Comparison of ondansetron and low dose Ketamine as agents for prevention of intraoperative nausea and vomiting during caesarean section under spinal anaesthesia

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Abstract

Introduction: Spinal anaesthesia is considered as gold standard for caesarean section due to its advantages of rapid and predictable onset, no airway handling, safe to mother and minimal drug exposure to fetus. But spinal anaesthesia caesarean section is associated with high incidence of IONV. Role of ondansetrone as antiemetic is well established. Not many studies are there for low dose ketamine in prevention of IONV.

Materials and Methods: A total of 225 pregnant patients scheduled for CS under spinal anaesthesia were included and divided into three groups Group I – Patients who received low dose ketamine, group II- Patients who received ondansetron, group III- Patients who received normal saline. The patients were compared for intraoperative hemodynamic parameters, IONV, side effects like sedation and shivering.

Results: The results of this study showed low dose ketamine group (group I) 26.6% and ondansetron (group II) 32% had lower incidence of IONV in comparison to control group 49.3%.

Conclusion: Low dose ketamine and ondansetron are both good agents for reduction of IONV during CS in pregnant patients under spinal anaesthesia without significant adverse effects.

Keywords: Ondansetron, Ketamine, (IONV) Intraoperative nausea vomiting, (CS) Caesarean section, (NMDA) N- methyl D-aspartate, (ASA) American society of Anaesthesiology.

Introduction

Spinal anaesthesia is the most commonly used anaesthesia for caesarean section with it being safely, quickly and easy to administer.[1] Current literature indicates a high incidence of intraoperative nausea and vomiting during caesarean section under spinal anaesthesia for which many factors may contribute like hypotension, stimulation of pharyngeal reflex noticed in abdominal surgeries, physical rupture and manipulation of abdominal viscera, due to the release of humoral 5-HT substances, which trigger the 5-HT_3 receptors on vagal afferent neurons.[2,3] During abdominal surgery under regional anesthesia, nausea may happen due to several contributing factors such as sympathetic blocks followed by parasympathetic dominance with hypotension which is the most important cause of nausea after spinal anesthesia, decreased perfusion of central nervous system, anxiety, and sudden abdominal movements during surgery and prescription of drugs.[4]

Ondansetron is considered as an effective drug for prevention and treatment of nausea and vomiting that is well tolerated by the patients.[3] It is used in surgeries which may be accompanied by nausea and vomiting without many severe adverse side effects.[5] Ketamine is a NMDA receptor antagonist that has unique central sympathomimetic, vagolytic and analgesic properties.[6,7] These properties of ketamine are assumed to reduce the incidence of spinal induced hypotension consequently nausea and vomiting.

The present study was undertaken to compare the anti emetic efficacy of low dose ketamine and ondensetron to decrease the incidence of IONV during CS under spinal anesthesia.

Materials and Methods

After approval by institutional ethical committee and obtaining a written informed consent from patients, this study was done in the time period from January 2016 to August 2017. We studied a total of 225 patients aged from 20 to 40 years who were scheduled to undergo caesarean section under spinal anaesthesia. Exclusion criteria included history of motion sickness, post-operative nausea and vomiting, allergy to (bupivacaine, fentanyl, ondansetron or ketamine), ASA grade 3 or more, pregnancy induced hypertension, smoking, obese patients (body weight >80 kg), epileptic patients, patients given antiemetics or corticosteroids within 24 h before CS, and patients having contraindications to spinal anaesthesia. Included patients were allocated randomly (using computer generated randomization table) into three equal groups: Group I- the ketamine group (n = 75), group II-the ondansteron group (n=75) and group III-the control group (n =75). The drugs used were prepapred by a separate anaesthesiologist in a syringe diluted to total volume of 5ml syringe (In the ketamine group- Ketamine 0.25 mg/ kg bodyweight diluted in 5ml saline, in the ondansetron group- Ondensetron 4mg in 5 ml saline and In the control group 5 ml normal saline) given after clamping of umbilical artery.

Preanaesthetic Preparation

All patients were hospitalized and kept fasting for at least 6 hours before surgery. A 18-G cannula was inserted and Ringer lactate infusion started 15 min before shifting the patient to the main operating theatre. In the operating room, patients were monitored with ECG, noninvasive arterial blood pressure and pulse oximetry. All patients were

reminded to report any side effect or discomfort including nausea during surgery.

