Effect of Subhypnotic Doses of Propofol and Midazolam for Nausea and Vomiting During Spinal Anesthesia for Cesarean Section

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Received: April 9, 2014; Revised: May 30, 2014; Accepted: June 10, 2014

Background: Spinal anesthesia has been associated with intraoperative nausea and vomiting (IONV), especially during cesarean section, which is attributed to several mechanisms.

Objectives: In the present study, therapeutic and preventive properties of subhypnotic dose midazolam and propofol and their effects on the occurrence and severity of intraoperative nausea and vomiting during elective cesarean section under spinal anesthesia were evaluated.

Patients and Methods: In a randomized, double-blind, and placebo-controlled clinical trial, 90 parturients, ASA class I and II, aged 20-30 years, who underwent spinal anesthesia for cesarean section were randomly allocated to one of three groups receiving midazolam (1 mg bolus and 0.1 mg/kg/hr, n=30), propofol (20 mg bolus and 0.1 mg/kg/hr, n = 30), and placebo (saline, n=30) intravenously (IV) immediately after umbilical cord clamping. Bupivacaine hydrochloride (10 mg) was used for induction of the anesthesia. Patients’ hemodynamics was monitored at 3-minute intervals. Furthermore, intraoperative and post-delivery emetic episodes, severity of emesis, scores of sedation and ephedrine consumption were recorded.

Results: The incidence of nausea, retching, and vomiting was significantly higher in the control group compared to propofol and midazolam groups. Overall, PONV (postoperative nausea and vomiting) in midazolam group was as low as propofol group without any significant hemodynamic changes as seen in placebo group or even with propofol group.

Conclusions: Subhypnotic doses of midazolam or propofol are effective in the prevention of nausea and vomiting during and after cesarean section with spinal anesthesia and does not significantly influence hemodynamic of the patients.

Keywords: Propofol; Midazolam; Nausea; Vomiting; Cesarean section
3.1. Ethics
The study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Islamic Republic of Iran.

3.2. Allocation
Ninety parturients with ASA physical status of I and II, aged 20-30 years, undergoing spinal anesthesia for elective cesarean section were randomly allocated to one of three groups. Perfusion systems and syringes for the medications were prepared and covered according to the random number list by an anesthesia assistant who was blinded to the study. Randomization was carried out by a computer-generated list of random numbers. IONV after delivery were recorded by an anesthesiologist who was blind to the study.

3.3. Intervention
All patients received 150 mg of oral ranitidine 90 minutes prior to the surgery as premedication to decrease the risk of acid pneumonitis. Lactated Ringer's solution (20 ml/kg) was administered IV for all patients prior to the induction of spinal anesthesia, which was achieved by 10 mg (2 ml) hyperbaric bupivacaine 0.5% plus fentanyl 10 µg. To achieve the level of insensibility at T4-T5 dermatomes, the anesthetics were injected through a 25-gauge spinal needle at L3-L4 intervertebral interspace. Patients were placed in a left tilt position to avoid aortocaval compression. Oxygen 5 L/min was administered via face mask. Blood pressure was monitored with an automated cuff blood pressure monitor at 2-minute intervals until neonatal delivery and then at 5-minute intervals. Hypotension, a decline of more than 20% from baseline pressure or systolic blood pressure of less than 90 mmHg, was managed with ephedrine (10 mg at incremental doses). Patients were randomly allocated to placebo (saline, n = 30), propofol (20 mg bolus and 1.0 mg/kg/h, n = 30) and midazolam (1 mg bolus and 1.0 mg/h, n = 30) groups. Medications were used intravenously at subhypnotic doses instantly upon umbilical cord clamp- ing. Nausea and vomiting were evaluated by means of Bellville scoring score (0: no symptoms, 1: nausea 2: retching 3: vomiting) (15). An antiemetic (metoclopramide 10 mg) was administered in case of two or more emesis episodes. Sedation was assessed just after delivery and postoperatively for 6 hours using the modified Ramsay Sedation Scoring (where 1 = awake/alert, 6 = no response to painful stimulus).

