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Comparative Study on Efficacy of Intrathecal Injection Midazolam (2 mg) Versus Injection Metoclopramide IV in Prevention or Reduction of Nausea and Vomiting in Women during Caesarean Delivery under Spinal Anaesthesia

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Authors' contributions

This work was carried out in collaboration among all authors. Author VJ designed the study and wrote the protocol. Authors VJ, PPH and SHS managed the patients, collected all data, performed the statistical analysis and wrote the first draft of the manuscript. Authors VJ, PPH and SHS did the literature search and also wrote part of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Nausea and vomiting after spinal anaesthesia in caesarean are frequent causing distress to the patient and surgeon. To diminish the incidence various pharmacological agents were used with their limitations. This study compares intrathecal midazolam with intravenous metoclopramide for prevention of nausea and vomiting during surgery and in the early postoperative period after caesarean delivery performed with spinal anaesthesia.

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Materials and Methods: In a randomized single blind manner, 100 women (ASA Grade I and II) undergoing elective caesarean delivery were enrolled for the study with 0.5% hyperbaric bupivacaine 2 ml (10 mg) spinal anaesthesia were randomly allocated in to two groups. Group I received intravenous metoclopramide 10 mg (n = 50 in each group). Group II received intrathecal midazolam preservative free 2 mg (n = 50). Emetic episodes were recorded during anaesthesia and in the initial period after caesarean delivery (0 – 6 hrs) and compared between two groups by using Chi – square test. P value of <0.05 was taken to be significant.

Results: The incidence of patients who were emesis – free in the intraoperative and postoperative period was 39 (78%) with intravenous metoclopramide and 49 (98%) with intrathecal midazolam, respectively **(**p< 0.001). No clinically important adverse events were observed in either group.

Conclusion: We conclude that use of intrathecal midazolam (2 mg) is more effective than intravenous metoclopramide (10 mg) for preventing nausea and vomiting in women undergoing caesarean delivery under spinal anaesthesia with bupivacaine (0.5%) hyperbaric.

Keywords: Nausea; vomiting; caesarean delivery; antiemetic; metoclopramide; midazolam; spinal anaesthesia.

1. INTRODUCTION

The common and distressing symptoms which follow anaesthesia and surgery are pain, nausea and vomiting. Nausea and vomiting are the most common side effects in the post anaesthetic care unit. But post-operative nausea and vomiting have received less attention, though there are extensive literature, data are frequently difficult to interpret and compare. Nausea and vomiting have been associated for many years with the use of general anaesthetics for surgical procedures. First extensive description was given by John Snow, published in 1848. In spite of the advances like using less emetic anaesthetic agents, improved pre and post-operative technique and identification of patient predictive factors, nausea and vomiting still occur with unacceptable frequency in association with surgery and anaesthesia, and is described as "the big little problem". Early studies reported incidence of post-operative nausea and vomiting (PONV) as high as 75 – 80%. But in the second half of 20th century, however these incidences have decreased by almost 50% for various reasons. PONV may be associated with wound dehiscence, pulmonary aspiration of gastric contents, bleeding, and dehydration and electrolytes disturbances. Hence vomiting can potentially delay hospital discharge or lead to unexpected hospital admissions and increased hospital cost and can result in serious medical and surgical complications. There are many different modes of interventions to prevent Nausea and Vomiting. Antiemetic drugs play an important role in therapy of Nausea and Vomiting. Though many drugs have been tried as prophylaxis and treatment of Nausea and Vomiting. In a review article, regarding the study on children undergoing tonsillectomy, they have suggested that midazolam is an effective antiemetic agent [1]. In a prospective randomized double blind placebo controlled study on 60 patients undergoing elective caesarean delivery they gave a conclusion that intrathecal injection of midazolam 1 mg and 2 mg gives best prophylaxis against intraoperative and postoperative nausea and vomiting [2].

In a study with intrathecal midazolam as adjuvant in spinal anaesthesia gave a conclusion that it provides a greater sensory and motor blockade, prolongs postoperative analgesia. It is safe without side effects and it significantly reduces Nausea and Vomiting [3]. A randomized double blind study conducted and suggests that midazolam 2 mg IV is more effective [4]. In a study with 672 patients, intrathecal midazolam reduced the incidence of nausea and vomiting and improves perioperative analgesia during caesarean delivery [5]. The study conducted about efficiency of intrathecal midazolam for prevention of nausea and vomiting during surgery and in the early postoperative period after caesarean delivery under spinal anaesthesia was followed by new era in the treatment of nausea and vomiting [6]. Metoclopramide is in use as antiemetic for many years but intrathecal midazolam as antiemetic is being used recently. Oondansetron inhibit the action of histamine at the H_1 receptor, and anticholinergic agents inhibit the action of acetylcholine at the muscarinic receptor. A comparative effectiveness of these two drugs in reducing incidences of Nausea and Vomiting in LSCS under subarachnoid block was evaluated in this study.

