrence of PONV.<sup>18</sup> Our study showed that the incidence and severity of PONV induced by hemabate were significantly

reduced in the dexmedetomidine group. The mechanism of dexmedetomidine reducing the incidence of PONV may be related to the reduction of sympathetic tone and catecholamine release.<sup>19</sup>

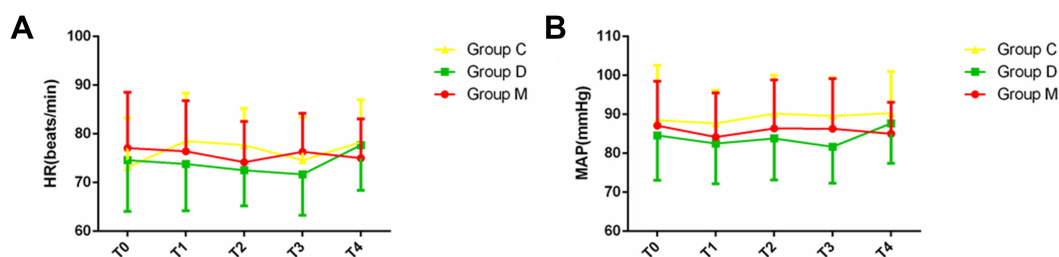
Furthermore, the incidence of chest distress in the dexmedetomidine group was significantly reduced compared with control group, which may be related to the inhibition of airway smooth muscle contraction.<sup>20</sup> However, some research work is needed to clarify its mechanism in the future.

Several investigations have reported that midazolam, used in a subhypnotic dose, was effective in treating PONV.<sup>21,22</sup> Our study found that patients who received midazolam experienced significantly fewer episodes of PONV compared with the control group, which was similar to the finding of O. Tarhan et al.<sup>8</sup> The detailed antiemetic mechanism of midazolam still remains unknown. Midazolam related antiemetic effect may be attributed to reducing synthesis, release, and postsynaptic effect of dopamine by acting on CRTZ-mediated regions.<sup>7,23</sup>

Parturients who are awake during surgery may suffer anxiety, fear, and stress, and a certain degree of sedation can increase the patient satisfaction and affect PONV.<sup>24</sup> In the present study, patient satisfaction was significantly higher in group D and group M, in which patients experienced a higher degree of sedation and a lower incidence of PONV, compared with group C. Although there was no significant difference in the incidence of PONV between the group D and group M, the patient satisfaction in group D was higher compared with group M, which may be related to the fact that the number of PONV and other adverse reactions (such as flushing and chest distress) in group D was less than that in group M.

## Conclusions

In conclusion, intravenous dexmedetomidine (1  $\mu\text{g}/\text{kg}$ ) and midazolam (0.02 mg/kg) were equally effective in preventing PONV introduced by hemabate and improve satisfaction in



**Figure 2** The HR changes (A) and MAP changes (B) at T0, T1, T2, T3, T4 in three groups. T0: 1 min prior to hemabate administration; T1: 5 min after hemabate administration; T2: 20 min after hemabate injection; T3: 40 min after hemabate injection; T4: 60 min after hemabate injection.

patients undergoing cesarean delivery, furthermore, dexmedetomidine is superior to midazolam in patient satisfaction.

## Data Sharing Statement

We are willing to share all relevant data in this study. Readers can contact the corresponding author to obtain data by email after 6 months of publication of this article. The study protocol, statistical analysis plan, and clinical study report will also be available.

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## Disclosure

The authors declare that they have no conflicts of interest.

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