Evaluation of Ondansetron and Low Dose Propofol for Control of Emetic Symptoms during Cesarean Delivery with Spinal Anesthesia

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Abstract
Nausea and vomiting during cesarean delivery are distressing to the patients and a disturbance to the surgeon. Propofol is believed to have antiemetic properties. In recent studies, continuous infusion of a subhypnotic dose of propofol was effective for reducing emetic symptoms during cesarean delivery without clinical serious adverse events. Ondansetron had been used prophylactic to reduce the incidence of intraoperative nausea and vomiting in patients undergoing cesarean section under regional anesthesia.
60 ASA I and II parturient, between the age of 21 and 38, scheduled for elective cesarean delivery were enrolled. Patients were randomized to receive either propofol 1mg kg^{-1} hr^{-1}(GP) or ondansetron 4 mg (GO). The patients were evaluated for the presence of nausea, retching and vomiting. Also, severity of nausea, satisfaction with the study drug and degree of sedation, was evaluated at the end of the observation period.
Patients with complete response (no nausea or vomiting) were significantly high in GO group compared to GP. Incidence of nausea, retching, and vomiting in GP was high and significant when compared to GO. No patient in GO need rescue, while two patients in GP were received ondansetron 4 mg as rescue.
Ondansetron 4 mg is more effective than propofol 1 mg $kg^{-1}hr^{-1}$ to prevent emetic symptoms during and postdelivery in patients undergoing cesarean section under spinal anesthesia. Moreover, ondansetron reduced requirement for further rescue antiemetic which may provides great benefit.

Introduction

Nausea and vomiting during cesarean delivery are distressing to the patients and a disturbance to the surgeon. The reported incidence of nausea and vomiting during cesarean section performed under regional anesthesia varies from 50% to 80% when no prophylactic antiemetic is given, especially if the uterus is exteriorized ***(Santos & Datta 1984)*** and ***(Lussos et al., 1992).***

Several investigations have demonstrated that prophylactic therapy with droperidol or metaclopromide reduces the incidence of emetic symptoms in cesarean patients under spinal anesthesia ***(Santos & Datta 1984)*** and ***(Lussos et al., 1992)***. However, these drugs

occasionally cause undesirable adverse effects, such as excessive sedation, restlessness, dystonic reactions, and extrapyramidal signs ***(Watcha & White 1992).***

Propofol is believed to have antiemetic properties and therefore useful to decrease the incidence of postoperative nausea and vomiting when used at a subhypnotic dose ***(Smith et al., 1994***) and ***(Borgeat et al., 1992).*** However, a bolus injection of low-dose (10 mg) propofol was not effective for the prevention of nausea and vomiting during cesarean because of the short duration of propofol or the dose of propofol used may be insufficient ***(Shi et al., 1994)***. In a recent studies, continuous infusion of a sub-hypnotic dose 1mg $kg^{-1}hr^{-1}$ of propofol was effective for reducing emetic symptoms during cesarean delivery without clinical serious adverse events ***(Fujii & Numazaki 2002)*** and ***(Numazaki & Fujii 2000).***

Ondansetron is a serotonin antagonist that selectively inhibits 5-hydroxytryptaminne type 3 (5-HT_3) receptors and is devoid of dopamine, histamine, cholinergic, or adrenergic receptor activity. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema ***(Hawthorn et al., 1988)*** and ***(Kilpatrick et al., 1988)***. Ondansetron had been used prophylactic to reduce the incidence of intraoperative nausea and vomiting in patients undergoing cesarean section under regional anesthesia ***(Pan & Moore 1996)*** and ***(Fujii et al., 1998)***. We therefore conducted this trial which is prospective and randomized to evaluate and compare the efficacy and safety of propofol at a dose of 1 mg $kg^{-1}hr^{-1}$ with ondansetron 4 mg for preventing emetic symptoms in patients undergoing cesarean section under spinal anesthesia.

Materials and methods

After obtaining informed consent, 60 ASA I and II parturient, between the age of 21 and 38, scheduled for elective cesarean delivery were enrolled. Patients who had gastrointestinal diseases, those who had a history of motion sickness, hyperemesis gravidarum, contraindication to regional anesthesia or previous emesis in a perioperative, postdelivery period, and those who had

taken antiemetic within 24 hours before surgery were excluded from the study.

