ORIGINAL ARTICLE

Comparison of intrathecal fentanyl and midazolam for prevention of nausea-vomiting during cesarean section under spinal anesthesia

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ABSTRACT

Aims and Objectives: Nausea and vomiting remain as "the big little problem" in cesarean section under spinal anesthesia. Incidence of nausea-vomiting during and immediately after surgery in spinal anesthesia is high. It is physically as well as mentally distressing to the patient and disturbing to the surgeon and the anesthesiologist. Purpose of this study was to compare the clinical efficacy of intrathecal fentanyl and midazolam for prevention of nausea-vomiting in parturients undergoing cesarean section under spinal anesthesia.

Methodology: This prospective randomized double blind study was conducted in 90 women aged between 18-31 years (ASA physical status I) scheduled to undergo elective cesarean section under spinal anesthesia. Subjects were randomly divided into three equal groups. Group A received 0.5 ml normal saline, Group B received 2 mg midazolam and Group C received 12.5 μg fentanyl with 2 ml of hyperbaric bupivacaine 0.5% intrathecally. Nausea-vomiting was assessed according to Belville's score. The statistical analysis of data was done by using statistical package for social science (SPSS) evaluation version 20. Results were expressed as mean, standard deviation, and range values. Frequencies expressed as number and percentage. ANOVA was used for multiple group comparisons, and categorical data were analyzed by Chi-square test.

Results: 24 subjects out of 30 in the placebo group developed intraoperative and early postoperative nausea-vomiting compared to 11 in midazolam group and 8 in fentanyl group. Incidence of intraoperative and early postoperative nausea-vomiting was 79.5% with placebo, 36.6% with midazolam and 26.6% with fentanyl.

Conclusion: Intrathecal fentanyl 12.5 μg or midazolam 2 mg, both reduce the incidence and severity of nausea-vomiting when administered with bupivacaine for cesarean section.

Key words: Nausea and vomiting, Cesarean section, Spinal anesthesia, Intrathecal fentanyl, Intrathecal midazolam

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INTRODUCTION

The most common and distressing symptoms which follow anesthesia and surgery are pain, nausea and vomiting. Nausea and vomiting remain as "the big little problem" in cesarean section (CS) under spinal anesthesia (SA)[1]. The causes of PONV are multifactorial and can largely be categorized as patient risk factors, anesthetic technique, and surgical procedure. Antiemetic drugšds work on several different receptor sites to prevent or treat PONV.[2]

The incidence of nausea-vomiting during and immediately after surgery in SA is high and is an annoying problem to all concerned. It is distressing

to both physically and mentally to the patient and disturbing to the surgeon and anesthesiologist. Vomiting can lead to medical complications like dehydration, electrolyte imbalance, decreased patient satisfaction, and also causes an economic burden.[3-5] Intra operative nausea and vomiting occurs in as many as 66% of CSs performed under regional anesthesia. This can be distressing to the patient, and may increase the risk of aspiration of gastric contents[6].

Intrathecal midazolam and fentanyl produce postoperative pain relief for women undergoing CS, while also having antiemetic effect.[7] With this in mind, this study was designed to assess and compare the efficacy and clinical profile of intrathecal fentanyl and midazolam for prevention of nausea-vomiting.

Following parameters were also observed, compared and studied:

1. The hemodynamic effects
2. Incidence of adverse intra and postoperative events.
3. Neonatal effects
4. Postoperative analgesia

METHODOLOGY

A prospective randomized double blind controlled study was planned. The study was conducted between 1st January 2013 to 31st December 2013 at Karnataka Institute of Medical Sciences, Hubli, Karnataka, India. After obtaining prior approval from ethical committee and a valid written and informed consent from the patients, 90 patients of ASA I physical status aged between 18-31 years scheduled to undergo elective CS under SA and satisfying all the inclusion criteria were enrolled in the study and randomly allocated into three groups of 30 each. The ladies with history of hyperemesis gravidarum, obesity with body weight > 120 Kg and height < 150 cm, any contra-indication to spinal anesthesia e.g. hypotension, coagulation defects or spine deformity, local site infection, fetal prematurity (36 weeks), those who had received antiemetic 24 hours prior to surgery, severe systemic disease or allergy to the study drugs were excluded from the study. All of the participants in all the three groups completed the study. Randomization was done by simple lottery method. Sample size was calculated by power analysis.

