Archives of Anesthesiology and Critical Care (In Press); x(x): xx-xx.

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Research Article

Dose-Dependent Antiemetic Effect of Intravenous Dexamethasone Compared with Paracetamol for Prevention of Postoperative Nausea and Vomiting after Cesarean Delivery under Spinal Anesthesia: A Triple-Blind Randomized Controlled Trial

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ARTICLE INFO

Article history:
Received 18 June 2026
Revised 09 July 2026
Accepted 23 July 2026

Keywords:
Cesarean section;
Dexamethasone;
Paracetamol;
Postoperative nausea and vomiting;
Spinal anesthesia;
Dose-response relationship

ABSTRACT

Background: Postoperative nausea and vomiting (PONV) are common after cesarean delivery under spinal anesthesia and may impair maternal recovery and early postoperative comfort. Dexamethasone is an established antiemetic, but the optimal prophylactic dose in obstetric patients remains unclear. This study evaluated the dose–response effect of intravenous dexamethasone compared with paracetamol and placebo for the prevention of PONV after cesarean delivery.

Methods: In this randomized triple-blind clinical trial, 239 parturients undergoing cesarean delivery under spinal anesthesia were allocated to five groups: placebo, paracetamol 1 g, dexamethasone 2 mg, dexamethasone 4 mg, and dexamethasone 6 mg. The primary outcome was the incidence of PONV during the first six postoperative hours. Secondary outcomes included PONV severity, treatment effect expressed as odds ratios, and dose–response trend across dexamethasone groups.

Results: The incidence of PONV was highest in the placebo group at 70%. PONV occurred in 55% of patients receiving paracetamol, 40% receiving dexamethasone 2 mg, 25% receiving dexamethasone 4 mg, and 12% receiving dexamethasone 6 mg. Compared with placebo, paracetamol reduced the odds of PONV, although the effect was smaller than that observed with dexamethasone. Dexamethasone showed a significant dose-dependent reduction in both incidence and severity of PONV. The strongest effect was observed with dexamethasone 6 mg, which was associated with the lowest PONV incidence and no cases of severe vomiting.

Conclusion: Intravenous dexamethasone significantly reduced the incidence and severity of PONV after cesarean delivery under spinal anesthesia in a dose-dependent manner. Dexamethasone 4 mg appears to offer an effective balance between antiemetic efficacy and limited steroid exposure, while 6 mg provides the greatest reduction in PONV. Paracetamol showed a smaller antiemetic effect and may be more

The authors declare no conflicts of interest.
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DOI:

appropriate as an analgesic adjunct than as a primary antiemetic.

Introduction

Postoperative nausea and vomiting (PONV) remain among the most frequent and distressing complications following cesarean delivery performed under spinal anesthesia. Reported incidence rates range from approximately 50% to 80%, depending on maternal risk factors, anesthetic techniques, and perioperative management strategies [1–3]. In obstetric patients, PONV is not merely a minor discomfort; it can delay maternal recovery, interfere with early breastfeeding and maternal–infant bonding, reduce overall patient satisfaction, and increase the need for rescue antiemetic medications or prolonged post-anesthesia care unit (PACU) observation [1-2,4].

Parturients represent a particularly high-risk population for PONV due to several physiological and perioperative factors, including hormonal influences, heightened vagal tone, neuraxial anesthesia, and perioperative hypotension [3,5]. The widely used Apfel risk score identifies female sex, history of motion sickness or PONV, nonsmoking status, and postoperative opioid use as key predictors of PONV, with obstetric patients often fulfilling multiple criteria simultaneously [6]. Consequently, current consensus guidelines recommend routine prophylactic antiemetic strategies in high-risk populations such as women undergoing cesarean delivery [7].

Among available antiemetic agents, dexamethasone has been widely studied and consistently shown to reduce the incidence of postoperative nausea and vomiting across various surgical procedures. Early systematic reviews and meta-analyses demonstrated that perioperative dexamethasone significantly decreases both nausea and vomiting compared with placebo [8]. The antiemetic mechanisms of dexamethasone are not fully understood but are thought to involve inhibition of prostaglandin synthesis, reduction of serotonin release within the gastrointestinal tract, and central anti-inflammatory effects that modulate vagal afferent signaling in the brainstem vomiting centers [9-10].