Patients were randomized and divided into two groups (n= 30), to receive either, lidocaine intravenous 1mg kg^{-1} (for injection pain relief) followed by propofol 1mg kg^{-1} hr^{-1} as intravenous infusion (GP) or ondansetron 4 mg (GO) given after spinal anesthesia. In GP, the drug administration was stopped at the end of surgical procedure (after skin-sutures) to avoid delayed discharge. As preanesthetic medication, patients received oral rantidine 150 mg night before and 90 minutes before surgery. Each patient received 20 ml kg^{-1} of lactated ringer's solution before the induction of spinal anesthesia. Standard monitors were used ECG, Spo_2 and non-invasive blood pressure measurements were performed at 2 min intervals for 15 min, then 5 min intervals for the remainder of the procedure. All patients received supplemental oxygen via nasal cannula throughout the procedure. Hyperbaric bupivacaine 0.5% (3 ml) was injected through a 25-gauge needle inserted at the level L3-4 interspace. The block was performed with the patient in the right lateral decubitus position. After the injection of anesthetic solution, the patient was turned to the supine position with a 15-degree wedge under the right hip for left uterine displacement. The decrease in systolic blood pressure (more than 20% from baseline values and/or less than 100 mm Hg) immediately after spinal injection was treated by increasing the rate of fluid administration, exaggerating the uterine tilt, and/or injection of ephedrine 5-10 mg intravenously. Thus, maternal hypotension related emetic symptoms were avoided. The level of anesthesia was assessed by pinprick 10 min after intratheacal injection and recorded. Patients in all groups were allowed to receive, increments, up to 100 µg fentanyl intravenously, if required for pain relief, after the delivery of fetus.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit. Retching was defined as the labored spasmodic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. The patients were evaluated for the severity of

nausea, satisfaction with the study drug and degree of sedation at the end of the observation period. The evaluations were performed on a linear numerical scale ranging from 0 (no nausea, complete satisfaction, no sedation) to 10 (sever nausea, complete dissatisfaction, extreme sedation). Vomiting and retching were graded as (0= no vomiting or retching or 1= vomiting or retching). Study variables were assessed at eight sequential intervals during the procedure: spinal placement until skin incision, skin incision until delivery, delivery until uterine exteriorization, uterine exteriorization until replacement of uterus, uterine replacement until start of fascial closure, fascial closure until skin closure, skin closure until arrival in recovery room, and recovery room stay. The details of any other adverse effects were recorded. If two or more episodes of emesis occurred, another rescue antiemetic was given, for GP we give ondansetron 4 mg, for GO we give metaclopromide 10 mg. Postoperative, when the patients were wide awake, they were transferred to the post-anesthesia care unit and remained there before being moved to the ward.

Statistical analysis of data between the treatment groups were performed by using analysis of variance with Bonferroni correction for multiple comparison, X^2 test, two-tailed Fisher's exact probability test, or the Mann-Whitney *U*-test, as appropriate. A *P* value of <0.05 was considered significant.

Results

There were no significant differences among the treatment groups with regard to maternal demographics, age, height, weight, average number of previous deliveries, gestational age, number of patients with previous cesarean delivery and baseline systolic blood pressure table (1). Operative management data as duration of surgery, uterus exteriorized, duration of uterian exteriorization, tubal legation, interval from skin incision to delivery of fetus, interval from uterine incision to delivery of fetus, total dose of ephedrine and fentanyl, also show no significant differance table (2). The level of analgesia was sufficient for the surgical procedure because no patient had a sensory level below T_5 or above T_4. Despite this, several patients required supplementation with

fentanyl when the peritoneum was being manipulated. Amount of fentanyl for pain relief show no significant difference between the groups. The amount of ephedrine administered for the treatment of hypotension was similar in both groups.

Table (1) Maternal Demographics Data

	GP	**GO**
Age	27 ± 4	26 ± 3
Height (cm)	165 ± 7	163 ± 9
Weight (kg)	76 ± 11	75 ± 10
***Multiparous (n)**	3 ± 1	2 ± 1
Gestational age (wk)	39 ± 1	39 ± 2
Patients with previous cesarean delivery (n)	15	16
Baseline systolic blood pressure (mmHg)	125 ± 11	123 ± 12

**Average numbers of previous deliveries.*

Table (2) Operative Management Data

	GP	**GO**
Duration of surgery (min)	50 ± 10	49 ± 11
Uterus exteriorized	28	27
Duration of uterine exteriorization (min)	20 ± 3	19± 4
Tubal legations performed	4	3
I-D interval (min)	7 ± 3	6 ± 4
U-D interval (sec)	121 ± 23	120 ± 21
Total dose of ephedrine (mg)	3.5 (0-10)	3.5 (0-10)
Total dose of fentanyl (µg)	60 (0-100)	65 (0-100)

I-D interval= interval from skin incision to delivery of fetus; U-D interval= interval from uterine incision to delivery of fetus. Values are mean ± standard deviation or number of patients.