3.4. Statistical Analysis
Sample size calculation was performed using a 2-sided significant level of 0.05 and a power of 80% with 40% accuracy. In this study, P was calculated as 0.5 for the midazolam and propofol groups and as 0.9 for placebo. Demographic data and other study variables were recorded and later analyzed by analysis of variance (ANOVA) for quantitative variables and chi-square test. Fisher exact test was used for the frequency of adverse events and the number of patients without emesis (had no nausea, retching, or vomiting) and those with nausea, retching, or vomiting. Mann-Whitney U test was used to analyze the severity of nausea and sedation. P value of less than 0.05 was considered statistically significant.

4. Results
There were a total number of 90 patients in this study. Demographic data had shown no significant differences except for gravidity between groups (Table 1). All patients had an adequate sensory level of spinal block for surgery, i.e. T3-T5 sensory level. None of the patients experienced failure of spinal anesthesia. Hemodynamic changes, including systolic, diastolic, mean arterial pressure, heart rate, and total ephedrine consumption are presented in Tables 2 and 3. As shown in Table 3, blood pressure changes in each group at different times, i.e. before and after anesthesia as well as before and after infusion of drugs or placebo were significant (P < 0.001); however, comparison between these groups revealed that variations in blood pressure was not significantly different for systolic, diastolic and mean arterial pressures (P = 0.81, P = 0.21 and P = 0.58, respectively). There were also no significant differences in heart rate in each group at different times and also between groups (P > 0.05 for each group and P = 0.29 between three groups).

Table 3 shows the number of patients and ephedrine consumption in each group. There were not any significant differences in administered ephedrine dose in each group after anesthesia and at the end of drug infusion compared to preanesthesia stage (P < 0.001); however, the difference in ephedrine dose consumption was significant between midazolam and placebo or propofol groups (P = 0.03, and P = 0.001, respectively). The difference, however, was insignificant between propofol and placebo groups (P = 0.45).

Comparison of nausea, vomiting and retching in the study groups (Table 4) revealed that although the incidence of nausea, retching and vomiting was not different among the groups, the total incidence of both nausea-vomiting and rescue treatment use (metoclopramide) was significantly lower in propofol and midazolam groups than placebo (P < 0.001).

5. Discussion
High incidence of IONV during spinal anesthesia for caesarean section was confirmed in our study similar to the previous studies. On the other hand, the parturients who received low dose of midazolam or propofol after delivery and clamping of umbilical cord experienced less nausea and vomiting compared to parturients who received saline. In addition, at these subhypnotic doses, no significant depressant effects on respiration or sedation was observed, which provided acceptable sedation throughout surgery.
### Table 1. Demographics Data

|                      | Propofol (n = 30) | Midazolam (n = 30) | Placebo (n = 30) | Total (n = 90) | P value a |
|----------------------|-------------------|--------------------|-----------------|---------------|-----------|
| **Age, y**           | 29.33 ± 5.9 b     | 28.53 ± 5.4        | 28.8 ± 5.3      | 28.89 ± 5.5   | 0.85      |
| **Height, cm**       | 162.53 ± 6.5      | 160.43 ± 6.6       | 161.5 ± 5.7     | 161.49 ± 6.3  | 0.44      |
| **Weight, kg**       | 78.13 ± 8.7       | 75.53 ± 10.8       | 80.67 ± 16.2    | 78.11 ± 12.38 | 0.27      |
| **BMI, kg/m²**       | 29.71 ± 4.04      | 29.33 ± 3.7        | 30.86 ± 5.4     | 29.97 ± 4.4   | 0.39      |
| **Gravid**           | 2.1 ± 0.81        | 1.9 ± 0.78         | 1.4 ± 0.62      | 1.8 ± 0.8     | 0.001     |
| **Duration of surgery, min** | 48.0 ± 5.1       | 50.66 ± 5.6        | 49.16 ± 5.09    | 49.27 ± 5.38  | 0.15      |
| **Sensory level No. (%)** | 29/96.7          | 28/93.7            | 27/90.0         | 84/93.3       | 0.58      |
| T4                   | 1/3.3             | 1/6.7              | 3/10.0          | 6/6.7         |           |

a P < 0.05 is considered significant, between groups.
b Data are presented as Mean ±SD.