2. MATERIALS AND METHODS

The present clinical study was conducted in 100 women undergoing elective LSCS under spinal anaesthesia in Bapuji Hospital, Chigateri General Hospital and Women and Children Hospital attached to J.J.M.Medical College, Davanagere. After ethical committee approval and written informed consent, women posted for elective LSCS under spinal anaesthesia were selected. The study populations were subdivided into 2 groups of 50 women each by using simple random technique. DR. Vijay Jalaki was carried the work.

2.1 Group I

The group which received injection hyperbaric Bupivacaine 0.5% 10 mg (2 ml) in to Spinal anaesthesia site and IV injection of Metoclopramide 10 mg.

2.2 Group II

The group which received injection hyperbaric Bupivacaine 0.5% 10 mg (2 ml) in to Spinal anaesthesia site and intrathecal injection Midazolam 2 mg.

Inclusion criteria: Women aged between 19 – 30 years. Women belonging to ASA I and II grade scheduled for elective LSCS under spinal anaesthesia.

Pre-operative order: All patients received premedication with ranitidine 150 mg orally and remain nil orally, this was done 2 hours before the surgery.

Spinal anaesthesia: Procedure **-**When the patient was brought to the operation theatre, her pulse rate, BP, respiratory rate and SpO_2 were recorded. An IV access with 18G cannula was obtained. Each patient preloaded with 20 ml/kg of ringer lactate solution before the spinal anaesthesia to prevent hypotension. 50 patients were received injection Metoclopramide 10mg IV, 3 – 5 min before subarachnoid block with bupivacaine 0.5% hyperbaric 2 ml (10 mg). 50 patients were received injection Midazolam 2 mg intrathecally along with Bupivacaine 0.5% during subarachnoid block.

Subarachnoid block was performed with all aseptic precautions at $L_3 – L_4$ interspace using 23G spinal needles, with the patient in left lateral position. After clear free flow of CSF was noted, according to the group allocated injection Bupivacaine Hyperbaric. 0.5% 2 ml and injection Bupivacaine Hyperbaric 0.5% 2 ml plus injection Midazolam 2 mg injected into subarachnoid space. After spinal anaesthesia patients were placed in supine position with 15° wedge under right buttock for left uterine displacement. Oxygen was supplemented with mask. Level of sensory block was assessed with loss of sensation to cold and pin prick to T_6 level. Surgery was started. SpO_2, pulse rate, respiratory rate and blood pressure were monitored and recorded every 5 minute during surgery and postoperatively every hour up to 6 hour. The decrease in systolic blood pressure (more than 20% of baseline value and/or less than 90 mm of Hg) after spinal anaesthesia was treated by increasing the rate of intravenous fluid administration, by exaggerating the uterine tilt and 5 mg increments of ephedrine administered intravenously until resolution of hypotension.

Duration of surgery and stages were noted. Episodes of emesis were identified by direct questioning at 5 minutes interval during the surgical procedure and at hourly intervals during postoperative period, or by spontaneous complaint by the patient at any time during the study period. Nausea, retching and emesis were recorded at 1 hour, 2 hour, 3 hour, 4 hour, and 6 hour.

The number of episodes of emesis and type were recorded. Repeated vomiting within 1 – 2 minute period was recorded as single emesis. The data were taken as fallows.

No emesis – complete control.
1 – 2 episodes – nearly complete control.
3 – 5 episodes – partial control.
> 5 episodes – failure.

Similarly, the numbers of episodes of retching (dry heaves) were also registered.

Nausea was graded as 0, 1, 2 and 3.

0 - None
1 - Mild (one or two times).
2 - Moderate (three to five times)
3 - Severe. (Six or above six)

The results were tabulated at 1 hour, 2 hour, 3 hour, 4 hour and 6 hours post operatively. Severe nausea and vomiting was labelled as failure. All the observations and particulars of each patient were recorded in a proforma, a copy of which is enclosed.

2.3 Statistical Analysis

Interval data are expressed as mean and standard deviation. Chi – square test was used for comparing two groups. A p value of less than 0.05 was considered for statistical difference. The level of significance was taken as $P < 0.05$ – Significant.

3. RESULTS

Maternal characteristics were not different between two groups. The level of anaesthesia was considered sufficient for the surgical procedure as an adequate sensory block up to T_6 was documented in all the patients. There were no significant differences in blood pressure, heart rate, and respiratory rate between two groups. No patient demonstrated a SpO_2 below 98%.

During intraoperative and postoperative period only one woman (2%) out of 50 women who had received intrathecal midazolam experienced nausea and vomiting and rest 49 women (98%) were emesis free. Emetic episodes did not occur in 39 of 50 women (78%) and 11 woman (22%) had emetic episodes who had received intravenous metoclopramide ($P < 0.001$). The results of different parameters as follows (Tables 1-4).