In table (3) regarding patients with complete response (no nausea or vomiting), there is a difference between GP and GO where 24 and 27 patients had complete response in each group respectively which is statistically significant ($P<0.05$). Incidence of nausea, retching, and vomiting in GP was high and significant when compared to GO. No patient in GO need rescue, while two patients in GP were received ondansetron 4 mg as rescue, this is significantly low ($P<0.05$).

Table (3) Number of Patients Free of Symptoms or Experiencing Nausea, Retching, Vomiting or Need Rescue

	GP	**GO**
Complete response (no nausea or vomiting)	24 (80%)	27 (90%)
Nausea	6 (20%)	3 (10%)
Retching	3 (10%)	1 (3%)
Vomiting	4 (13%)	1 (3%)
Rescue	2 (7%)	0 (0%)

Table (4) shown that, severity of nausea score, degree of sedation score were significantly high in GP compared to GO. On the other hand degree of satisfaction score was significantly high in GO compared to GP. Two patients in GO complain from headache, which was transit, continue for less than 10 min and resolved spontaneously.

Table (4) Assessment of Nausea, Satisfaction and Sedation Scores

	GP	**GO**
Severity of nausea	7 ± 3	4 ± 3
Degree of satisfaction	4 ± 2	6 ± 2
Degree of sedation	4 ± 3	1 ± 0

Discussion

Nausea and vomiting during regional anesthesia for cesarean delivery have a complex and multifactorial etiology. A number of factors, including age, sex, pain, and anesthetic technique are considered to influence the incidence of emesis (***Watcha & White 1992).*** Operative procedures as peritoneal traction, exteriorization of uterus, fundal pressure during delivery of the baby ***(Biswas etal 2002)*** and ***(Manullang et al., 2000)***, this problem may be accompanied by visceral pain, which occurs dispite apparently adequate dermatomal sensory blockade ***(Alahuhta et al., 1990).*** In this clinical trial, however, the treatment groups were similar with regard to maternal demographics and operative management, and patients with a history of motion sickness and/or previous emesis during cesarean were excluded because they had a relatively high incidence of emetic symptoms ***(Watcha & White 1992).*** Maternal hypotension and its associated brainstem hypoxemia, as a cause of intraoperative nausea and vomiting during cesarean delivery under spinal anesthesia ***(Datta et al., 1982) (Kang et al., 1982)*** and ***(Ratra et al., 1972)*** were aggressively prevented and/or treated in our study with generous prehydration, nasal oxygen, left uterine displacement, and if necessary intravenous ephedrine together with rapid fluid infusion.

The exact mechanism by which propofol acts as an antiemetic remains unclear, but propofol is not considered to have vagolytic properties ***(Patra et al., 1972)***. In addition, the efficacy of propofol as an antiemetic is not based on the lipid emulsion in the formulation of propofol ***(Ostman et al., 1990). Hammas et al., (1998)*** have evaluated the effect of propofol on nausea and vomiting induced by "ipecacuanha", known to release (5-HT_3), and have demonstrated that propofol reduce the intensity of retching after "ipecacuanha" administration, suggesting that propofol may have a weak 5-HT_3 antagonistic effect.

Propofol at a subhypnotic dose 1 mg $kg^{-1}hr^{-1}$ reduced the incidence of intraoperative and postdelivery nausea and vomiting in patients undergoing spinal anesthesia for cesarean ***(Numazaki & Fujii 2000).*** Also, they tried to use different doses of propofol 1 and 2 mg $kg^{-1}hr^{-1}$ and demonstrated that propofol 1mg was as effective as

propofol 2 mg for the control of emesis in an intraoperative and postdelivery period, and showed no difference in the rate of emesis-free episodes. This result suggest that propofol in a minimum effective subhypnotic dose of 1 mg $kg^{-1}hr^{-1}$ was effective with less sedation ***(Fujii & Numazaki 2002).***