### Table 2. Hemodynamic Changes During Surgery

|                      | Propofol (n = 30) | Midazolam (n = 30) | Control (n = 30) | P Value (between groups) a |
|----------------------|-------------------|--------------------|-----------------|---------------------------|
| **Systolic, mmHg**   |                   |                    |                 |                           |
| Before anesthesia (basic) | 123.1 ± 10.3 b   | 124.7 ± 10.2       | 125.1 ± 10.9    |                           |
| After induction of anesthesia | 108.2 ± 14.1     | 109.8 ± 11.6       | 110.6 ± 11.1    |                           |
| Before drug administration | 107.7 ± 11.1    | 111.8 ± 9.7        | 109.3 ± 10.6    |                           |
| After drug administration | 102.4 ± 19.3    | 101.4 ± 19.1       | 107.5 ± 8.8     |                           |
| **Diastolic, mmHg**  |                   |                    |                 |                           |
| Before anesthesia (basic) | 79.2 ± 10.8      | 78.0 ± 9.7         | 80.6 ± 9.07     |                           |
| After induction of anaesthesia | 63.7 ± 12.0     | 63.4 ± 12.7        | 64.4 ± 12.4     |                           |
| Before drug administration | 63.5 ± 12.9     | 63.0 ± 10.6        | 61.2 ± 10.6     |                           |
| After drug administration | 55.0 ± 9.4      | 53.5 ± 11.8        | 59.4 ± 10.9     |                           |
| **Mean, mmHg**       |                   |                    |                 |                           |
| Before anesthesia (basic) | 90.8 ±12.8       | 91.8 ± 11.4        | 97.0 ± 8.8      |                           |
| After induction of anesthesia | 76.4 ± 14.4     | 79.4 ± 11.2        | 79.7 ± 11.4     |                           |
| Before drug administration | 75.2 ± 10.0     | 77.8 ± 9.4         | 74.7 ± 10.7     |                           |
| After drug administration | 70.1 ± 9.0      | 69.1 ± 10.5        | 73.4 ± 9.6      |                           |
| **HR, beat/min**     |                   |                    |                 |                           |
| Before anesthesia (basic) | 99.6 ±17.1       | 97.2 ± 15.3        | 95.0 ± 14.6     |                           |
| After induction of anesthesia | 101.9 ± 17.7    | 97.8 ± 18.0        | 95.6 ± 16.7     |                           |
| Before drug administration | 99.0 ± 16.9     | 95.8 ± 16.7        | 95.7 ± 18.3     |                           |
| After drug administration | 99.2 ± 16.8     | 99.1 ± 11.0        | 93.6 ± 13.3     |                           |
| **P value within groups** a |              |                    |                 |                           |
| BP                   | < 0.001           | < 0.001            | < 0.001         |                           |
| HR                   | 0.79              | 0.83               | 0.41            |                           |

a P < 0.05 is considered significant, between groups.
b Data are presented as Mean ±SD.

### Table 3. Number of Patients and Mean Ephedrine Dose Consumption in Each Group

| Group (n = 30) | Number of Patients | Mean Ephedrine Dose, mg | P Value a |
|---------------|--------------------|-------------------------|-----------|
| Propofol      | 13                 | 9.2 ± 1.8 b             | 0.001     |
| Midazolam     | 12                 | 5.8 ± 1.9               |           |
| Placebo       | 11                 | 8.1 ± 2.5               |           |

a P < 0.05 is considered significant.
b Data are presented as Mean ±SD.
Table 4. Frequency of Intraoperative Nausea, Retching, and Vomiting and Antiemetic Consumption in Three Groups

|                          | Propofol (n = 30) | Midazolam (n = 30) | Control (n = 30) | P Value \(^a\) |
|--------------------------|-------------------|--------------------|-----------------|----------------|
| Nausea                   | 2 (6.7) \(^b\)    | 2 (6.7)            | 2 (6.7)         | 1.00           |
| Vomiting                 | 1 (3.3)           | 0 (0)              | 7 (23.3)        | 0.65           |
| Retching                 | 0 (0)             | 0 (0)              | 8 (26.7)        | 1.00           |
| Nausea-vomiting metoclopramide consumption | 3 (10)          | 2 (6.7)            | 17 (56.7)       | < 0.001        |

\(^a\) P < 0.05 is considered significant.
\(^b\) Data are shown with number.

