SUBHYPNOTIC DOSES OF PROPOFOL VERSUS MIDAZOLAM TO PREVENT NAUSEA AND VOMITING DURING SPINAL ANESTHESIA FOR CAESAREAN SECTION

Amir Murad Khudadad [a] and Bafrin Samad Aghawaise [b]

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ABSTRACT

Background

Nausea and vomiting is a common complication in parturients with cesarean delivery under spinal anesthesia it may causes significant distress to the patient and increases the chance of aspiration pneumonitis, it also affects the surgical procedure. Many drugs have been used to prevent this complication but none proved to be effective to abolish it completely.

Objectives

Subhypnotic dose of Midazolam or Propofol were evaluated to prevent intraoperative nausea and vomiting during elective cesarean section under spinal anesthesia.

Methods

This study is a randomized control clinical trial, after local ethical committee approval A 93 consenting (ASAII) parturients, who underwent spinal anesthesia for caesarean section were divided randomly into three groups received Propofol (20 milligram bolus and 0.1 milligram /kilogram/hour by infusion immediately after the bolus dose, 30 parturients), Midazolam (1 milligram bolus and 1 milligram/hour by infusion after bolus dose, 31 parturients), and placebo (saline, 32 parturients) intravenously after umbilical cord clamping. Bupivacaine 0.5% (12.5-15 milligram) used for spinal anesthesia. Intraoperative and post delivery emetic episodes were recorded.

Results

The incidence of nausea and vomiting was significantly less in the propofol and Midazolam groups in compared to placebo group. There was insignificant difference between Propofol and Midazolam group in perioperative nausea and vomiting (P = 0.616) and there were no significant hemodynamic changes in all the groups.

Conclusion

The use of Propofol is as effective as Midazolam in decreasing nausea and vomiting during Caesarean section under spinal anesthesia.

Keywords: *Propofol, Midazolam, Nausea and vomiting, Caesarean section, Spinal anesthesia.*

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[a] Department of Surgery, College of Medicine, University of Sulaimani, Kurdistan Region, Iraq.
Correspondence: amir.boujan@univsul.edu.iq
[b] Sulaimani Surgical Teaching Hospital.

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INTRODUCTION

Spinal anesthesia has been shown to be an easy, rapid and safe technique for Caesarean section [1] .However, there are a few side effects observed with this technique, including intraoperative nausea and vomiting [2].

The abrupt diaphragmatic contractions 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 [3, 4].

Occurrence of intra operative nausea and vomiting during spinal anesthesia for non-obstetric operations ranges from 7% to 42%. The overall incidence of intra- operative nausea and vomiting during regional anesthesia for cesarean section is extremely variable, up to 80%, depending on the anesthetic technique(specially spinal anesthesia) used and on the preventive and therapeutic measures taken. The incidence of intra operative nausea and vomiting may also vary significantly according to the stages of the surgical procedure (e.g. pre-delivery vs. post-delivery), different factors being implicated in the etiology [5].

Intraoperative nausea and vomiting during cesarean section under neuraxial block has multiple causes, which include: hypotension, vagal hyperactivity, exteriorization of the uterus and visceral stimulation, use of the neuraxial opioids, uterotonic agents, increased intra gastric pressure, Progesterone-induced reduction in the lower esophageal sphincter tone.

Propofol is a phenol derivative (2, 6-Di-isopropylphenol). It is a short-acting general anesthetic drug, with an onset of action of approximately 30 seconds according to scientific daily dose of propofol which is 2mg/kg. Propofol is extremely lipid-soluble, but almost insoluble in water [6].

Two notable side effects of propofol are its antiemetic effects and a sense of well-being in patients. Propofol increases dopamine concentrations in the nucleus accumbens (a phenomenon noted with drugs of abuse and pleasure-seeking behavior). Propofol antiemetic action may be explained by the decrease in serotonin levels it produces in the area postrema, probably through its action on gamma amino butyric acid (GABA) receptors. It has been used successfully to treat postoperative nausea in a bolus dose of 10 mg. The median concentration of propofol that was associated with an antiemetic effect was 343 nanogram/milliliter. This concentration can be achieved by a propofol infusion of 10 mg loading dose followed by 10 microgram/kilogram/mint [7].

The onset of hypnosis after a dose of 2.5 milligram/kilogram is rapid, with a peak effect seen at 90 to 100 seconds. The median effective dose (ED_{50}) of propofol for loss of consciousness is 1 to 1.5 milligram/kilogram after a bolus. The duration of the hypnosis is dose-dependent, being 5 to 10 minutes after 2 to 2.5 mg/kg. At sub hypnotic doses, propofol provides sedation and amnesia.

