Prevention of Postoperative Nausea and Vomiting by Administration of Sub Hypnotic Doses of Propofol and Midazolam during Spinal Anesthesia for Cesarean Section

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Received October 2010; Revised and accepted December 2010

Abstract

Objective: To evaluate, the efficacy of sub hypnotic doses of midazolam and propofol, in prophylactic control of postoperative nausea and vomiting, in parturients undergoing elective cesarean section under spinal anesthesia.

Materials and methods: In a double–blind, placebo–controlled, randomized trial, 114 ASA physical status I–II parturient undergoing elective cesarean section under spinal anesthesia (using 0.5% bupivacaine 12 mg) were allocated randomly to receive propofol (20 mg bolus and 1.0 mg/kg/hr infusion, n=38) or midazolam (1 mg bolus and 2.0 mg/hr infusion, n=38) or saline (2 cc IV, n=38) immediately after clamping of umbilical cord. The occurrence of nausea and/or vomiting and respiratory depression was recorded during operation until 12 hr after that.

Results: The incidence of nausea and vomiting was significantly lower in midazolam and propofol groups compared with saline group in all 12 hr, (nausea: 19%, 15.8% versus 57.9%), vomiting (7.9%, 5% versus 34.2%). There was not manifestation of respiratory depression at the time of surgery and after it.

Conclusion: Sub hypnotic dose of midazolam was as effective as the sub hypnotic dose of propofol for preventing of nausea and vomiting in parturients undergoing cesarean section under spinal anesthesia. We undertook this study in regard to examine a simple, safe and non–expensive antiemetic method.

Keywords: Propofol, Midazolam, Nausea, Vomiting, Cesarean section

Introduction

Postoperative nausea and vomiting is common side effect in parturient undergoing cesarean section performed under spinal anesthesia and not only causes distress to the patient but also result in problems in managing their condition (e.g., dehydration, electrolyte imbalance and tension on suture strings) ,and can increase the risk of pulmonary aspiration of vomit (1, 2). Furthermore, it can result in hospitalization or later re–admission, thus increasing both healthcare costs and the psychological burden to the patient (2, 3). The incidence of PONV during cesarean section under regional anesthesia is estimated to be 50%–80% without administration prophylactic drug .

Therefore use of prophylactic antiemetics in these patients is logical (4, 5). Currently used antiemetics may induce undesirable side–effects, such as extrapy-

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ramidal symptoms (dopamine receptor antagonists), excessive sedation and tachycardia (antihistamine drugs) (6).

Recent researches have focused on the search for effective and well–tolerated antiemetic agents which lack the adverse effects of older agents (7, 8).

Propofol is a diisopropylphenol derivate used for induction and maintenance of surgeries. Propofol has been known to exert antiemetic properties even in subhypnotic doses (1, 7).

The precise mechanism of propofol's antiemetic effect has not been elucidated, several mechanisms have been proposed, including a direct depressant effect on CTZ, the vagal nuclei, and other centers implicated in PONV. In animal models, propofol has been shown to decrease synaptic nerve transmission in the olfactory cortex and a decrease serotonin levels in the area postrema (9,10).

Midazolam, a short acting benzodiazepine ,widely used as a premedication before surgery, for induction of anesthesia and for conscious sedation, it has been postulated that a possible mechanism for the antiemetic effect of benzodiazepines could be an action at the chemoreceptor trigger zone reducing synthesis release and postsynaptic effect of dopamine. Whether benzodiazepines reduce dopamine release centrally, or by blocking the re–uptake of adenosine, causing an adenosine–mediated reduction of dopamine release, has been matter of debate (10).

In this randomized, double–blind, placebo–controlled study we compared the effectiveness of intravenous subhypnotic dose of midazolam and propofol and placebo in patients undergoing cesarean section under spinal anesthesia.

