

Original Article

Prevention of nausea and vomiting in caesarean section under spinal anaesthesia with midazolam or metoclopramide?

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Abstract

Objective: To evaluate the efficacy and safety of bolus dose of midazolam and metoclopramide in reducing emetic symptoms during caesarean delivery under spinal anaesthesia.

Methods: In a double-blind study, 80 women undergoing elective caesarean section under spinal anaesthesia (using 0.5% bupivacaine 10 mg) were allocated randomly to receive midazolam 2 mg, or metoclopramide 10 mg at the beginning of surgery before skin incision. The frequency of nausea and vomiting, sedative score, respiratory depression, and side effects were recorded.

Results: The frequency of intraoperative nausea and vomiting was lower in the midazolam group compared with metoclopramide (15% versus 52.5%). Sedation scores within 3 hour postoperatively were significantly lower in the metoclopramide group. The frequency of respiratory depression was higher in midazolam group. There were some episodes of respiratory depression (respiratory rate of less than 10 bpm) in 17 patients in the midazolam group at the time of surgery treated by verbal stimulation, but no respiratory depression was seen in metoclopramide group. Neonatal outcome was similar in the two groups and all the neonates had Apgar scores ≥ 8 at one and five minutes.

Conclusions: A bolus dose of midazolam (2 mg) was more effective than metoclopramide (10 mg) for the prevention of nausea and vomiting in parturients patients undergoing caesarean section under spinal anaesthesia, however, further studies are needed to prove the safety of midazolam in parturient patients undergoing caesarean section (JPMA 59:756; 2009).

Introduction

Nausea and vomiting are common side effects in parturients undergoing caesarean delivery performed under spinal anaesthesia can be very unpleasant to the patients. The reported incidence of nausea and vomiting during caesarean performed under regional anaesthesia varies from 50% to 80% when no prophylactic antiemetic is given.^{1,2} Therefore, use of prophylactic antiemetics in parturients undergoing caesarean delivery is recommended by some authors.^{3,4}

A number of treatments have been introduced in order to reduce post operative nausea and vomiting (PONV), such as 5-HT₃ antagonists (ondansetron and granisetron), dopamine receptor antagonists, and antihistamine drugs. However, each of these treatments is associated with critical limiting factors, namely cost with 5-HT₃ antagonists, extrapyramidal symptoms with dopamine receptor antagonists, excessive sedation and tachycardia with antihistamine drugs.³⁻⁵

Some authors used infusion of propofol with a subhypnotic dose (1.0 mg/kg/hr) and found that it was effective in the prevention of emetic symptoms during spinal anaesthesia for caesarean section.⁶

Recently some authors⁷ evaluated the effects of infusion of midazolam for prevention of post operative nausea and vomiting in parturients undergoing caesarean delivery performed under regional anaesthesia, and they found a similar result to that of infusion of propofol. However, it seems that the infusion of midazolam or propofol is not an effective method for prevention of nausea and vomiting at the beginning of the operation.

Midazolam is a short-acting benzodiazepine with a rapid onset of action. In recent years, midazolam has been reported to be effective for prophylaxis of PONV by bolus administration before or after induction of anaesthesia or postoperative continuous infusion.⁸⁻¹⁰

The principal objective of our study was to evaluate the efficacy and safety of bolus dose of midazolam for prevention of nausea and vomiting in patients undergoing caesarean section under spinal anaesthesia and to compare it with a traditional antiemetic drug: metoclopramide.

Patients and Methods

The present prospectively designed study was approved by the ethics and clinical studies committee of Zahedan University of medical sciences and informed and signed consent was obtained from all the patients who were enrolled in the study.

We enrolled 80 full term women weighting between 50 and 75 Kg, classified as ASA I, between the ages 18 to 38 years, scheduled for elective caesarean section under spinal anaesthesia. Parturient who had obstetric complications or evidence of foetal compromise or patients who had gastrointestinal disease or administration of antiemetic medication in the previous 24 hours were excluded. Participants were randomly allocated equally to one of midazolam or metoclopramide groups using a computer-generated list. All patients were fasted over night and received premedication with ranitidine 150 mg orally the night before and 2 hours prior to surgery.