In the operating room, a good peripheral intravenous access was secured with 18G cannula. On arrival to the operating room, routine monitoring devices were attached and baseline blood pressure, heart rate, ECG and pulse oximetry values were recorded. All patients were preloaded with Ringer's lactate solution at 20 ml/kg before SA. Dural puncture was performed at L3–L4 interspace with a 25G spinal needle in the left lateral decubitus position by an anesthesiologist who was not involved in the patient care.

The patients were randomly allocated into three groups to receive one of the medications intrathecally. The study solutions were constituted as follows;

Group A: 2 ml of hyperbaric bupivacaine 0.5% + 0.5 ml of normal saline

Group B: 2 ml of hyperbaric bupivacaine 0.5% + 0.4 ml of midazolam + 0.1 ml of normal saline

Group C: 2 ml of hyperbaric bupivacaine 0.5% + 0.25 ml of fentanyl (12.5 μg) + 0.25 ml normal saline

Total volume of the injectate was made to 2.5 ml. Preservative-free midazolam used as adjunct in spinal anesthesia is available in our country as 1 mg/ml and 5 mg/ml concentrations. In this study, we used 5 mg/ml concentration. Fentanyl is available as 50 μg/ml.

After injection of the study solution, the patients were turned to the supine position with a 15○ wedge under the right hip for left uterine displacement. Oxygen (3 L/min) was administered via facemask. Cardiorespiratory parameters, e.g. oxygen saturation, respiratory rate, and non-invasive blood pressure, were monitored.

Intraoperative and post-delivery emetic episodes were recorded by direct questioning by an anesthesiologist blinded to the use of study drugs.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the labored, spasmodic, rhythmic contractions of the respiratory muscles without the expulsion of gastric contents; vomiting was defined as the forceful expulsion of gastric contents from the mouth.8 These were assessed according to the Belville's score9 (0 = no nausea; 1= nausea; 2 = retching and 3 = vomiting).

Metoclopramide 10 mg was administered IV as rescue antiemetic with the occurrence of two or more emetic episodes. The details of any other adverse events due to the study drug were recorded.

Table 1: Patient demographics

Demographic Variables	Summary	Group A	Group B	Group C	Total	F-value	p-value
Gestational Age	Mean	39.60	38.93	38.93	39.16	3.1974	0.0457
	SD	1.10	1.31	1.11	1.21		
Height	Mean	156.27	156.53	156.13	156.31	0.1554	0.8563
	SD	2.63	2.86	2.99	2.80		
Weight	Mean	57.50	57.70	58.43	57.88	0.3172	0.7290
	SD	4.20	5.37	4.70	4.74		

Table 2: Distribution of patients according to incidence of emetic episodes among three groups

Emetic episode	Group A	Group B	Group C
Vomiting (Belville's score 3)	7 (23.1%)	2 (6.6%)	1 (3.3%)
Retching (Belville's score 2)	7 (23.1%)	3 (10%)	3 (10%)
Nausea (Belville's score 1)	10 (33.3%)	6 (20%)	4 (13.3%)

The neonates were evaluated using APGAR score.

The statistical analysis of data was done by using Statistical Package for Social Science (SPSS) evaluation version 20. Results were expressed as mean, standard deviation, and range values. Frequencies expressed as number and percentage. ANOVA used for multiple group comparisons and categorical data analyzed by Chi-square test.

RESULTS

The mean values of patient demographics are shown in Table 1. It was observed that the distribution of mean values of these independent variables among the three groups was comparable.