Material and Methods

This study was approved by the ethics and clinical studies committee of Tehran University of Medical Science and informed consents was obtained from all the patients. Eligibility criteria for the trial included the following characteristic: Age between 18–40 yr, ASA grade I–II preoperative, term pregnancy, scheduled to undergo elective cesarean section under spinal anesthesia. Patients were excluded from trial if they had severe hepatic, renal, cardiac or pulmonary dysfunction, a history of drug allergy or anaphylactic symptoms, had a gastrointestinal disorder or a brain tumor or epilepsy history or motion sickness had received any opioid, steroid or antiemetic medication in 24 hours period before the administration of the study medication. Drugs or therapies that were considered to effect efficacy evaluation were prohibited within the 24 hours period before and after administration of the study drug.

In our study 114 full term classified as ASA I–II women randomly were assigned to a double–blind, placebo–controlled, clinical trial study, they were among 18–40 yr undergoing spinal anesthesia for elective cesarean section delivery.

Patients were randomly allocated to one of three groups (using a computer generated list): placebo group (saline 2cc, n=38), propofol group (20 mg bolus and then 1.0 mg/kg/hr, n=38), midazolam group (1 mg bolus and then 2 mg/hr, n=38) immediately after clamping of umbilical cord. The occurrence of nausea and/or vomiting and respiratory depression recorded during operation and the first 12 hr after procedure. All patients were fasted over night and received 15 cc/kg Ringer's solution just before initiation of anesthesia. Statistic tests were performed using SPSS 16. Results are reported as absolute value (mean ± SD).

Discontinuous data were analyzed using the chi square test and continuous data by one–way analysis. A p–value <0.05 was considered significant.

Discussion

PONV is one of the most common complications occurring after anesthesia and surgery including cesarean section and cause great distress to patients, with the electrolyte imbalance, tension on suture strings and increase the risk of pulmonary aspiration of vomit. This study evaluated the efficacy of subhypnotic doses of midazolam and propofol for preventing of PONV in parturient undergoing spinal anesthesia for cesarean section. We chose this study because nausea and vomiting disturb most of the mothers after delivery and even they call it more intolerable than pain, also can affect relation of mother with neonate in first hours after delivery, so we looked for a safe and non–expensive way to reduce it. Every attempt was made to match groups for factors known to affect the incidence of PONV, so it is likely that observed differences between groups were mainly caused by treatment.

Some other studies demonstrated probable efficacy of midazolam and propofol on this complication (1, 11, 12). The mechanism of action of midazolam for preventing of emesis has not been fully understood. It is through that midazolam decreases dopamine input at the chemoreceptor trigger zone and decreases adenosine–reuptake. This leads to an adenosine mediated reduction in synthesis, release and postsynaptic action of dopamine at the CRTZ (13,14). It may also decree-

Table 1: Patients' demographic parameters

	Midazolam	Propofol	Salin	*P*–Value
Age (year) Mean ± SD	27.39 ± 5.14	28.87 ± 5.16	29.31 ± 4.97	NS
Weight (Kg) Mean ± SD	62.11 ± 5.33	65.34 ± 4.18	61.35 ± 6.25	NS
Duration of operation (minute) Mean ± SD	65.26 ± 8.21	65.79 ± 9.69	65.13 ± 7.92	NS
Baseline systolic blood pressure (mmHg) Mean ± SD	105.41 ± 9.03	107.76 ± 8.75	105.39 ± 9.25	NS

ses dopaminergic neuronal activity and 5–HT3 release by binding to the GABA receptors (14). The mechanism of propofol's antiemetic effects has not been elucidated.

Several mechanisms have been proposed, including a direct depressant effect on the CTZ, the vagal nuclei and other centers implicated in PONV (13,14).

Our study showed, in groups that were similar with regard to maternal demographics, propofol and midazolam in subhypnotic doses significantly reduced the incidence of PONV among parturient under spinal anesthesia for c/s (7.9%, 5% versus 34.2%).

We did not find a significant difference between the incidence of nausea and vomiting in midazolam group compared with propofol group. Studies investigating the use of various therapeutic management for PONV.

Rudra and Sen compared the prophylactic antiemetic efficacy of intrathecal midazolam (2 mg), with IV metoclopramide (10 mg), in spinal anesthesia for c/s (15). They showed in intrathecal midazolam group incidence of PONV was significantly lower than metoclopramide group. Orathly Patangi et al in their study compared the prophylactic efficacy of midazolam with ondansetron in bypass surgery, in midazolam group incidence of PONV was lower than ondansetron group (14).

