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ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Sub-hypnotic dose of midazolam is effective in reducing intraoperative nausea and vomiting during cesarean sections under spinal anesthesia

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ABSTRACT

Background & Objectives: Intra and postoperative nausea and vomiting under regional anesthesia is a common problem in cesarean sections. Globally, the incidence has been documented to be from 40−80%, and various drugs have been used to control it. We aimed to determine if a subhypnotic dose of midazolam will be effective to reduce intraoperative nausea and vomiting during an elective cesarean section under spinal anesthesia.

Methodology: A randomized interventional study was done through a period of 6 months from March 11, 2019 to September 11, 2019 and included 100 full term pregnant women undergoing elective cesarean sections (CS) under spinal anesthesia. The participants were allocated to one of two groups: Midazolam group (received midazolam 1 mg bolus then 1.0 mg/h infusion after umbilical cord clamping), and placebo group (received normal saline). Bellville score was used to evaluate nausea and vomiting (N/V). The hemodynamic parameters were monitored at three-minute intervals.

Results: No statistically significant differences were noted between study groups regarding mean arterial pressure, heart rate and total ephedrine used in the two groups. Intraoperative nausea and vomiting were recorded midazolam (81.6%) with a significant association between prevention of intraoperative N/V and receiving midazolam. Insignificant association was noticed between the level of sedation and receiving midazolam.

Conclusion: Administration of low dose of midazolam during cesarean sections under spinal anesthesia can lessen intraoperative nausea/vomiting without significantly effect on blood pressure or heart rate and without any negative side effects.

Abbreviations: BMI – Body Mass Index; CS - Cesarean Section; LA – Local Anesthesia; N/V - Nausea/Vomiting; RASS - Richmond Agitation Sedation Score SA - Spinal Anesthesia

Key words: Nausea; Vomiting; Anesthesia, Spinal; Midazolam; Cesarean Section

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1. INTRODUCTION

In order to lower the complications of general anesthesia (GA) such as related to difficult intubation, gastric contents aspiration and increased maternal mortality in the pregnancy, spinal anesthesia (SA) is a widely used anesthetic technique for CS.[1,2] SA has a number of benefits, being dependable and simple to perform, being less expensive, offering the surgeon better operating conditions, restoring normal gastrointestinal function more quickly, preserving the patient's airway, reducing the risk of pulmonary complications, and having a lower incidence of deep venous thrombosis and pulmonary emboli development.[3]

Even with the application of the essential therapies, one of the most frequent anesthesia-related complication is nausea and vomiting (N/V).[4] During CS, hypotension, defined as a 30% fall in mean blood pressure, is a frequent issue linked to N/V in the mother and the possibility of neonatal and fetal acidosis.[5] A variety of therapeutic options, including dopamine, serotonin receptor antagonists, antihistamines, corticosteroids, sedatives, and anticholinergic medications, have been used.[6] Previous research has examined the effectiveness of various anti-emetics in lowering the risk of N/V in CS patients, typically using a single medication.[2] Extensive research on SA has shown that multimodal prophylaxis is superior to prevent N/V, especially in CS.[7] Intense drowsiness, dystonic responses, restlessness, and extrapyramidal symptoms are some of the common side effects of the medications used to prevent or cure this complication. Following surgery, sedation is evaluated using the Richmond Agitation Sedation Score (RASS).[8] Therefore, in addition to midazolam, additional medication regimens have been utilized to manage N/V. It is still unclear how does midazolam work to prevent N/V. Midazolam appears to limit adenosine reuptake and dopamine input at the chemoreceptor trigger zone (CRTZ). As a result, adenosine-mediated dopamine synthesis, release, and postsynaptic action are reduced at the CRTZ. Adenosine also inhibits the release of 5-HT_3 and dopaminergic neuronal activity by binding to the receptors of gamma-aminobutyric acid.[9] Many studies have shown a lower incidence of postoperative N/V with intravenous midazolam before surgery is finished, as compared to giving it after operation.[10, 11, 12]

We aimed to determine if a sub hypnotic dosage of midazolam, according to a Delphi-study based international expert consensus report,[13] during elective CS under SA affects intraoperative nausea and vomiting.