The results of our study revealed that both intrathecal fentanyl and intrathecal midazolam decrease the incidence of intra operative and early postdelivery nausea-vomiting in comparison with placebo as shown in Table-2. While intrathecal fentanyl 12.5 μg reduced the incidence of nausea-vomiting to 3.34 percent, intrathecal midazolam 2 mg reduced the incidence of emetic episodes to 6.67 percent.

Intraoperative rescue antiemetic was required in 5 (16.67%) patients in the placebo group, however, the requirement was reduced to 2 (6.67%) in the midazolam group and 1 (3.34%) patient in the fentanyl group.

Intraoperative adverse effects: Hypotension was noted in 19 (62.7%) patients in Group B, compared to 17 (56%) in Group A and 14 (46.2%) patients in Group C, as shown in Table 3. Hypotension was treated with fluids and inj. mephentermine 3 mg IV. No significant difference in mephentermine use amongst the study groups was observed.

Table 3: Incidence of intraoperative adverse effects among three groups

Adverse effects	Group A	Group B	Group C
Hypotension	17 (56%)	19 (62.7%)	14 (46.2%)
Sedation	1 (3.3%)	12 (40%)	4 (13.3%)
Shivering	3 (10%)	2 (6.6%)	Nil
Pruritus	Nil	Nil	2 (6.6%)

Sedation was seen in 12 (40%) patients in midazolam group compared to 4 (13.3%) in fentanyl group and 1 (3.3%) in placebo group.

Shivering was observed in 3 (10%) patients in placebo group compared to 2 (6.67%) in midazolam group and none in fentanyl group. Only 2 (6.67%) patients complained of pruritus in the fentanyl group while none of the patients of the placebo or midazolam groups complained of pruritus. None of the patients had any neurologic deficits/symptoms 24 hours after surgery. Neonatal outcomes were similar in all the three groups (Table 4).

Study revealed that fentanyl provided good postoperative analgesia in the immediate postoperative period compared to midazolam

Table 4: Neonatal APGR scores at 1 and 5 min

Time intervals	Group A	Group B	Group C	F-value	P-value
1 min	8.47 ± 0.51	7.57 ± 0.82	7.97 ± 0.72	0.7268	0.4863
5 min	10.00 ± 0.00	9.77 ± 0.33	10.00 ± 0.00	0.1039	0.9014

and placebo. Requirement of rescue analgesic was found to be more among placebo group compared to midazolam and fentanyl group.

DISCUSSION

Nausea and vomiting commonly occur during CS performed with SA[6], and is frequently related to intraoperative hypotension, peritoneal traction, and exteriorization of uterus. These problems may be accompanied by visceral pain that stimulates vagal afferents, which occurs despite apparently adequate dermatomal sensory blockade.[10] Various studies have shown that adequate intra- and postoperative analgesia is necessary to decrease the incidence of nausea and vomiting.[10-13]

A number of adjuvants have been added to intrathecal local anesthetics including opioids e.g. morphine and fentanyl, and benzodiazepines e.g. midazolam, to provide improved postoperative analgesia and reduced PONV. Fentanyl, a phenyl piperidine derivative is a synthetic μ opioid receptor agonist. Intrathecal fentanyl improves the quality of SA increasing both the duration and intensity of SA and decreasing the intraoperative nausea and vomiting.[14]

Antiemetic effect of benzodiazepine could be an action at the chemoreceptor trigger zone (CTZ) reducing synthesis, release and postsynaptic effect of dopamine. Midazolam decreases dopamine input at CTZ and decreases adenosine-uptake, leading to adenosine mediated reduction in dopamine synthesis, release and postsynaptic action.[15,16] Intrathecal midazolam may also produce postoperative pain relief for women undergoing CS, in addition to antiemetic effects.[13,17]

There have been many earlier studies comparing the efficacy of intrathecal fentanyl and midazolam with other intrathecal opioids, intravenous sedatives, and anti-emetics in prevention of PONV. Ates Duman et al.[18] compared efficacy of intrathecal fentanyl 20 μg and morphine 200 μg as additive to hyperbaric bupivacaine and concluded that intrathecal opioids effectively decreased the incidence of PONV compared to placebo. Theodore R et al[19] compared the incidence of PONV in intrathecal fentanyl 20 μg with intravenous ondansetron. Study reported decreased incidence of PONV in fentanyl group. Sahar M et al[20] studied the efficacy of 12.5 μg intrathecal fentanyl as additive to hyperbaric bupivacaine. Fentanyl group had a less frequent incidence of side effects, such as severe hypotension, nausea, and vomiting. Smita Prakash et al[21] reported significantly lower incidence of nausea in intrathecal midazolam group compared to control group.