Despite strong evidence supporting dexamethasone as an effective antiemetic, most obstetric studies have used a single fixed dose, typically 8 mg, without exploring whether lower doses might achieve comparable benefits while minimizing corticosteroid exposure. A systematic review focusing on cesarean delivery confirmed the overall antiemetic efficacy of dexamethasone in this population but did not address the potential dose–response relationship between different dexamethasone doses and PONV prevention [11]. Dose-ranging studies in non-obstetric populations suggest that the antiemetic effect of dexamethasone increases with dose up to approximately 8–10 mg, after which the benefit plateaus [12]. However, evidence specifically addressing optimal dosing in cesarean patients remains limited.

Intravenous paracetamol (acetaminophen) has also been investigated as a potential strategy to reduce PONV, primarily through improved postoperative analgesia and opioid-sparing effects. Some studies have reported modest reductions in PONV when paracetamol is included as part of multimodal analgesia protocols [13], whereas others have demonstrated little or no antiemetic benefit in cesarean patients receiving spinal anesthesia [14]. Direct comparisons between paracetamol and dexamethasone, particularly within dose-response designs, remain scarce. Given these uncertainties, the present study aimed to evaluate the dose-response relationship of dexamethasone for the prevention of PONV after cesarean delivery under spinal anesthesia. In this randomized triple-blind clinical trial, we compared three doses of intravenous dexamethasone (2 mg, 4 mg, and 6 mg) with paracetamol 1 g and placebo. We hypothesized that dexamethasone would reduce both the incidence and severity of PONV in a dose-dependent manner and that its antiemetic effect would be superior to that of paracetamol.

Methods

Study Design and Ethical Approval

This randomized, triple blind, parallel group clinical trial was conducted at Beheshti Hospital, Isfahan University of Medical Sciences, between 2024 and 2025. The study protocol was approved by the Institutional Ethics Committee (IR.ARI.MUI.REC.1404.177) and registered in the Iranian Registry of Clinical Trials (IRCT20240221061070N9). Written informed consent was obtained from all participants before enrollment.

Participants

Full-term parturients with ASA physical status II who were scheduled for elective cesarean section under spinal anesthesia were eligible for inclusion.

Patients were excluded if they had:

- Known hypersensitivity to any of the study medications
- Preexisting nausea or vomiting
- Hyperemesis gravidarum
- Chronic corticosteroid use
- Diabetes mellitus requiring pharmacologic treatment
- Hypertensive disorders of pregnancy
- Contraindications to spinal anesthesia

Additional exclusion criteria included:

- Conversion to general anesthesia
- Intraoperative blood loss >1000 ml

- Incomplete postoperative PONV assessment

Randomization and Blinding

Participants were randomly assigned to one of five groups using a computer-generated block randomization sequence (block size = 10) prepared by an independent statistician. Study medications were prepared in identical 10-mL syringes by a nurse not involved in intraoperative management or data collection.

Patients, anesthesiologists, surgeons, recovery room staff, and investigators responsible for outcome assessment were all blinded to group allocation throughout the study.

Study Groups

Participants were allocated to one of the following five groups:

- Placebo group: 10 mL normal saline IV
- Paracetamol group: paracetamol 1 g IV
- Dexamethasone 2 mg group: dexamethasone 2 mg IV
- Dexamethasone 4 mg group: dexamethasone 4 mg IV
- Dexamethasone 6 mg group: dexamethasone 6 mg IV

The study medication was administered intravenously immediately after confirmation of a sensory block level at or above T4. Paracetamol was infused over 10 minutes, whereas placebo and dexamethasone solutions were administered as slow intravenous boluses over approximately one minute.

Anesthetic Technique

Upon arrival in the operating room, standard monitoring was applied, including ECG, noninvasive blood pressure, and pulse oximetry. Spinal anesthesia was performed at the L4–L5 interspace using 12.5 mg of 0.5% hyperbaric bupivacaine via a Quincke needle through a paramedian approach. Supplemental oxygen (4 L/min) was administered via face mask. Hypotension, defined as systolic blood pressure <90 mmHg or a decrease of >20% from baseline, was treated with incremental intravenous ephedrine according to institutional protocol. Oxytocin was administered after delivery according to routine obstetric practice. No prophylactic antiemetic drugs were administered intraoperatively or postoperatively.

Postoperative Analgesia

Postoperative analgesia was standardized in all patients. Intravenous paracetamol was administered starting 6 hours after surgery. Additional analgesia with ketorolac or diclofenac was given if needed. Opioids were avoided unless the pain score exceeded 7/10 and, when required, were administered only after clamping of the umbilical vessels.

Outcome Measures

Postoperative nausea and vomiting were assessed during the first 6 hours after surgery by a trained investigator blinded to group allocation.