2. METHODOLOGY

This randomized comparative interventional study was done at the Department of Gynecology and Obstetrics in Baghdad Teaching Hospital, Baghdad (Iraq), through March to September 2019. Institutional Ethical Committee, Al-farahide University approval (#56, Feb 2019) was obtained, and of total of 100 full term pregnant women, ASA-II, undergoing elective CS under SA, were allocated to one of the two groups:

- Midazolam group (Group M): Included 50 participants who received midazolam 1 mg bolus then 1.0 mg/h infusion midazolam, for 30−45 min after umbilical cord clamping.
- Placebo group (Group P): Included 50 participants who received normal saline and matched with the other group for age, parity and BMI.

Participants with multiple pregnancy, morbid obesity (BMI ≥ 40 kg/m^2), a known history of allergy for midazolam, postoperative N/V history or motion sickness or vertigo, had a previous CS or pelvic surgery, a known psychological disorders, those who were unfit for SA, received any antiemetic drugs, or refused to participate in this study were excluded from this study.

Randomization was done when each eligible participant assigned with a number, then individuals with odd numbers were included in Group M, while those with even numbers were assigned to Group P. Intraoperative nausea and vomiting after delivery were recorded by an anesthesiologist. Any case with failure of SA, vomiting before administration of midazolam, significant hypotension, hypoxia due to high spinal or excessive sedation, or postpartum hemorrhage was managed accordingly and dropped from the study (six cases dropped from the study due to these conditions).

An interviewer administered a pre-designed questionnaire which was utilized to collected information including: age, BMI, parity, duration of surgery, mean arterial pressure (MAP)[14], and heart rate at four points as follows; prior to anesthesia (baseline); post-induction, before study drug administration and post drug administration

Ephedrine was used to treat hypotension, defined as > 20% fall from the baseline or a systolic blood pressure of < 90 mmHg. Bellville score was used to evaluate N/V (0: no symptoms; 1: nausea; 2: retching; 3: vomiting).[2]

An antiemetic was described in case of 2 or more emesis episodes. Sedation was evaluated intra-operatively and postoperatively for 6 h according to modified RASS by Idei et al. (2023).[15]

All subjects received normal saline preload in both groups prior to the induction of SA. SA was accomplished by the administration of 12.5 mg (2.5 mL) of hyperbaric bupivacaine 0.5% with a 25-gauge pencil point spinal needle, in the sitting position. Participants were then positioned supine with a left tilt to prevent aortic compression. A face mask was used to give oxygen @ 5 L/min. Blood pressure was measured at 5-min intervals. Participants in the placebo group received saline whereas those in the midazolam group received midazolam.

Statistical analysis

The findings were analyzed by Statistical Package for Social Sciences (SPSS) version 26 (BMI, NY, US)). The variables have been documented as mean and standard deviation. Categorical variables reported as frequencies and percentage. Chi-square test used to test qualitative data and to find any relations between type of drug used and certain variables. Paired t-test used to compare the

Table 1: Comparison between groups by general characteristics.

Variable	Group M (n = 50)	Group P (n = 50)	P-value
Age (y)	27.2 ± 5.4	25.9 ± 4.9	0.211
Parity (median)	4	3	0.112
BMI (kg/m^2)	29.9 ± 6.1	29.2 ± 7.2	0.601
Duration of operation (min)	44.2 ± 8.9	42.7 ± 6.7	0.342

Data presented as Mean ± SD; P < 0.05 considered as significant

Table 3: Association between intraoperative clinical features and receiving midazolam, n (%).

Variable	Group M (n = 50)	Group P (n = 50)	P - value
Nausea and vomiting			
Yes	7 (18.4)	31 (81.6)	**0.001**
No	43 (69.4)	19 (30.6)	
Sedation level			
Drowsy	6 (85.7)	1 (14.3)	0.05
Alert	44 (47.3)	49 (52.7)	

continuous variables among groups. P < 0.05 was considered significant.

3. RESULTS

There was no significant difference (P ≥ 0.05) between Group M and Group P regarding age, parity, BMI, and time of surgery, respectively (Table 1). All cases had sensory block upto T4.

MAP was equivalent (P ≥ 0.05) between Group M and Group P, at all recording times. Similarly, heart rates were also equivalent in both groups at all recording times. Total ephedrine use (16.8 in both groups was not different statistically (Table 2).

The number of patients who complained intraoperative N/V was higher in Group P

(81.6%) compared to Group M (18.4%) and the difference was statistically significant (P = 0.001).

