IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 5 Ver. X (May. 2016), PP 49-53
www.iosrjournals.org

Comparative Study to Evaluate Antiemetic Efficacy of Intrathecal Fentanyl and Midazolam for Lower Segment Cesarean Section in Subarchnoid Block

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Abstract
Objective: *To compare antiemetic efficacy of fentanyl and midazolam as adjuvant to bupivacaine for preventing nausea-vomiting in women undergoing caesarean section under subarchnoid block.*
Study Design: *Prospective randomized, double-blinded, placebo-controlled study.*
Materials and Methods: *In present study 150 patients posted for elective caesarean section were included. A detailed history and thorough pre-anaesthetic evaluation was performed. All patients were randomly divided into three groups using computer generated randomization technique. Group C: patients received 2 ml of hyperbaric bupivacaine (0.5%) + 0.5 ml of normal saline intrathecally (n=50). Group M: patients received 2 ml of hyperbaric bupivacaine (0.5%) + 2.5 mg of midazolam intrathecally (n=50).Group F: patients received 2 ml of hyperbaric bupivacaine (0.5%) + 12.5 µg of fentanyl intrathecally (n=50). Hemodynamic parameters, intraoperative and postoperative emetic episodes were assessed using Belville's score. Perioperative complication like hypotension, sedation, shivering and pruritis were recorded. All data was expressed as Mean ± Standard deviation (SD). Statistically analysis was done by using student's unpaired t-test and ANOVA. p-value <0.05 was considered significant.*
Results:*. Demographic profile was comparable in all three groups. In the intraoperative and post-delivery period, an emesis free episode occurred in 31 of 50 patients (62%), 24 of 50 patients (48%) and 13 of 50 patients (26%) who had received IT fentanyl, IT midazolam or IT placebo respectively. Among fentanyl and midazolam groups, retching, nausea and vomiting was less in fentanyl group than midazolam group; however, that did not differ significantly (p-value>0.05).Intraoperative rescue antiemetic was required in 7(14%) patients in the control group, however, the requirement was reduced to 3 (6%) in the midazolam group and 2 (4%) patient in the fentanyl group. Sedation was mainly seen in midazolam group, shivering in control group and pruritis in fentanyl group.*
Conclusion:*. From present study it is concluded that, co-administration of intrathecal fentanyl 12.5 µg or intrathecal midazolam 2.5 mg with 0.5% hyperbaric bupivacaine in the subarachnoid block significantly reduces intraoperative and postoperative nausea-vomiting in cesarean sections.*
Keywords: *Bupivacaine , Caesarean section, Fentanyl, Midazolam, Subarachnoid block*

I. Introduction

Nausea and vomiting intraoperatively and in early postoperative period during caesarean delivery under subarchnoid block is a common distressing symptoms and is seen in up to 66% of cases [1]. Emetic symptoms more frequently occur in the parturient because of high progesterone levels, which decreases gastrointestinal motility, reduces lower esophageal sphincter tone and increases gastrin secretion [2]. These symptoms are reduced by several antiemetic drugs (like metoclopromide, domperidon, ondensatron etc), but none have been proved to be effective without significant adverse effects or high cost [3].

The causes of nausea and vomiting are multifactorial and can largely be divided as patient risk factors, anesthetic technique and surgical procedure. Intrathecal (IT) administration of lipophilic Opioids such as fentanyl [4] and benzodiazepines like midazolam [5] have been reported to minimize the incidence of intraoperative and early postoperative nausea and vomiting in caesarean delivery under subarchnoid block. Fentanyl, a phenyl piperidine derivative is a synthetic µ opioid receptor agonist. It is preferred as an adjuvant in subarchnoid block because of its rapid onset and short duration of action. It increases both the duration and intensity of spinal anesthesia and decreases the intraoperative nausea and vomiting without having any deleterious effects on the neonate or mothers [6,7].

Midazolam is a short acting benzodiazepine. It is GABA receptor agonist at γ-subunit. It is a CNS depressant, anticonvulsant and sedative. Its antiemetic effect could be due to an action at chemoreceptor trigger zone(CTZ) reducing synthesis, release and postsynaptic effect of dopamine [8].

Therefore, present study was conducted to compare antiemetic efficacy of fentanyl and midazolam as adjuvant with bupivacaine for preventing nausea-vomiting in women undergoing caesarean section under subarchnoid block.

II. Material & Methods

After approval from institutional ethical committee, present prospective randomized, double-blinded, placebo-controlled study was conducted in Department of Anaesthesiology, Osmania Medical College, Hyderabad, Telangana, during November 2008 to May 2010 in 150 patients posted for elective caesarean section.