PONV severity was graded using a validated four-point ordinal scale:

- 0 = no nausea or vomiting
- 1 = mild nausea
- 2 = moderate or severe nausea
- 3 = vomiting

Primary Outcome

The primary outcome was the incidence of PONV, defined as a score ≥1 within the first 6 postoperative hours.

Secondary Outcomes

Secondary outcomes included:

- Severity of PONV (mean ordinal score)
- Requirement for rescue antiemetic therapy
- Dose–response relationship of dexamethasone

Rescue antiemetic therapy consisted of ondansetron 4 mg IV, administered upon patient request or after an episode of vomiting.

Sample Size Calculation

The sample size was calculated to detect a clinically meaningful reduction in PONV incidence from 70% in the placebo group to 40% in the treatment group. With a statistical power of 80% and $\alpha = 0.05$, the required sample size was 50 patients per group.

Statistical Analysis

Data were analyzed using SPSS version 21.0. Continuous variables were presented as mean ± standard deviation (SD) and compared using one-way ANOVA. Categorical variables, including the incidence of PONV, were expressed as frequencies (percentages) and analyzed using the chi-square test or Fisher's exact test. For the primary outcome, logistic regression analysis was performed to calculate Odds Ratios (OR) and 95% Confidence Intervals (CI) for each treatment group compared to placebo. The severity of PONV was analyzed using ordinal logistic regression. To evaluate the dose–response relationship across the three dexamethasone doses, a linear-by-linear association test (P-for-trend) was employed. A two-sided P value < 0.05 was considered statistically significant.

Results

A total of 250 patients were assessed for eligibility. Eleven patients were excluded due to protocol violations or incomplete follow-up. Finally, 239 patients were included in the analysis and allocated into five groups: placebo (n=47), paracetamol (n=49), dexamethasone

2 mg (n=48), dexamethasone 4 mg (n=46), and dexamethasone 6 mg (n=49).

Baseline demographic and clinical characteristics, including age, body mass index (BMI), gestational age, duration of surgery, and history of PONV, were comparable among the five groups, indicating successful randomization (Table 1).

The overall incidence of PONV during the first 6 postoperative hours was highest in the placebo group (70%). All intervention groups showed a lower incidence compared with placebo. The incidence of PONV was 55% in the paracetamol group, 40% in the dexamethasone 2 mg group, 25% in the dexamethasone 4 mg group, and 12% in the dexamethasone 6 mg group. The difference among groups was statistically significant ($P < 0.001$) (Figure 1). The distribution of PONV severity scores (0–3) also differed significantly among the groups (Table 2). In the placebo group, a considerable proportion of patients experienced moderate or severe symptoms, including vomiting. In contrast, patients receiving dexamethasone demonstrated markedly lower severity scores. The dexamethasone 6 mg group showed the most favorable profile, with 88% of patients remaining symptom-free (Score 0) and no cases of vomiting (Score 3) reported. These findings indicate that dexamethasone not only reduced the incidence of PONV but also decreased symptom severity.

Logistic regression analysis demonstrated that all active treatments reduced the odds of PONV compared with placebo (Table 3). Paracetamol significantly decreased the risk of PONV (OR = 0.36; 95% CI: 0.18–0.71; $P = 0.003$).

Dexamethasone showed a stronger protective effect with increasing doses. The odds ratios were 0.29 for dexamethasone 2 mg, 0.15 for dexamethasone 4 mg, and 0.07 for dexamethasone 6 mg (all $P < 0.001$).

A significant dose–response relationship was observed across the dexamethasone groups, with higher doses associated with progressively lower incidence and severity of PONV (P-for-trend < 0.001).

The calculated Number Needed to Treat (NNT) further supported the clinical effectiveness of the interventions. The NNT was 4.3 for paracetamol, 2.0 for dexamethasone 2 mg, 1.7 for dexamethasone 4 mg, and 1.5 for dexamethasone 6 mg, indicating increasing efficacy with higher dexamethasone doses (Table 3).