Pallab Rudra, A. Rudra[22] compared efficacy of midazolam (2 mg) and fentanyl (12.5 μg) vs. placebo as additive to intrathecal bupivacaine in prevention of PONV. The reported incidence of intraoperative and early postoperative nausea-vomiting was 75% with placebo, 40% with midazolam and 25% with fentanyl. Hence concluded that intrathecal co-administration of midazolam or fentanyl significantly minimizes the incidence of nausea-vomiting during intraoperative and early postoperative period in cesarean delivery.

The results of our study revealed that both intrathecal fentanyl and intrathecal midazolam decrease the incidence of intraoperative and early postdelivery nausea-vomiting in comparison with placebo. The incidence of nausea-vomiting was reduced to 3.3% and 6.6% by low dose intrathecal fentanyl and midazolam respectively. The intraoperative rescue antiemetic (metoclopramide) requirement was least in the fentanyl group compared to midazolam and placebo groups.

Few other studies also compared efficacy of midazolam and fentanyl against other available options, including metoclopramide 10 mg, for prevention of nausea and vomiting with similar results.[13,23,24] The results of our study are in agreement with earlier studies.

In our study the incidence of hypotension was also comparable to the observations made by Palllab Rudra, A. Rudra,[22] who reported that hypotension was noted in 57.5% patients in placebo group, 62.5% patients intrathecal midazolam and in 50% patients in fentanyl group. There was no significant difference in ephedrine requirements amongst the study groups. Study concluded that the low dose of intrathecal study agents did not have any deleterious cardiovascular effects on the parturients.

In our study, sedation was observed more in midazolam group compared to fentanyl and placebo groups, while the requirement of inj. mephentermine was similar among the three groups. Incidence of shivering was more in the placebo group (10%) compared to the midazolam group (6.67%), while shivering was not observed in the fentanyl group. Pruritus was exclusively observed in fentanyl group (6.67%). None of the patients in all the three groups developed any neurological deficits postoperatively and neonatal outcomes were comparable among three groups. Low dose of either fentanyl or midazolam intrathecally had no detectable adverse impact on neonatal condition. Study revealed requirement of rescue analgesic was found to be more among placebo group compared to midazolam and fentanyl group.

An earlier study compared the efficacy of various doses of IT fentanyl as additive to IT bupivacaine. This study reported similar hemodynamic stability and neonatal outcomes among all groups and, also, increased incidence of sedation and pruritus in fentanyl group. The incidence of adverse effects increased with increase in the dose of IT fentanyl. The results of our study are comparable to the observations in the earlier studies.[22,25]

LIMITATION

Our study was restricted to patients undergoing elective CS under SA. We could not assess the incidence of PONV, pain, quality and effectiveness of analgesia, after mobilization of the patients as the parameters were followed up only for first 24 hours postoperatively. Further studies are needed to compare the efficacy of different doses of intrathecal fentanyl or intrathecal midazolam with other commonly used and well established antiemetics for reducing the incidence of emesis in an intraoperative, postoperative and post-delivery period.

CONCLUSION

Our results allow us to conclude that the co-administration of intrathecal fentanyl 12.5 μg or intrathecal midazolam 2 mg with 0.5% hyperbaric bupivacaine in the subarachnoid block significantly reduces the incidence of intraoperative and early postoperative nausea-vomiting in cesarean sections under spinal anesthesia, when compared to placebo. There was no significant change in hemodynamic status and side-effects.

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The only thing necessary for the triumph of evil is for good men to do nothing

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