Ondansetron, a highly selective 5-HT_3 receptor antagonist, which acts peripherally on vagus nerve endings and centrally on the chemoreceptor trigger zone. Ondansetron is effective for reducing the incidence of intraoperative emetic symptoms in cesarean patients under epidural anesthesia ***(Pan & Moore 1996). Pearman (1994)*** and ***Pan & Moore (1996)*** suggested that 8 mg ondansetron may have more benefit than 4 mg in females with high risk of emetic symptoms, but several studies have demonstrated that ondansetron 4 mg is as effective as 8 mg ***(claybon 1994) (castle et al., 1992)*** and ***(Alon & Himmelseher 1992). Tramer et al., (1997)*** compared intravenous ondansetron 1, 4, or 8 mg with placebo in 2812 male and female patients in three different studies. The combined results showed that ondansetron 4 mg was the optimal dose for treating established postoperative nausea and vomiting. According to the results of ***(Tramer et al., 1997)***, we use ondansetron 4 mg and compare it with propofol 1 mg $kg^{-1}hr^{-1}$ as continuous infusion where the results showed that both are effective in preventing emetic symptoms during and postdelivery in patients undergoing cesarean section with spinal anesthesia, but ondansetron is moor effective, where patients free from emetic symptoms 24 (80%) in propofol group and 27 (90%) in group treated by ondansetron. Also number of patients with nausea, retching, vomiting were high in propofol group. Moreover, ondansetron reduced requirement for further rescue antiemetic which may provides greater benefit.

Scuderi et al., (1999) noted that patients for whom prophylaxis with ondansetron was ineffective had no better response to a subsequent dose of ondansetron. It may be reasonable to use a drug from a class other than the one used for prophylaxis for treating break through postoperative nausea and vomiting. In our study, we used ondansetron as rescue in propofol group and planed to use

metaclopromide as rescue in ondansetron group, but no patient needed.

Pan & Moore (1996) and ***Abouleish et al., (1999)*** were give ondansetron, 8 mg and 4 mg respectively, intraoperative after umbilical-cord clamping for patients undergoing cesarean section under regional anesthesia, but ***Manullang et al., (2000)*** give ondansetron intravenous after spinal placement and found no effect in Apger score of babies. In our study, intravenous ondansetron was given immediately after spinal placement depending on the results of ***Manullang et al., (2000)*** because we believe that ondansetron when given by this method will be more effective.

When ondansetron used for patients undergoing cesarean section under regional anesthesia. ***Abouleish et al., (1999)*** concluded that, the intraoperative administration of 4 mg ondansetron intravenously during cesarean section under spinal anesthesia significantly reduces the incidence of vomiting and the severity of nausea. Also, ***(Pan & Moore 1996)*** compared prophylactic droperidol and ondansetron during cesarean delivery under epidural anesthesia and recommended consideration of ondansetron on the basis of equivalent efficacy and decreased side effects.

Prophylactic antiemetic efficacy of propofol at a subhypnotic dose 1 mg $kg^{-1}hr^{-1}$, droperidol 1.25mg, and metaclopromide 10 mg are comparable in parturients undergoing cesarean delivery. Moreover, propofol at a subhypnotic dose is effective in the prevention of sever nausea ***(Numazaki & Fujii 2003)***. When we compare propofol 1 mg kg^{-1} hr^{-1} with ondansetron 4 mg, we found that ondansetron is better. But ***(Fujii & Numazaki 2004)*** used a combination of subhypnotic dose propofol 1 mg $kg^{-1}hr^{-1}$ and dexamethasone 8 mg and found that, it was more effective than propofol alone for reducing the incidence of emetic symptoms in the parturients undergoing cesarean delivery under spinal anesthesia.

Ondansetron may cause transient headaches and mild elevation of liver enzymes ***(Castie et al., 1992)***. Headaches occur and recognized as side effect in ondansetron group in this clinical trail, but it was mild and transit, didn't need treatment.

Ondansetron was not associated with extrapyramidal effects or sedation ***(Gan et al., 1993).*** But, extrapyramidal reaction to ondansetron had been reported when ondansetron had been used in high and repeated doses ***(Matthews & Tancil 1996)*** and ***(Kristenansky et al., 1996).*** Also, this side effect may occur with single, small intravenous dose (4mg) of ondansetron ***(Stonell 1996).*** Extrapyramidal side effect not detected in our patients of ondansetron group.

Conclusion

Ondansetron 4 mg is more effective than propofol 1 mg $kg^{-1}hr^{-1}$ to prevent emetic symptoms during and postdelivery in patients undergoing cesarean section under spinal anesthesia. Moreover, ondansetron reduced requirement for further rescue antiemetic which may provides great benefit.

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