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

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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 sub hypnotic 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 undergone 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

1. Background

Spinal anesthesia is a widely-accepted as the anesthesia method of choice for cesarean section owing to its safety and speed (1). However, there are a few trivial yet disturbing side effects observed with this technique, including intraoperative nausea and vomiting (IONV) (2, 3). IONV is associated with immediate contractions of diaphragm which could lead to both patient discomfort and protrusion of the abdominal viscera; the latter would contribute to the increased probability of visceral injuries. From anesthesia point of view, abrupt contractions add to the hazard of aspiration, especially in full-stomach patients, and are recommended to be prevented or at least reduced. This can be achieved using drugs, including droperidol, metoclopramide, which in turn produce side effects such as agitation, extrapyramidal symptoms, and dystonic reactions (4, 5).

Recently, it has been shown that low doses of propofol can reduce IONV during spinal anesthesia for caesarean section more efficiently than droperidol and metoclopramide (6-8). Benzodiazepines have been reported to have some benefits with regard to nausea and vomiting by reducing anxiety via lowering dopaminergic input to chemoreceptor trigger zone (CRTZ) (9-11).

2. Objectives

Regarding that IONV during spinal anesthesia, especially in pregnant women might be associated with many factors like hypotension due to sympatecthomy or excitation of a conscious mother, the goal of this study is also to evaluate the efficiency and safety of these two sedative agents (propofol and midazolam) compared to each other as well as placeboin preventing IONV during spinal anesthesia and also the effect of these agents on hemodynamics of the patients during caesarean delivery. Moreover, after delivery, most of the patients require sedation, which could be provided with midazolam or propofol administration (12-14).

3. Patients and Methods

This randomized, double-blind, and placebo-controlled clinical trial was performed at Al-Zahra Obstetrics and Gynecology Educational Hospital, Tabriz, Iran.

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 clamping. 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 Ramsey 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. (%)					0.58
T4	29/96.7	28/93.7	27/90.0	84/93.3	
T5	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				0.67
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				0.81
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				0.21
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 ± 11.0	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				0.29
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	3 (10)	2 (6.7)	17 (56.7)	< 0.001
metoclopramide consumption	2 (6.7)	1 (3.3)	12 (40)	< 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 gastrin 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 anesthesiais 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 metoclopramide10 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.