4. DISCUSSION

Postoperative nausea and vomiting is the most distressing and unpleasant experience for a patient undergoing anaesthesia and surgery. Furthermore, severe postoperative emesis may lead to dehydration, electrolyte imbalance, which in turn may alter the overall outcome of the entire surgical procedure. Postoperative vomiting may though rarely, lead to a life threatening complication like aspiration pneumonitis. The incidence of nausea and vomiting during spinal anaesthesia for caesarean delivery is relatively high when no prophylactic antiemetic was given. Factors attributed are younger age, surgical skill, peritoneal traction, and exteriorization of the uterus, fundal pressure during difficult delivery, anaesthetic management and prevention of hypotension in women undergoing caesarean delivery with spinal anaesthesia. However in our study, most of these factors were well controlled, so that any difference in emesis – free episodes during spinal anaesthesia for caesarean delivery can be attributed to the study drugs. Antiemetic effect of metoclopramide is well established to decrease intraoperative nausea and vomiting during caesarean delivery with spinal anaesthesia, however the agent may produce Extrapyramidal symptoms [7].

Midazolam hydrochloride is a potent imidazobenzodiazepine presented as an aqueous solution. Midazolam acts through GABA receptors which are abundantly present in the dorsal horn of the spinal cord with the highest density of these receptors found within lamina II of dorsal horn ganglia. Administration of exogenous benzodiazepines into the CSF around spinal cord reached GABA receptors in high concentration and could have a pronounced effect on local GABA activity. Therefore benzodiazepines can gain access to analgesic system mediated by GABA. GABA is synthesized

Table 1. Maternal demographics and operative management

	Metoclopramide 10 mg IV (Group I) (n = 50)	**Midazolam 2 mg intrathecal (Group II) (n = 50)**
Age (years)	23.66±3.13	24.18±3.08
Weight (kg)	62.10±7.63	60.41±6.93
Gestational age (week)	38±1.77	38±0.60
Multiparous (n)	8	8
Baseline blood pressure	115±11.18	125±7.21
(mm Hg) Systole Diastole	80±8.16	80±6.01
Pulse rate / min.	88.8±12.03	85.5±8.73
Respiratory rate / min	15±1	15±1
Duration of surgery (min)	54±17.21	57.5±15.10
Duration of exteriorization of uterus (min)	18.75±5	17.5±4.86
Hypotension	9 (18%)	3 (6%)
Apgar score		
At 1 min	8±0.64	8±0.64
At 5 min	10	10

Values are mean±SD or number of patients

from glutamate in the presynaptic nerve ending and is generally inhibitory in effect. GABA on binding with $GABA_A$ receptors opens Ligand gate chloride channels. Chloride conductance is increased, leading to hyperpolarisation and presynaptic inhibition of afferent terminals in spinal cord. This results in less central propagation of action potential carrying nociceptive stimuli information. Intrathecal midazolam has been used in man have been described to provide pain relief.

Table 2. EMESIS (EPISODES)

	EMESIS (EPISODES)	
	Metoclopramide	**Midazolam**
1st hour	8	1
2nd hour	5	1
3rd hour	3	0
4th hour	2	0
6th hour	0	0

Table 3. Nausea grades

	Metoclopramide	**Midazolam**
1st hour	17	05
2nd hour	15	02
3rd hour	06	00
4th hour	05	00
6th hour	00	00

Incidence of nausea was more common in 1st hour and decreases with time

Table 4. Number of patients free of emetic episodes and with emetic episodes from 0 – 6 hours after spinal anaesthesia

	Vomiting absent	**Vomiting present**
Intravenous metoclopramide 10 mg (Group I) (n = 50)	39 (78%)	11 (22%)
Intrathecal Midazolam 2 mg (Group II) (n = 50)	49 (98%)*	1 (2%)

* *P value<0.001*

In the current study we have demonstrated that the number of emesis – free women were 49 (98%) was higher with intrathecal midazolam than in those who had received intravenous metoclopramide were 39 (78%) [P < 0.001]. The exact reason for this difference is not known, but may be related to improved intraoperative analgesia provided by midazolam when administered with bupivacaine intrathecally and thus avoiding the initiation of emetic episodes by peritoneal traction, exteriorization of the uterus and visceral pain [8,9]. The present study results were in correlation with previous studies [3,5,6]. We found that there is a decrease in the incidence of PONV in patients who received intrathecal midazolam in our study. In Prakash et al. [3] also reported similar findings in patients undergoing caesarean section. We have observed the better post-operative analgesia in our study with midazolam, our result in agreement with studies of Y. K. Batra et al. [10] and N Agarwal [11]. In study of Lee Y et al. [6] shows similar result that we found in our study Midazolam vs ondansetron for preventing postoperative nausea and vomiting, that Midazolam is better than ondansetron.

5. CONCLUSION

Our findings indicate that preservative free intrathecally administered midazolam 2 mg could provide safe and excellent prevention of emetic episodes during caesarean delivery performed under spinal anaesthesia with bupivacaine. Moreover intrathecally administered midazolam improves quality of anaesthesia during the spinal procedure and it avoids other antiemetic drugs and its complications. Therefore in future, it may find a place in clinical use in caesarean delivery with spinal anaesthesia to avoid perioperative emetic episodes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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