Inclusion Criteria: 1. ASA grade I and II women posted for elective cesarean section
2. Age between 18 to 32 years

Exclusion Criteria: 1. ASA grade III and above
2. Emergency surgeries
3.History of hyperemesis gravidarum
4. Patients who had received antiemetic within 24 hours prior to surgery
5. H/o gastrointestinal disease
6. H/o allergy to study drugs
7. Contraindications to regional anaesthesia
8. Refusal for participation

After a thorough pre-anaesthetic evaluation of all patients, a written and informed consent was obtained, both for conduct of study as well as administration of subarchnoid block. They were kept nil by mouth for eight hours before surgery. Intravenous access was established with a 18G intravenous canula and preloading was done with 15 ml/kg Ringer Lactated solution. Anaesthesia machine, accessories, monitors & drugs were checked.

Sample size was calculated using Open Epi, Version 3, open source calculator – SS mean on internet with confidence interval of 99% , power of 95% and ratio of two groups at 1:1 ; which was minimum 36 participants per group. All patients were randomly divided into three groups using computer generated randomization technique.

Under all strict aseptic precautions, in lateral position, subarachnoid block was performed at L3-L4 intervertebral space with a 25G spinal needle .

•GroupC: patients received 2 ml of hyperbaric bupivacaine(0.5%)+0.5 ml of normal saline intrathecally (n=50).
•GroupM:patients received 2 ml of hyperbaric bupivacaine (0.5%) + 2.5 mg of midazolam intrathecally (n=50).
•Group F: patients received 2 ml of hyperbaric bupivacaine (0.5%) + 12.5 µg of fentanyl intrathecally. (n=50).

Following parameters were recorded:

- Hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure at 2 minute intervals for 10 minutes, then at 5 minute intervals for next 30 minutes and at 15 minute intervals till 2 hours after giving study drug.
- ECG and SpO2 monitored continuously.
- Intraoperative and postoperative emetic episodes were assessed using to the Belville's score [9]
  Grade 0 - No nausea,
  Grade 1- Nausea,
  Grade 2- Retching
  Grade 3- Vomiting.
  at 30 min,1 hours, 2 hours,4 hours,6 hours,12 hours and 24 hours .

These emetic episodes were recorded by direct questioning by an anaesthesiologist blinded to study drug the patients have received.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the laboured, 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 [10]. If two or more episodes of emesis occurred, another rescue antiemetic (ondensetron 4 mg) was given. Perioperative complication like hypotension, sedation, shivering and pruritis were observed.

Statistical analysis : All data was expressed as Mean ± Standard deviation (SD). Statistical analysis was done using student's unpaired t-test and ANOVA. p-value <0.05 was considered significant.

III. Results

Table-I Distribution according to Demographic profile (N=150)

S.No	Parameters	Group-C (n=50) (Mean ± SD)	Group-M (n=50) (Mean ± SD)	Group-F (n=50) (Mean ± SD)	p - value
1	Age (year)	23.21±3.7	24.5±4.6	24.7±3.6	>0.05
2	BMI (kg/m2)	24.32±2.2	25.34±3.7	25.56±4.5	>0.05
3	Gestational age (wks)	39.10±1.7	37.85±2.4	38.25±2.15	>0.05

p-value <0.05 is taken as significant

Table-II Distribution of perioperative emetic episodes in groups according to Belville's score (N=150)

S.No	Belville's score	Group-C (n=50) No. of patients (%)	Group-M (n=50) No. of patients (%)	Group-F (n=50) No. of patients (%)
1	Grade 0 - No nausea	13 (26%)	24 (48%)	31 (62%)
2	Grade 1- Nausea	16 (32%)	14 (28%)	11(22%)
3	Grade 2- Retching	12 (24%)	7 (14%)	5 (10%)
4	Grade 3- Vomiting	9 (18%)	5 (10%)	3 (6%)

Table – III : Comparison of the incidence of emetic symptoms of the three groups

Emetic episode	Group-C vs Group-M		Group-C vs Group-F		Group-M vs Group-F	
	Z-value	p-value	Z-value	p-value	Z-value	p-value
Nausea	1.17	>0.05	2.05	<0.05	0.69	>0.05
Retching	1.67	>0.05	2.17	<0.05	0.41	>0.05
Vomiting	1.11	>0.05	1.23	<0.05	1.07	>0.05
Overall presence of any episode	3.27	<0.05	4.43	<0.05	1.41	>0.05

p-value <0.05 is taken as significant

In the intraoperative and post operative period, an emesis free episode according to Belville's score Grade 0 - No nausea, occurred in 31 of 50 patients (62%), 24 of 50 patients (48%) and 13 of 50 patients (26%) who had received IT fentanyl, IT midazolam or IT placebo respectively [Table-II]. Among fentanyl and midazolam groups, the incidence of retching, nausea and vomiting were less in fentanyl group than midazolam group; however, that did not differ significantly (p-value>0.05) [Table-III]. Intraoperative rescue antiemetic was required in 7(14%) patients in the control group, however, the requirement was reduced to 3 (6%) in the midazolam group and 2 (4%) patient in the fentanyl group.