Propofol is present in breast milk 4 to 8 hours in concentrations ranging from 0.12 to 0.97 milligram/milliliters (mg/ml). After an induction dose of propofol, the effects on the newborn would be negligible [7].

Midazolam is a short acting benzodiazepine used for anaesthetic induction, midazolam produces sedation, anxiolysis, and amnesia. There is rapid onset of action .the onset after intravenous administration is 1 to 2 minutes; the elimination half-life of Midazolam is approximately 1 to 4 hours [7].

Midazolam acts as a positive modulators of gamma amino butyric acid ($GABA_A$) receptors and have some benefits with regard to nausea and vomiting by reducing anxiety via reduction of dopamine and 5-hydroxytryptamin (5-HT3), or serotonin receptor activity in the chemoreceptor trigger zone (CRTZ) and decrease in adenosine reuptake, thereby leading to decrease synthetic, release and post synaptic activity of dopamine in the chemoreceptor trigger zone [8].

The small amounts of Midazolam excreted into breast milk would not be expected to cause adverse effects in most breastfed infants. Two expert panels advocates waiting for at least 4 hours after a single intravenous dose of Midazolam before resuming nursing. [9, 10]

The amount of Midazolam and propofol excreted into milk within 24 hours of induction of anesthesia provides insufficient justification for interrupting breast-feeding [8].

PATIENTS AND METHODS

The study is a randomized, placebo controlled study conducted at the department of anesthesiology of Sulaimani Maternity teaching Hospital. After approval of the local ethical committee, a written informed consent obtained from 93 female patients classified American Society of Anesthesiologists (ASA) physical status II, in reproductive age, planned for Elective

Cesarean Section Surgeries under spinal anesthesia between 1st of Jun 2015 and 25th of September 2015. The selected patients were randomly allocated to one of three groups:

Group P: 30 parturients received Propofol (20 milligram bolus and 1 milligram / kilogram/hour infusion by using a syringe pump).

Group M: 31 parturients received Midazolam (1 milligram bolus and 1 milligram /hour infusion by using syringe pump).

Group N: 32 parturients received placebo (Normal saline).

The subhypnotic doses administered intravenously immediately after the umbilical cord was clamped. Exclusion criteria included patients with convulsions, pre-eclampsia, coronary artery disease, thyroid dysfunction (ASA lll, lV), those with known allergy to the study drugs (Midazolam, Propofol), and any contraindication to regional anesthesia (e.g. local infection, coagulation abnormality, tight valvular heart lesion or patient refusal) where excluded.

The study protocol was explained to each patient during the preoperative period. No premedication was given to the patients.

On arrival to the operating theatre, before the spinal anesthesia 16-18 Gauge intravenous cannula was inserted and intravenous fluid (normal saline or ringer lactate) was given at a rate 6-10 ml/kg/hr as a preload, the monitor was attached to the patients to take preoperative readings of heart rate, non-invasive arterial blood pressure, and oxygen saturation by pulse oximetry (we considered mean arterial pressure less than 65 mmHg as hypotension and pulse rate less than 50 beats per minute as bradycardia).

Spinal anesthesia was performed in the sitting position, at L3–L4 or L4–L5 lumber vertebral space, using 26-27 gauge Quincke or pencil point spinal needle with 2.5-3 ml heavy bupivacaine 0.5% (12-15 mg), and the patients were put in the supine position with left lateral tilt and monitored by pulse oximetry, and non-invasive arterial blood pressure measurement every 5 min, intra operative post delivery emetic episodes were recorded.

Statistical Analysis: Sample size calculation was performed using a 2-sided significant level of 0.05. Demographic data and other study variables were recorded and later analyzed by analysis of variance (ANOVA) for quantitative variables and chi-square test. Mann-Whitney U test was used to analyze the severity of nausea and vomiting. P value of less than 0.05 was considered statistically significant.

RESULTS

We studied 93 parturients anaesthetized by using spinal anesthesia for caesarian section and we found that there were no significant differences between the three groups regarding the demographic data like patient's ages or Haemodynamic parameters like mean arterial pressure and pulse rate, (Table 1) (Table 2) (Table 3).

In comparing Propofol group (32.3%) to placebo group (34.4%) we found nausea and vomiting was significantly less in Propofol group.(Table 4, Figuer 1).

In comparing Midazolam group (33.3%) to placebo we found that nausea and vomiting significantly less in Midazolam group. (Table 4, Figure 1).