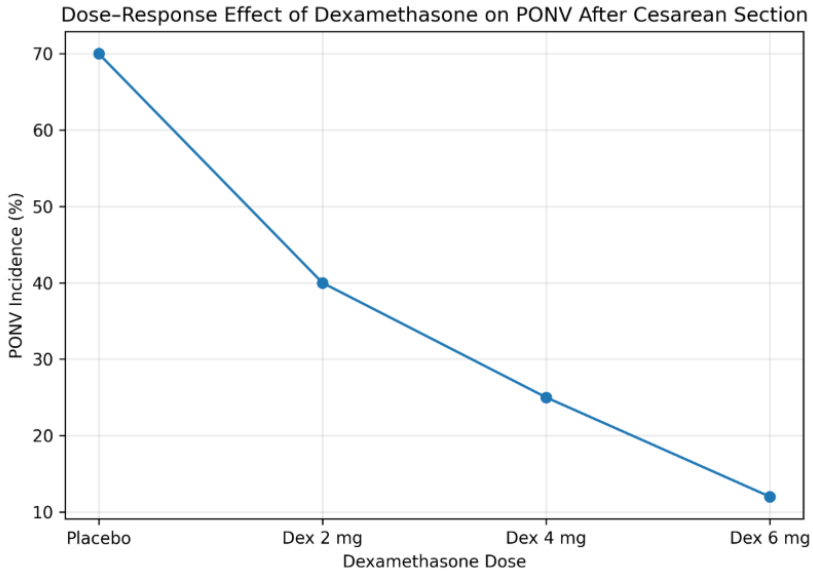

Figure 1- Dose–response relationship of dexamethasone on postoperative nausea and vomiting (PONV) after cesarean section. Increasing the dexamethasone dose was associated with progressively lower incidence and severity of PONV.

Table 1- Baseline Characteristics of Patients.

Variable	Placebo (n=47)	Paracetamol (n=49)	Dex 2 mg (n=48)	Dex 4 mg (n=46)	Dex 6 mg (n=49)	P value
Age (years)	30.1 ± 5.3	29.8 ± 5.1	30.4 ± 4.9	29.6 ± 5.0	30.5 ± 5.4	0.912
BMI (kg/m²)	28.6 ± 4.1	28.1 ± 3.9	28.8 ± 4.2	28.3 ± 4.0	29.1 ± 4.4	0.781
Gestational Age (wk.)	38.2 ± 1.1	38.4 ± 1.0	38.1 ± 1.2	38.3 ± 1.1	38.0 ± 1.3	0.629
Surgery Duration (min)	42.3 ± 8.1	41.8 ± 7.9	43.1 ± 8.4	42.0 ± 8.0	43.5 ± 8.6	0.912
History of PONV, n(%)	8 (17%)	7 (14.3%)	9 (18.8%)	6 (13%)	10 (20.4%)	0.821

Table 2- Distribution of PONV Severity Scores (0–3).

Group	Score 0 (None)	Score 1 (Mild)	Score 2 (Mod/Sev)	Score 3 (Vomiting)	Total PONV (%)
Placebo	30%	20%	30%	20%	70%
Paracetamol	45%	30%	17%	8%	55%
Dex 2 mg	60%	30%	8%	2%	40%
Dex 4 mg	75%	19%	5%	1%	25%
Dex 6 mg	88%	9%	3%	0%	12%

Note: P < 0.001 for comparison across all groups (Ordinal Logistic Regression).

Table 3- Efficacy Analysis of Interventions vs. Placebo.

Intervention	Incidence (%)	Odds Ratio (95% CI)	P value	NNT
Placebo	70%	Reference	—	—
Paracetamol	55%	0.36 (0.18–0.71)	0.003	4.3
Dex 2 mg	40%	0.29 (0.15–0.55)	<0.001	2.0
Dex 4 mg	25%	0.15 (0.07–0.32)	<0.001	1.7
Dex 6 mg	12%	0.07 (0.03–0.13)	<0.001	1.5

NNT: Number Needed to Treat; CI: Confidence Interval.

Discussion

In this randomized triple-blind clinical trial, intravenous dexamethasone significantly reduced both the incidence and severity of postoperative nausea and vomiting (PONV) during the first six hours after cesarean delivery under spinal anesthesia. The antiemetic effect followed a clear dose–response pattern, with progressively lower PONV rates observed as the dose of dexamethasone increased from 2 mg to 6 mg. Paracetamol also reduced the risk of PONV compared with placebo; however, its effect was smaller than that observed with dexamethasone, particularly with the 4 mg and 6 mg doses.

The incidence of PONV was highest in the placebo group and decreased from 70% to 40%, 25%, and 12% in the dexamethasone 2 mg, 4 mg, and 6 mg groups, respectively. This reduction was not limited to overall incidence; the distribution of severity scores also shifted favorably across dexamethasone groups. In particular, the dexamethasone 6 mg group showed the most favorable outcome, with the majority of patients remaining symptom-free and no cases of severe vomiting recorded. These findings suggest that dexamethasone does not merely reduce the occurrence of PONV but also attenuates its clinical severity.

Our results are consistent with previous evidence supporting dexamethasone as an effective prophylactic antiemetic. Henzi et al. demonstrated in a quantitative systematic review that dexamethasone significantly reduced postoperative nausea and vomiting across different surgical populations [1].