Table-IV Comparison of Perioperative Complications (N=150)

S.No	Complication	Group-C (n=50) No. of patients (%)	Group-M (n=50) No. of patients (%)	Group-F (n=50) No. of patients (%)
1	Hypotension	42 (84%)	38 (76%)	42 (84%)
2	Sedation	1 (2%)	8 (16%)	4 (8%)
3	Shivering	7 (14%)	4 (8%)	1 (2%)
4	Pruritis	0 (0%)	0(0%)	3 (6%)

Sedation was mainly seen in midazolam group, shivering in control group and pruritis in fentanyl group. Hypotension was observed in 42 patients in control group, 38 patients in midazolam group and 42 patients in fentanyl group. [Table-IV].

IV. Discussion

In present clinical study, we have compared the efficacy of fentanyl and midazolam to minimize the incidence of nausea vomiting when co administered with hyperbaric bupivacaine (0.5%) intrathecally with that of placebo in caesarean section. Factors such as age, history of motion sickness, hormonal changes,

hypotension, pain, surgical procedure and anesthetic technique influence emetic symptoms. However, in present study, the study groups were similar with regard to maternal demographics and operative management. Therefore, the difference in the frequency and severity of emetic symptoms can be attributed to the study drugs administered.

Nausea and vomiting commonly occur during caesarean section performed under subarchnoid block [1], and is frequently related to intraoperative hypotension, peritoneal traction and exteriorization of uterus. These problems may be accompanied by visceral pain that stimulate vagal afferents, which occurs despite apparently adequate dermatomal sensory blockade [2]. Various pharmacological agents have been used prophylacticaly, however, either undesirable effects or cost of the agents limited their routine use [11].

Intrathecal fentanyl and midazolam as adjuvants with bupivacaine in subarchnoid block for caesarean section, may provide better intraoperative and postoperative analgesia and thereby decreases discomfort from peritoneal manipulations which may initiate emetic episodes [2,4,12,13].

Benzodiazepines, including midazolam, have been shown to be effective in chemotherapy induced nausea and vomiting. This mechanism of the anti-emetic effect is not well known. It has been speculated that they act by reduction in anxiety and decrease in dopaminergic input to the CTZ. Midazolam may reduce the reuptake of adenosine, which decreases synthesis, release and postsynaptic action of dopamine at CTZ. Gamma-amino-butyric acid (GABA)-ergic neurones are also thought to exert an inhibitory effect on central dopaminergic pathways. It is possible that benzodiazepines reduce dopaminergic neuronal activity by binding to GABA- benzodiazepine receptor complex. 5HT3 release may also be reduced by benzodiazepines binding to GABA- benzodiazepine receptor complex. High doses of midazolam allosterically inhibit the function of 5HT3 receptors [11].

Intrathecal fentanyl improves the quality of spinal anesthesia increasing both the duration and intensity of spinal anesthesia and decreasing the intraoperative nausea and vomiting [14].

The results of present study revealed that both IT fentanyl and IT midazolam significantly decrease the incidence of intraoperative and early postoperative nausea-vomiting in comparison with placebo ($p<0.05$), which are in agreement with the observations of [3,7,12-15].

Intraoperative rescue antiemetic was required in 7(14%) patients in the control group, however, the requirement was reduced to 3(6%) in the midazolam group and 2(4%) patient in the fentanyl group which is similar to [11,12,15,16].

In present study the incidence of hypotension was also comparable to the observations made by [12,15]. Hypotension was aggressively treated with I.V. fluids and I.V. ephedrine. Therefore, the low dose of intrathecal agents did not have any deleterious cardiovascular effects on the parturients. Incidence of sedation was more in midazolam group whereas incidence of shivering was more in the control group and pruritis in fentanyl group.

V. Conclusion

From present study it is concluded that, co-administration of intrathecal fentanyl 12.5 μg or intrathecal midazolam 2.5mg with 0.5% hyperbaric bupivacaine in the subarachnoid block significantly reduces intraoperative and postoperative nausea-vomiting in cesarean sections under subarchnoid block.

Acknowledgements

We express our deep gratitude to all patients for their co-operation.

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