After arrival in the operating room and intravenous (IV) access, 15 ml/Kg of Ringer solution with an addition of 10mg ephedrine was infused within 10 minutes before the initiation of the spinal block. Spinal anaesthesia was performed in the sitting position with a 25 gauge Whitacre needle, using a midline approach at L4-5 interspace. Once free flow of CSF had been recognized the intrathecal anaesthetic solution was injected over 15 seconds, aspirating CSF at the end of injection to confirm needle position. All patients received 10mg of 0.5% bupivacaine. After

intrathecal injection, the patients were turned in supine position with left uterine displacement. Surgery was started when a sensory block up to T5 dermatome was obtained.

Baseline maternal heart rate and arterial blood pressure were measured by an automatic non invasive monitor and recorded before the induction, every 2 minutes in the operating room, and every 5 minutes until discharge from recovery room. Hypotension (defined by a decrease in systolic blood pressure to less than 90 mm Hg or less than 30 mm Hg from baseline value) was treated with IV ephedrine 5 mg and dose incremented with additional Ringer solution. Maternal bradycardia (defined as heart rate less than 60 beats/min) was treated with IV atropine 0.5 mg. The assessments of sensory block to pinprick using a small needle were performed every one minute until 15min after intrathecal injection. The Ramsey sedation score was graded as follows: 1) patient anxious and agitated or restless or both; 2) patient cooperative, oriented, and tranquil; and 3) patient responding to commands only. Asleep levels were dependent on the patient's response to a light glabellar tap: 4, a brisk response; 5, a sluggish response; and 6, no response.¹¹

Midazolam 2 mg, or metoclopramide 10 mg was injected slowly over one minute at the beginning of operation before skin incision. Oxygen was administered to all patients via a face mask. Times of skin incision, delivery of baby and completion of surgery were recorded. The surgical technique was uniform for all patients. Apgar scores were obtained at 1 and 5 minutes.

The patients were evaluated for possible adverse effects, including sedation, respiratory depression, nausea and vomiting, by a researcher who was blinded to the details of the study until 3 hours after the end of surgery. Assessment for PONV was continued every 4 hours until the first 24 h.

Sample size was determined prospectively; with 40 patients per treatment group, a difference of 20% in the incidence of postoperative nausea and vomiting among treatments could be determined with a statistical power of 80% ($\beta = 0.2$) and a statistical significance of 0.05.

Statistical tests were performed using SPSS 11 for Windows. Results are reported as absolute value, mean $\pm$ SD. Continuous variables were analyzed using Student's T test. Nominal or ordinal variables were analyzed by Chi square test and Fisher exact test or Mann-Whitney U test. $P < 0.05$ was considered statistically significant.

Results

Full data collection was achieved for all patients of the 80 patients that participated in the study. There was no difference between the two groups with regard to patient

Table-1: Patients characteristics and duration of surgery.

Characteristics	midazolam (n=40)	metoclopramide (n=40)
Age (yr)	24.6 ± 7.6	25.8 ± 8.4
Weight (Kg)	65.3 ± 7.8	66.4 ± 6.8
Height (cm)	165.6 ± 3.7	167.2 ± 4.7
Duration of surgery (min)	52.4 ± 11.2	51.6 ± 10.7

Data are expressed as mean ± SD.

age, weight, and duration of surgery (Table-1).

The maximal height of sensory block was similar in both groups. The frequency of hypotension did not differ between groups (Table-2).

Table-2: Comparison of side effects between two groups.

Side effects	midazolam (n=40)	metoclopramide (n=40)	P value
Hypotension	5 (12.5%)	4(10%)	NS
Respiratory depression	17(42.5%)	0(0%)	P < 0.001
Nausea	6(15%)	21(52.5%)	P < 0.001
Patient satisfaction	40(100%)	37(92.5%)	NS

Data are expressed as n (%).

The time interval between injection of midazolam or metoclopramide and the clamping of the foetal umbilical cord varied between 4 to 5.5 minutes in all patients.