In comparing nausea and vomiting in propofol group with Midazolam group we found that there were no statistically significant difference. Table, Figure 1).

Table 1. Age distribution among the drugs used in the study.

Age (Years)	Placebo (N=32)	Propofol (N=30)	Midazolam (N=31)	P value
16-24	4(12.5%)	1(3.3%)	5(16.1%)	0.292293
25-32	12(37.5%)	15(50.0%)	13(41.9%)	0.750137
33-41	16(50.0%)	14(46.7%)	13(41.9%)	0.894377
Mean ±SD*	31.88 ± 7.23	32.07 ±5.25	30.19 ± 6.15	0.440

*Standard deviation

Table 2. Mean blood pressure in different groups of the study.

Mean Arterial Blood Pressure (MAP) in mmHg	Placebo (N=32)	Propofol (N=30)	Midazolam (N=31)	P value
MAP1 (min) Mean ±SD	94.16 ±13.57	92.33 ±9.09	90.87 ±11.66	0.535
MAP2 (min) Mean ±SD	75.47 ± 13.79	77.97 ±11.54	75.42 ±11.81	0.660
MAP3 (min) Mean ±SD	68.38 ±11.03	69.67 ±9.71	68.94 ±11.24	0.893
MAP4 (min) Mean ±SD	67.09 ±8.97	68.77 ± 7.18	69.32 ± 8.82	0.549
MAP5 (min) Mean ±SD	67.50 ±7.80	69.37 ±7.99	70.35 ± 7.77	0.346
MAP6 (min) Mean ±SD	70.44 ±7.31	71.60 ±7.72	69.19 ±7.67	0.465
MAP7 (min) Mean ±SD	72.53 ±5.70	74.47 ±7.23	73.1 ±5.41	0.451
MAP8 (min) Mean ±SD	73.75±5.02	75.74±6.36	74.43 ± 5.63	0.579
MAP*(mmHg)	73.66 ± 6.99	74.97±5.89	73.89±6.02	0.690

* Mean MAP

Table 3. Pulse Rates in different study the groups.

Pulse Rates (PR) Mean ±SD	Placebo (N=32)	Propofol (N=30)	Midazolam (N=31)	P value
PR1	97.26 ±20.40	103.97 ±16.59	97.93 ±16.38	0.282
PR2	92.50 ±18.93	94.27 ±14.36	93.77 ±13.62	0.902
PR3	88.41 ±14.57	86.90 ±16.49	87.42 ±17.70	0.934
PR4	86.31 ± 11.358	82.23 ±12.08	81.87 ±13.17	0.282
PR5	86.28 ±11.31	79.33 ±11.66	78.77 ±12.75	0.024
PR6	86.22 ±10.63	78.20 ±10.33	80.74 ±9.94	0.009
PR7	83.07 ±8.03	78.53 ±7.80	80.50 ±7.14	0.077
PR8	80.92 ±10.64	78.90 ±7.12	80.86 ±5.77	0.692
PR*	88.39 ±11.00	85.59±9.02	85.69 ±9.56	0.449

* Mean PR

Table 4. Comparison of frequency of Nausea and vomiting in relation to drugs used.

Compare groups	Nausea and vomiting	p-value
Placebo : Propofol	19 : 7	0.004
Placebo: Midazolam	19 :9	0.016
Propofol : Midazolam	7 :9	0.616