More recently, De Oliveira et al. reported a dose-ranging effect of dexamethasone on PONV prevention, with increasing efficacy up to a plateau range [2]. The present study extends these observations to an obstetric population undergoing cesarean delivery under spinal anesthesia and suggests that clinically meaningful prophylaxis can be achieved with doses lower than the traditionally used 8 mg regimen.

The obstetric setting has unique features that may increase susceptibility to nausea and vomiting, including pregnancy-related hormonal changes, neuraxial anesthesia, uterotonic administration, visceral manipulation, and perioperative hypotension [3-4]. PONV in cesarean delivery is clinically important because it can impair maternal comfort, interfere with early recovery, and negatively affect early breastfeeding and maternal–infant interaction [5]. Therefore, preventive strategies in this population should be effective, safe, and practical.

Several previous studies have evaluated dexamethasone in cesarean delivery. Allen et al. reported that dexamethasone reduced PONV in parturients undergoing cesarean delivery, although most included trials used single-dose regimens rather than a dose-comparison design [6].

Other randomized trials comparing dexamethasone with ondansetron have also shown comparable antiemetic efficacy in cesarean patients under spinal anesthesia [7-8]. However, these studies did not formally evaluate a graded dose–response relationship. The multi-arm design of the present trial is, therefore, an important strength, allowing comparison of 2 mg, 4 mg, and 6 mg dexamethasone within the same standardized anesthetic protocol.

The mechanisms responsible for the antiemetic effect of dexamethasone remain incompletely defined. Proposed mechanisms include inhibition of prostaglandin synthesis, decreased inflammatory mediator release, reduction of serotonin release in the gastrointestinal tract, and modulation of vagal afferent input to central emetic pathways [9-10].

Dexamethasone may also improve postoperative comfort through analgesic and anti-inflammatory effects, which could indirectly reduce nausea by decreasing pain-

related stress responses and opioid requirements [11]. In the present study, the dose-dependent reduction in PONV supports the likelihood of a true pharmacological antiemetic effect rather than a nonspecific clinical effect.

Paracetamol produced a smaller antiemetic benefit than dexamethasone. This finding is biologically plausible because paracetamol is not a primary antiemetic agent. Its potential influence on PONV is usually indirect and may occur through improved analgesia and opioid-sparing effects. Memis et al. reported that intravenous paracetamol could reduce postoperative pain and PONV in some surgical settings [12].

However, Jokela et al. found that intravenous paracetamol did not reduce nausea after cesarean delivery under spinal anesthesia [13]. In our study, where the anesthetic protocol was opioid-sparing, the antiemetic contribution of paracetamol may have been limited. These findings support the use of paracetamol primarily as an analgesic adjunct rather than as a stand-alone prophylactic antiemetic.

Current consensus guidelines recommend prophylactic antiemetic therapy for patients at moderate or high risk of PONV and identify dexamethasone as one of the established agents for prevention [14]. Obstetric patients frequently meet several PONV risk criteria, including female sex and nonsmoking status, and may have additional pregnancy- and anesthesia-related risk factors [15]. Our findings support the inclusion of intravenous dexamethasone in routine prophylactic protocols for cesarean delivery, particularly in patients with prior PONV or other risk factors.

This study has several strengths. It was randomized and triple-blinded, reducing selection, performance, and observer bias. The five-group design included both placebo and active comparator arms, allowing direct assessment of dexamethasone dose response as well as comparison with paracetamol.

Baseline characteristics were comparable across groups, and anesthetic management was standardized. In addition, both incidence and ordinal severity outcomes were analyzed, providing a more clinically informative assessment of PONV.

Some limitations should be acknowledged. First, follow-up was limited to the first six postoperative hours; therefore, delayed PONV could not be evaluated. Second, biochemical outcomes such as maternal blood glucose and neonatal metabolic parameters were not assessed. Third, this was a single-center study, and results may not be fully generalizable to centers with different anesthetic techniques, uterotonic protocols, or postoperative analgesic regimens.

Conclusion

In conclusion, this trial demonstrated a clear and clinically meaningful dose–response relationship between intravenous dexamethasone and prevention of PONV after cesarean delivery under spinal anesthesia. Dexamethasone 4 mg and 6 mg provided strong protection, while 2 mg also showed significant benefit. Considering efficacy and steroid exposure, 4 mg may represent a practical, balanced dose for routine prophylaxis, while 6 mg may be considered in patients at particularly high risk of PONV.

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