Anaesthesia

Anaesthesia was standardized, by giving spinal anaesthesia in the lateral position using a 25-Guage pencil point type spinal needle, 25 microgram fentanyl and 2.2 to 2.5ml (depending on height of patient) of hyperbaric bupivacaine 0.5%, once free flow of clear CSF was obtained. All the patients were immediately returned to supine position after subarachnoid injection, table given 15-20 degree left tilt and supplemented with oxygen 4 L min_1 via facemask. Sensory block was assessed by pinprick method and above T-6 dermatomal level was the acceptable level before surgical incision. Patients in whom the level of analgesia was insufficient were excluded from the study. Mean arterial blood pressure (MAP) was measured every 3min for the first 10 min then every 5min thereafter till end of surgery. Hypotension was treated with ephedrine 3mg and bradycardia was treated with atropine 0.6 mg. Oxytocin was given immediately after baby delivery and clamping of the umbilical cord starting by an IV bolus dose of (3 units) followed by infusion of 10 units in 500ml saline at rate 125ml/hr or according to uterine contractility and as per the obstetrician opinion. The 5 ml of the prepared drug was given just after clamping of umblical cord. Intraoperative nausea was recorded as follow (no nausea, nausea only, nausea and vomiting single episode, More than one episode of intraoperative nausea and vomitting). Nausea with retching or vomiting were managed by a rescue dose of 8mg dexamethasone, while nausea only was managed by assurance. Maternal side effects (such as desaturation, hallucinations, shivering) as well as fetal well-being (assessed with the Apgar scoring) were recorded. Maternal sedation was assessed by Ramsay Sedation Scale (RSS; 1 =anxious and agitated, 2= co-operative and tranquil, 3 = drowsy but responsive to command, 4 = asleep but responsive to glabellar tap, 5= asleep with a sluggish response to tactile stimulation, 6= asleep and no response).

The three groups were then compared with reference to patient's characteristics, intraoperative clinical data (intraoperative hemodynamics, intraoperative nausea and vomiting, sedation).

Statistical Analysis

Sample Size and Sample Technique

The response within each subject group was normally distributed with standard deviation 2. We needed to study minimum 64 experimental subjects in each group to be able to reject the null hypothesis that the population means of the experimental groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Data Analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables were presented as mean ± SD, and categorical variables as absolute numbers and percentages. Data was checked for normality before statistical analysis using Shaipro Wilk test. Normally distributed continuous variables were compared using ANOVA. Student *t*-test was used to compare between three groups of normally distributed data categorical variables were analyzed using the chi-square test. For all statistical tests, a p-value less than 0.05 were taken to indicate a statistically significant difference.

Results

There were no significant differences between the groups in terms of baseline patient characteristics (p>0.05) (Table 1)

Table 1: Demographic data and hemodynamic parameters as mean±SD

Demographic data and baseline preoperative parameters	Group I n=75 (Ketamine)	Group II N=75 (Ondansetron)	Group III N=75 (control)	*P* value
Age (years)	27.6±2.5	28.8±2.2	26.9±2.8	0.52
Weight (kg)	70.35±4.3	69.5±4.2	69.7±5.3	0.54
MAP (mmHg)	77.1±6.9	79.04±7.8	78.7±5.8	0.73
HR/min	78.5±4.2	75.29±6.9	79.6±4.4	0.54
SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate, SD=Standard deviation				

There were lower incidences of hypotension in ketamine group and MAP and HR was higher (statistically insignificant) in the Ketamine group as compared to ondansetron and control group.