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References

1. Juhani TP, Hannele H. Complications during spinal anesthesia for cesarean delivery: a clinical report of one year's experience. *Reg Anesth.* 1993;**18**(2):128–31.
2. Balki M, Carvalho JC. Intraoperative nausea and vomiting during cesarean section under regional anesthesia. *Int J Obstet Anesth.* 2005;**14**(3):230–41.
3. Naghipour B, Aghamohamadi D, Azarfarin R, Mirinazhad M, Bilehjani E, Abbasali D, et al. Dexamethasone added to bupivacaine prolongs duration of epidural analgesia. *Middle East J Anesthesiol.* 2013;**22**(1):53–7.
4. Mishriky BM, Habib AS. Metoclopramide for nausea and vomiting prophylaxis during and after Caesarean delivery: a systematic review and meta-analysis. *Br J Anaesth.* 2012;**108**(3):374–83.
5. Santos A, Datta S. Prophylactic use of droperidol for control of nausea and vomiting during spinal anesthesia for cesarean section. *Anesth Analg.* 1984;**63**(1):85–7.
6. Numazaki M, Fujii Y. Subhypnotic dose of propofol for the prevention of nausea and vomiting during spinal anaesthesia for caesarean section. *Anaesth Intensive Care.* 2000;**28**(3):262–5.
7. Hosseinzadeh H, Eidy M, Golzari SE, Vasebi M. Hemodynamic Stability during Induction of Anesthesia in ElderlyPatients: Propofol + Ketamine versus Propofol + Etomidate. *J Cardiovasc Thorac Res.* 2013;**5**(2):51–4.
8. Seyedhejazi M, Eydi M, Ghojazadeh M, Nejati A, Ghabili K, Golzari SE, et al. Propofol for laryngeal mask airway insertion in children: Effect of two different doses. *Saudi J Anaesth.* 2013;**7**(3):266–9.
9. Rodola F. Midazolam as an anti-emetic. *Eur Rev Med Pharmacol Sci.* 2006;**10**(3):121–6.
10. Di Florio T, Goucke CR. The effect of midazolam on persistent postoperative nausea and vomiting. *Anaesth Intensive Care.* 1999;**27**(1):38–40.
11. Di Florio T. The use of midazolam for persistent postoperative nausea and vomiting. *Anaesth Intensive Care.* 1992;**20**(3):383–6.
12. Hosseinzadeh H, Golzari SE, Torabi E, Dehdilani M. Hemodynamic Changes following Anesthesia Induction and LMA Insertion with Propofol, Etomidate, and Propofol + Etomidate. *J Cardiovasc Thorac Res.* 2013;**5**(3):109–12.
13. Kim SI, Han TH, Kil HY, Lee JS, Kim SC. Prevention of postoperative nausea and vomiting by continuous infusion of subhypnotic propofol in female patients receiving intravenous patient-controlled analgesia. *Br J Anaesth.* 2000;**85**(6):898–900.
14. Shi JJ, Wang YP, Sun WZ, Hung CP, Cherng YG, Lin SY, et al. The effect of low dose propofol for prevention of nausea and vomiting during spinal anesthesia for cesarean section. *Acta Anaesthesiol Sin.* 1994;**32**(2):95–8.
15. Bellville JW, Bross ID, Howland WS. A method for the clinical evaluation of antiemetic agents. *Anesthesiology.* 1959;**20**:753–60.
16. Reid M, Herrera-Marschitz M, Hokfelt T, Terenius L, Ungerstedt U. Differential modulation of striatal dopamine release by intranigral injection of gamma-aminobutyric acid (GABA), dynorphin A and substance P. *Eur J Pharmacol.* 1988;**147**(3):411–20.
17. Samimi S, Davari F, Sadeghi S. Prevention of Postoperative Nausea and Vomiting by Administration of Subhypnotic doses of Propofol and Midazolam during Spinal Anesthesia for Cesarean Section. *Reproduc Health J.* 2010;**4**:175–8.
18. Tarhan O, Canbay O, Celebi N, Uzun S, Sahin A, Coskun F, et al. Subhypnotic doses of midazolam prevent nausea and vomiting during spinal anesthesia for cesarean section. *Minerva Anestesiol.* 2007;**73**(12):629–33.
19. Shahriari A, Khooshideh M, Heidari MH. Prevention of nausea and vomiting in caesarean section under spinal anaesthesia with midazolam or metoclopramide? *J Pak Med Assoc.* 2009;**59**(11):756–9.
20. Sanjay OP, Tauro DI. Midazolam: an effective antiemetic after cardiac surgery--a clinical trial. *Anesth Analg.* 2004;**99**(2):339–43.
21. Elhakim M, Abd-Elfattah H, El-Din DN, El-Kabarity R, Atef A, El-Fakey A. Midazolam as an antiemetic in patients receiving epidural morphine for postoperative pain relief. *J Opioid Manag.* 2009;**5**(4):189–95.
22. Simon L, Provenchere S, de Saint Blanquat L, Boulay G, Hamza J. Dose of prophylactic intravenous ephedrine during spinal anesthesia for cesarean section. *J Clin Anesth.* 2001;**13**(5):366–9.
23. Ngan Kee WD, Khaw KS, Ng FF. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for Caesarean section. *Br J Anaesth.* 2004;**92**(4):469–74.
24. Nagizadeh S, Azari S, Mohammady F, Ebrahimpour mirza rezaei Sehhati F. Maternal Satisfaction about Prenatal and postnatal Cares in Vaginal and Cesarean Section Delivery at Teaching and Non-teaching Hospitals of Tabriz/Iran. *Int J Women's Health Reproduction Sci.* 2014;**2**(3):146–54.