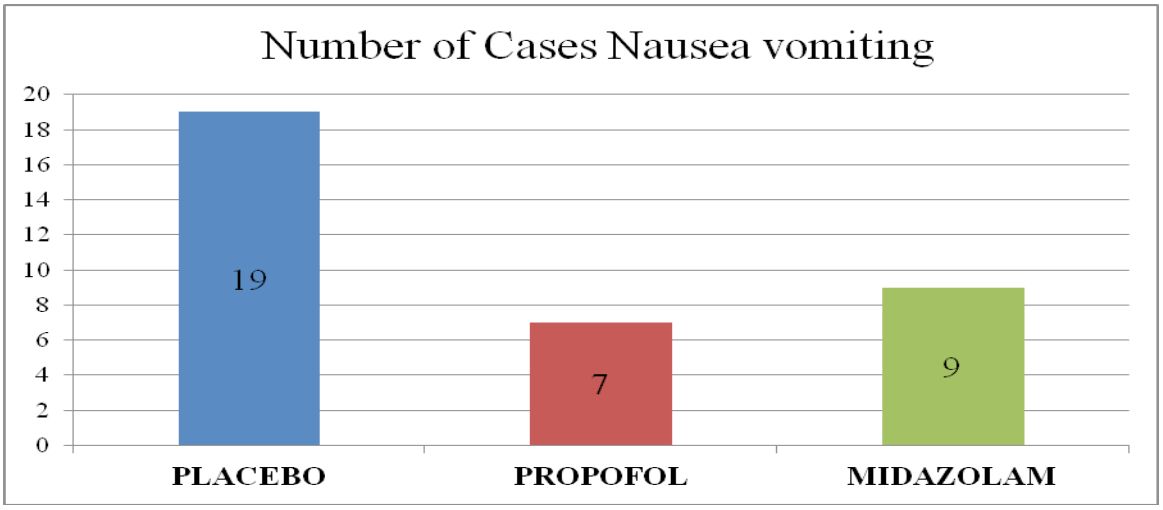

Figure 1. The number of cases with nausea and vomiting

DISCUSSION

Nausea and vomiting during spinal anesthesia for caesarean section is relatively high without prophylactic antiemetic [11]. Previous researches suggest that as many as 75% of women who receive spinal anesthesia during a cesarean delivery can develop nausea or vomiting during the procedure[12]. The etiology of emetic symptoms is complex and depends on a variety of factors Including operative procedures, anesthetic techniques, peritoneal traction, exteriorization of uterus and maternal hypotension [13].

Intraoperative nausea and vomiting occurs more frequently in parturient than non-pregnant women who undergo abdominal surgeries under regional anesthesia. Physiological changes of pregnancy are considered as an important factor for intra operative nausea and vomiting 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 [14],

One of the important factors that may influence the incidence or severity of intra operative nausea and vomiting with spinal anesthesia is sympathectomy-related hypotension [15]. In our study, decrease in systemic blood pressure was seen in all groups after spinal anesthesia; however, the difference between groups was insignificant. In this study, all patients were pregnant and all groups were identical regarding the surgical procedure.

High incidence of intra operative nausea and vomiting during spinal anesthesia for caesarean section was found to be due to hypotension in our study. On the other hand, the parturient who received low dose of Midazolam or Propofol after delivery and clamping of umbilical cord experienced less nausea and vomiting

compared to the parturients who received saline. In addition, at these sub hypnotic doses, also provided acceptable sedation throughout surgery.

The following studies concluded that the incidence of nausea and vomiting were significantly higher in control group (normal saline) in compared to propofol and Midazolam groups. There were no significant differences between propofol and Midazolam groups (table 5).

Table 5. Different study groups that agree with our study.

	Authors	Total number of patients
1	Sousan Rasooli et al. [16]	90
2	Samimi Sadeh et al. [17]	114
3	Tarhan O et al. [18]	90
4	Current study	93

Propofol antiemetic action may be explained by the decrease in serotonin levels it produces in the area postrema probably through its action on GABA receptors [8]. Propofol infusion at sub hypnotic doses as an antiemetic has been broadly investigated [14, 15].

The following studies compared propofol to placebo and showed that low dose of propofol reduces intra operative nausea and vomiting during caesarean section under spinal anesthesia (Table 6).

Table 6. Different study groups that agree with our study.

	Authors	Total number of patients
1	Numazaki et al. [19]	80
2	M Tramèr et al. [20]	84
3	Yoshitaka Fujii et al. [21]	90
4	Khosrou Naghibi et al. [22]	104
5	Yusuf Unal et al. [23]	60
6	Yerrramsetti Atchyutha Ramaiah et al. [24]	120

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 [15], moreover, Midazolam is an efficient agent in reducing refractory nausea-vomiting in ICU patients [25].

Yoshitaka Fujii et al. studied 90 parturient Women Undergoing Laparoscopic Gynecologic Surgery to receive 1 of 2 different Midazolam doses (50 or 75 micrograms/kilogram intravenous) or placebo immediately after induction of anesthesia. They found that the Midazolam was associated with significantly less post operative nausea and vomiting compared with placebo [26].

Sub hypnotic doses of propofol or Midazolam are not only effective in providing sedation and anxiolysis but are also appropriate for the prevention of nausea and vomiting increasing the patients satisfaction which is an important factor in conscious patients undergoing a surgery like Caesarean section, especially in teaching hospitals which is lower than nonteaching hospitals [27], we can obtain to this purpose with appropriate use of low doses of agents with no adverse effect of drugs overdose.

In conclusions, the use of propofol is as effective as Midazolam in decreasing nausea and vomiting during caesarean section. The use of propofol or Midazolam to prevent nausea and vomiting during spinal anesthesia in caesarean section is recommended

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