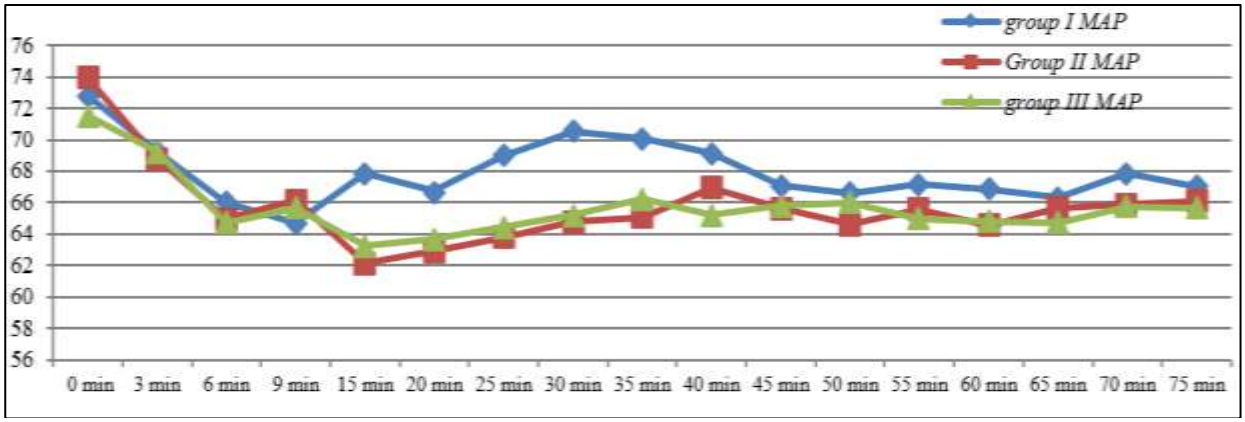

Fig. A: Mean arterial pressure variation (MAP)

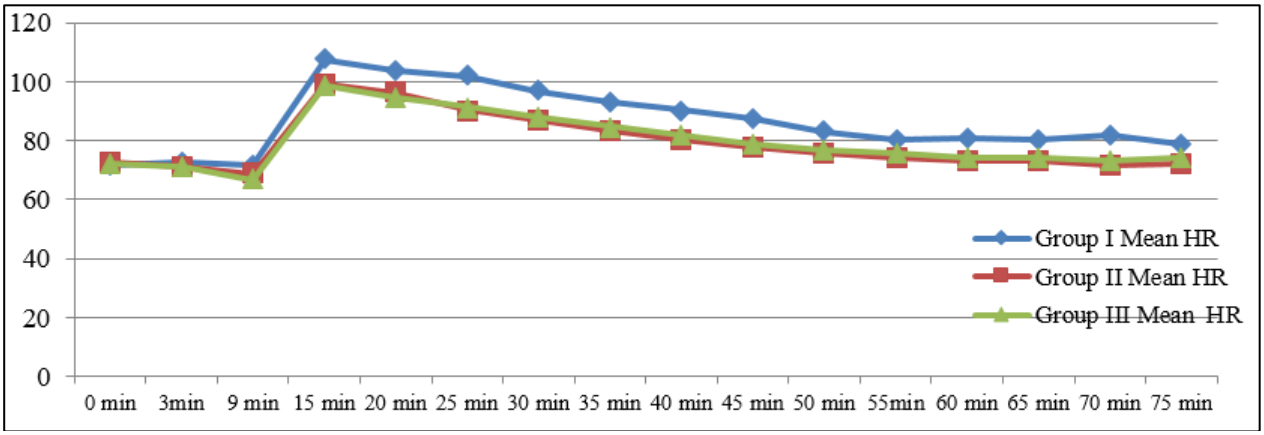

Fig. B: Mean heart rate variation (HR)

The incidence of intraoperative nausea in the ketamine group 26.6% (20 out of 75) compared with Ondansetron 32% (24 out of 75) and control group 49.3% (37 out of 75), which was statistically significant between group I and Group III, GroupII and Group III, and insignificant between Group I and Group II. Both vomiting episodes and number of patients who required rescue anti-emetics in the ketamine group and ondansetron group were less compared with control group.

Table 2: Nausea and vomiting episodes

	Group I N=75 (Ketamine)	**Group II N=75 (Ondansetrone)**	**Group III N=75 (control)**	***P* value Group I & group II**	***P value group I & III***	***P value Group II & III***
No nausea	56	52	40	0.52	0.004*	0.003*
Nausea only	9	11	18	0.54	0.06	0.24
Nausea and Vomitting 1 episode	7	8	11	0.73	0.13	0.23
Nausea and Vomitting more than 1 episode	3	4	6	0.66	0.24	0.27
Rescue antiemetic dexamethasone	10	12	17	0.24	0.1	0.26
Total Intraoperative nausea & vomitting	20 (26.6%)	24 (32%)	37 (49.3%)	0.21	0.004*	0.029*

Only 11 patients of Group I had Ramsay sedation score of 3 or more while in ondansetron and control group had postoperative RSS 2.