Fujii and Numazaki compared the prophylactic efficacy of metoclopramide with droperiol and propofol and there was not significant difference among three groups (15). Tarhan et al They found, midazolam's antiemetic efficacy is similar to propofol (1). Shahriari and associates compared midazolam with metoclopramide, in their study a bolus dose of midazolam (2 mg) was more effective than metoclopramide (10 mg) for the prevention of nausea and vomiting in parturient undergoing cesarean section under spinal anesthesia, but there was a higher incidence of respiratory depression among patients in midazolam group (16).

In our study the incidence of PONV was lower than Tarhan's and higher than Shahriari's but one of the advantages of our drug protocol was lack of respiatory depression despite of its efficacy in preventing PONV.

Conclusions

Administration of a sub hypnotic dose of midazolam (1 mg bolus and 2.0 mg/hr) was as effective as the sub hypnotic dose of propofol (20 mg bolus and 1 mg/kg/hr) for preventing nausea and vomiting in parturient undrgoing cesarean section under spinal anesthesia, without causing respiratory depression, in addition to, their cost efficacy and safety. Further studies are needed to prove the safety of drugs for neonates.

Table 2: Comparison of side effects among three groups

	Midazolam n (%)	Propofol n (%)	Salin n (%)	*P*–Value
Respiratory depression	0 (0%)	0 (0%)	0 (0%)	NS
Nausea	7 (19%)	6 (15.8%)	22 (57.9%)	< 0.05
Patient's satisfaction	3 (7.9%)	2 (5%)	13 (34.2%)	< 0.05

References

1. Tarhan Ö, Canbay Ö, Çelebi N, Uzun S, Sahin A, Cos¸kun F et al. Subhypnotic doses of midazolam prevent nausea and vomiting during spinal anaesthesia for caesarean section. *Minerva Anesthesiol* 2007; 73: 629–34.
2. Naylor RJ, Inall FC .The physiology and pharmacology of postoperative nausea and vomiting. *Anaesthesia* 1994; 49: S2–5.
3. Tramer MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part 2. Recommendations for prevention and treatment, and research agenda. *Acta Anaesthesiol Scand* 2001; 45: 14–9.
4. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs* 2000; 59: 213–43.
5. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, et al. Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg* 2003; 97: 62–71.
6. Fujji Y, Tanaka H, Kobayashi N. Prevention of nausea and vomiting after middle ear surgery: Granisetron versus ramosetron. *Laryngoscope* 1999; 109: 1988–90.
7. Strunin L, Rowbotham D, Miles A, eds. The effective management of postoperative nausea and vomiting. London: Aesculapius Medical Press, 1999: 1–42.
8. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; 350: 2441–245.
9. Peck TE, Williams M, Hill SA. Pharmacology for anaesthesia and intensive care. 2nd ed. European *Journal of Anaesthesiology* 2005; 22: 733–4.
10. Phillis JW, Bender AS, Wu PH. Benzodiazepines inhibit adenosine uptake into rat brain synaptosomes. *Brain Res* 1980; 195: 494–8.
11. Heidari SM, Saryazdi H, Saghaei M. Effect of intravenous midazolam premedication on postoperative nausea and vomiting after cholecystectomy. *Acta Anaesthesiol Taiwan* 2004; 42: 77–80.
12. Watts JC, Brierley A. Midazolam for the treatment of postoperative nausea. *Anaesthesia* 2001; 56: 1129.
13. Sen A,RudraA.Intrathecal midazolam prevent nausea and vomiting during cesarean delivery with spinal anesthesia. *Journal of Anesthesiology* 2002; 18: 21–5.
14. Sanjay OP, Tauro DI. Midazolam: An effective antiemetic after cardiac surgery. *AnesthAnalg* 2004; 99: 339–43.
15. 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: 262–5.
16. Shahriari A, Khooshideh M, Heidari MH. Prevention of nausea and vomiting in cesarean section under spinal anesthesia with midazolam or metoclopramid. *J Pak Med Assoc* 2009; 59: 756–9.