IONV occurs more frequently in parturients than non-pregnant women who undergo abdominal surgeries under regional anesthesia. Physiological changes of pregnancy are considered as an important factor for IONV during caesarean section. These changes composed of high level of progesterone and its subsequent smooth muscle relaxation, increased gastric secretion, decreased gastrointestinal motility, and lowered esophageal sphincter tones (8). Age, sex, surgical procedure, anesthetic technique and concomitant opioid administration may influence emetic symptoms. Another important factor which can be responsible for IONV during spinal anesthesia is hypotension, especially in pregnant patients (9). In this study, all patients were pregnant and all groups were identical regarding the operation and their anesthetic management.

The incidence and severity of nausea and vomiting can be lowered with some medications such as propofol and midazolam. Propofol infusion at subhypnotic doses as an antiemetic has been broadly investigated (8, 9). Numazaki et al. showed that low dose of propofol reduces IONV during caesarean section under spinal anesthesia (6). In a similar study, it is highlighted that the severity of nausea was also less in patients who had received propofol than in those who had received placebo (8). Our study confirmed that, in patients who received propofol, the incidence of nausea and vomiting reduced significantly without more sedation or respiratory depression, but due to vasodilator effect of propofol, hypotension and subsequent need for sympathomimetic drug was higher with respect to the two other groups. Benzodiazepines induce their effects on nausea and vomiting via anxiolysis following lowered dopaminergic influx to chemoreceptor trigger zone and decrease in adenosine reuptake; nevertheless, the precise antiemetic mechanism for midazolam is poorly-understood (9-13, 16). In our study, overall incidence of nausea-vomiting and antiemetic (metoclopramide) consumption was lower in both propofol and midazolam groups. In addition, the severity of nausea and especially vomiting in subjects without medication (placebo group) was higher necessitating rescue treatment with metoclopramide.

In a study, Samimi et al. did not report any significant difference in the incidence of nausea and vomiting when subhypnotic doses of propofol or midazolam were used (17). Tarhan and colleagues suggested that antiemetic effect of midazolam is similar to that of propofol (18). Shahriari et al. compared midazolam with metoclopramide and proposed that a bolus dose of midazolam was more effective than metoclopramide 10 mg IV for the prevention of nausea and vomiting in parturients undergoing caesarean section with spinal anesthesia (19). In another study, it is compared midazolam with ondansetron after cardiac surgery and showed that low dose midazolam infusion (0.2 mg/kg/h) was more effective than IV ondansetron in the prevention of PONV (20). Elhakim et al. used low dose midazolam infusion for patients undergoing total abdominal hysterectomy and morphine epidural for postoperative pain relief and concluded that the incidence of total PONV, frequency of rescue antiemetic requests and epidural morphine induced pruritus was lower in patients who received midazolam (21). Moreover, Di Florio et al. showed that midazolam is an efficient agent in reducing refractory nausea-vomiting in ICU patients (11).

One of the important factors that may influence the incidence or severity of IONV with spinal anesthesia is sympathectomy-related hypotension (22, 23). In our study, decrease in systemic blood pressure was seen in all groups after spinal anesthesia; however, the difference between groups was insignificant. Mean ephedrine consumption dose in propofol and placebo groups was higher than midazolam group indicating that although the number of patients receiving ephedrine was not significantly different, the severity of hypotension was more with propofol and placebo, which necessitates higher vasopressor consumption.

Subhypnotic doses of propofol or midazolam are not only effective in providing sedation and anxiolysis but also are appropriate for the prevention of nausea and vomiting during and after cesarean section with spinal anesthesia. Furthermore, as less severe hemodynamic changes are seen with midazolam, it seems that midazolam can be a much better choice than propofol. Also, to increase the patients satisfaction which is an important factor in conscious patients undergone a surgery like cesarean section, especially in teaching hospitals which is lower than nonteaching hospitals, as presented with Nagizadeh et al. (24), we can reach to this purpose with appropriate use of low doses agents with no adverse effect of drugs overdose.
Acknowledgements

The authors would like to thank the Vice Chancellor of Research Centre of Tabriz University of Medical Sciences for funding this research. We also thank the anesthesia staff for their help in sample collection and preparation.

Funding/Support

This research was financially supported by Tabriz University of Medical Sciences.

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