Table 3

	RSS	Group I n=75 (Ketamine)	Group II N=75 (Ondansetron)	Group III N=75 (control)
Post op Sedation Score RSS	1	0	0	0
	2	64	75	75
	3	10	0	0
	4	1	0	0
	5			
Intraoperative shivering		4	7	9

Discussion

Spinal anaesthesia is considered as gold standard for caesarean section due to its advantages of rapid and predictable onset, no airway handling, maternal safety and minimal drug exposure to fetus. But spinal anaesthesia is associated with intraoperative hypotension, and IONV. IONV is an uncomfortable feeling for patients, causes surgical problems to obstetricians, and may increases the risk of visceral injury during surgery because of the involuntary uncontrolled abdominal movements.[1,2]

Nausea and vomiting during spinal anaesthesia has been associated with multiple factors like sympathetic blocks followed by parasympathetic dominance, hypotension which is the most important cause of nausea after spinal anesthesia, decreased perfusion of central nervous system, psychological changes (anxiety), and sudden abdominal movements during surgery and concomitant opioid administration.[4,8,9] There are many drugs used for treatment of PONV in parturients undergoing CS under spinal anaesthesia like metoclopramide, domperidone, phenothiazines, butyrophenones, anticholinergics, antihistamines and ondansetron.[10] These drugs have been used either alone or in combination and have proved effective for prevention of nausea and vomitting. Ondansetron is a selective antagonist of the 5-hydroxytryptamine (5-HT_3) receptors and is a very effective agent in the prevention and treatment of nausea and vomiting. It is effective in the prevention and treatment of chemotherapy induced,[11] intraoperative[12] and postoperative nausea and vomiting.[13,14] Hypotension is probably the most important cause of IONV that occurs during CS under spinal anesthesia. Hypotension can induce the emetic symptoms by leading to cerebral hypoperfusion.[15] Prevention of hypotension is therefore important for the prevention of IONV. [16] We took the necessary measures like fluid administration at faster rate after making patient supine and using ephidrine to manage hypotension in all of our patients. We used ondansetron 4mg as at this dose it has been found to effective in the prevention of IONV during CS under spinal anaesthesia.[17,18] Of the different agents used, droperidol 2.5 mg and 5mg has been used in controlling nausea and vomiting in CS,[19,20] dexamethasone 8mg and metachopromide 10mg also have been quiet effective in controlling nausea and vomiting during CS,[21,22] and have been compared for their effectiveness.[23] Glycopyrrolate, due to its vagolytic effect was studied in prevention of intraoperative nausea and vomiting during CS and compared with ondansetron. It was seen that effect of glycopyrrolate on nausea and vomiting during cesarean section are comparable to ondansetron, but with an increased incidence of dry mouth.[24]

Ketamine is an intravenous dissociative anaesthetic agent related to phencyclidine group which works by antagonizing N-methyl D-aspartate (NMDA) receptors.[6] Because of its unique analgesic and dissociative criteria in addition to the distinct symatho-mimetic, vagolytic pharmacological properties, ketamine is used frequently in anaesthesia practice for purposes of analgesia, sedation and induction of anaesthesia many years ago. Ahmed hasnain and A M Shabana used low dose ketamine infusion in CS and found reduction in incidence of nausea.[25,26] The APGAR score at 1 min and 5 min in all the neonates was more than 9. Ketamine use during CS has been found safe interms of both maternal and fetal safety, with neonatal 1 min and 5 min APGAR scores being more than 9 when used as IV inducing agent in CS.[27] Ketamine use intrathecally as adjuvant to bupivacaine in CS has also shown to stablise haemodynamics and decrease the incidence of nausea and vomiting.[28] There was statistically significant decrease in incidence of IONV in ketamine and ondansetron group as compared to control group. The antiemetic effect of low dose ketamine and ondansetron was comparable.

The ketamine group showed statistically insignificant higher HR and MAP compared to ondansetron and control group. This can be explained to sympathomimetic and vagolytic propetrties of ketamine.

There were 11 patients in ketamine group with higher sedation levels (RSS =3 or more), although Ketamine use during spinal anaesthesia nor was it associated with increased incidence of either respiratory depression or hallucinations. The non-significant difference in the sedation level measured by RSS can be explained because of low dose of ketamine used in contrast to ketamine used for sedation in higher doses (0.5mg/kg/hr or higher) or in combination with midazolam.[29]

The incidence of shivering in ketamine group was lower as compared to control group and overall shivering incidence was lower than reported due to use of intrathecal fentayl. Ketamine is competitive receptor antagonist of N-methyl-D-aspartic acid (NMDA) has a role in thermoregulation in various levels. Ketamine probably controls shivering by non- shivering thermo genesis either

influencing the hypothalamus or by the beta-adrenergic effect of nor epinephrine.[30]

Conclusion

Low dose ketamine and ondansetron are both good agents for reduction of IONV during CS in pregnant patients under spinal anaesthesia without significant adverse effect.

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Conflict of Interest: None.

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