Midazolam group recorded a 15% frequency of nausea (6 patients) and no incidence of vomiting, whereas Group metoclopramide had a 52.5% incidence of nausea (21 patients) and no incidence of vomiting (P < 0.001; Mann-Whitney U-test; statistically significant).

The sedation scores showed that the patients in midazolam group showed a sedation level between 3 and 5, but the patients in metoclopramide group had a sedation score between 1 and 3.

Nausea was often seen at the time of removal of the foetus or at the time of replacement inside the abdomen, when the peritoneum was manipulated.

There were some episodes of respiratory depression (respiratory rate of less than 10 bpm) in 17 patients in the midazolam group in the time of surgery treated by verbal stimulation, but no respiratory depression was seen in metoclopramide group. (P < 0.001) Neonatal outcome was similar in the two groups and all the neonates had an Apgar scores ≥ 8 at one and five minutes.

Discussion

This prospective study demonstrates that administration of intravenous midazolam intraoperatively can reduce the incidence of nausea and vomiting among

patients under spinal anaesthesia.

Multiple factors can cause nausea and vomiting during spinal anaesthesia for caesarean delivery. Hypotension may cause brain stem hypoperfusion, thus triggering emesis. Some authors recommended the prophylactic infusion of ephedrine for prevention of maternal hypotension.¹² In our study, rapid fluid infusion with addition of administration of infusion of ephedrine 10 mg was performed for the prevention of maternal hypotension.

In the present study, the treatment groups were similar with regard to maternal demographics and operative management and we found a low incidence of hypotension. Therefore, the difference in the incidence of emetic symptoms during caesarean section under spinal anaesthesia among the groups can be attributed to the mesenteric manipulations and study drugs administered.

The mechanism of action of midazolam for prevention of emesis has not been fully understood. It is thought that midazolam decreases dopamine input at the chemoreceptor trigger zone (CRTZ) and decreases adenosine re-uptake. This leads to an adenosine-mediated reduction in synthesis, release, and postsynaptic action of dopamine at the CRTZ.¹³ It may also decrease dopaminergic neuronal activity and 5-HT₃ release by binding to the gamma-aminobutyric acid (GABA) receptor.¹⁴⁻¹⁷

Midazolam is also an effective antiemetic in patients having chemotherapy.¹⁸ Unlugenc et al reported that midazolam was effective for treatment of established PONV. They also suggested that antiemetic effect of midazolam lasted longer than that of the sedative effect.¹⁹

Lee et al. in their study compared the prophylactic anti-emetic efficacy of midazolam 2mg and ondansetron 4 mg in 90 patients scheduled for minor gynaecological surgery. They did not find a significant difference between the incidence of nausea and vomiting between the two groups.²⁰

Tarhan et al. in their study found an incidence of 66% nausea, 10% retching, 10% vomiting in the group of patients undergoing caesarean section under spinal anaesthesia who received the infusion of midazolam, compared with the incidence of 60% nausea, 3.3% retching, 6.6% vomiting in the group of patients who received the infusion of propofol as antiemetic, compared with the incidence of 96% nausea, 43.3% retching, 46.6% vomiting in the control group. The results of their study show that the incidence of nausea is higher in the beginning of the operation: 53.3% nausea before delivery versus 10% nausea

after delivery in the midazolam group.⁷ The incidence of nausea and vomiting in our study was lower than Tarhan' study. The only side effect seen in our study was respiratory depression.

However, there are some limitations in our trial for example: plasma level measurement of midazolam was not available in our hospital for evaluation of the newborns.

Conclusions

A bolus dose of midazolam (2 mg) was more effective than metoclopramide (10 mg) for the prevention of nausea and vomiting in parturient undergoing caesarean section under spinal anaesthesia, but there was a higher incidence of respiratory depression among patients in midazolam group. Further, studies are needed to prove the safety of midazolam in parturient undergoing caesarean section; the mothers should be observed carefully for respiratory depression and the neonates must be evaluated for any side effects.

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