There was insignificant difference (P = 0.05) between sedation level and receiving midazolam in Group M (85.7%) and Group P (14.3%) (Table 3).

4. DISCUSSION

It is thought that pregnancy-related physiological changes, including great levels of progesterone and the subsequent relaxation of smooth muscles, raised gastrin secretion, declined gastrointestinal motility, and reduced esophageal sphincter tone, play a significant role in N/V during CS. Therefore, pregnant women who have abdominal procedures under SA experience N/V more frequently than non-pregnant women.[16]

Table 2: Comparison in means of mean arterial pressure (MAP), heart rate, and ephedrine use between groups.

Variable	Group M (n = 50)	Group P (n = 50)	P-value
MAP (mmHg)			
• Before anesthesia	97.8 ± 10.1	99.5 ± 11.2	0.427
• After induction of anesthesia	82.7 ± 8.8	84.2 ± 9.1	0.403
• Before drug administration	81.6 ± 9.1	82.4 ± 9.4	0.665
• After drug administration	76.2 ± 8.3	79.5 ± 9.3	0.063
Heart rate (beats/min)			
• Before anesthesia	94.2 ± 10.9	93.1 ± 11.4	0.621
• After induction of anesthesia	91.4 ± 11.6	91.7 ± 10.5	0.892
• Before drug administration	93.2 ± 9.6	91.3 ± 8.6	0.299
• After drug administration	90.4 ± 11.9	89.1 ± 9.2	0.543
Total ephedrine use (mg)	16.8 ± 2.7	15.9 ± 2.3	0.075

Data presented as Mean ± SD; P < 0.05 considered as significant

In the current study, participants who didn't receive medication (Group P) showed high incidence of nausea and vomiting during CS, and the results were similar to previous studies comparing those received low dose of midazolam with the control group, without a significant difference in sedation. This result is similar to the study

conducted by Ding et al., who mentioned that at all times, except the thirteenth minute, N/V were lower in the midazolam group and a statistical difference was seen between two categories.[1] Another recent study by Ghasemloo et al. found results that were similar and concluded that a bolus dose of midazolam (2 mg) was more effective than metoclopramide (10 mg) for preventing N/V in parturient patients undergoing CS under SA. They found that the frequency of intraoperative nausea and vomiting was lower in the midazolam group compared with metoclopramide (15% vs. 52.5%).[17] A study by Griffiths et al in 2021 found that the frequency of N/V and the rescue drug use (metoclopramide) was significantly less in propofol and midazolam groups than the placebo. In our study, decline in MAP dropped in both groups after SA; however, the difference was statistically insignificant. Mean ephedrine consumption in midazolam and placebo arms was also not significantly different. This result was similar to results obtained by Ding et al.,[1] Ghasemloo et al. [17] and Griffiths et al.[2]

No single antiemetic drug has the full ability to prevent N/V. Therefore, combinations of antiemetics have been used for the at-risk patient. Recently, many authors emphasized that multimodal treatment with a combination of three antiemetic agents was superior to a single-drug therapy in the prevention of N/V.[18,19,20] Earlier, one study found that a combination of droperidol, ondansetron, and metoclopramide, as antiemetic prophylaxis, was highly effective in minimizing N/V in post office-based surgery with a desflurane-based anesthesia.[21]

Previously some meta-analyses suggested that combination of dexamethasone with a 5-HT^3 receptor antagonist resulted in high antiemetic efficacy, and this combination was determined as the 'optimal' choice for prophylaxis against N/V.[22,23] However, some other authors concluded that an addition of dolasetron or ondansetron failed to improve the anti-emetic efficacy of dexamethasone when they were used for routine prophylaxis to prevention of N/V.[24,25] In the absence of any consensus, it is prudent to explore more options and more therapeutic measures.

5. LIMITATIONS

A small sample size is the main limitation. Larger, multi-center, randomized studies are required to further validate the results of this study.

6. CONCLUSION

Administration of a low dosage of midazolam during cesarean sections under spinal anesthesia, after the umbilical cord is clamped, can lessen intraoperative nausea/vomiting without significantly lowering blood pressure or heart rate and without any negative side effects from the drug.

7. Data availability

Numerical data generated in this study is available on request.

8. Conflict of interests

All authors declare no conflict of interest. No external or industry funding was involved in the conduct of this study.

9. Authors' contribution

IGI in the only author contributor for this article.

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