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IS LOW DOSE KETAMINE EFFECTIVE AS ANTIEMETIC PROPHYLAXIS FOR INTRAOPERATIVE NAUSEA AND VOMITING DURING CAESAREAN SECTION UNDER SPINAL ANAESTHESIA: A PROSPECTIVE RANDOMIZED STUDY

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ABSTRACT

Background: Intra-operative nausea and vomiting (IONV), which occurs in around 40- 60% of the patients undergoing CS under regional anaesthesia, is an uncomfortable feeling for patients, upsets obstetricians, distresses anaesthetists and may increases the risk of visceral injury during surgery because of the involuntary uncontrolled abdominal movements. Hypotension can induce the emetic symptoms by leading to cerebral hypo perfusion. Ketamine has unique central sympathomimetic, vagolytic and analgesic properties. These properties of ketamine are assumed to reduce the incidence of spinal induced hypotension and consequently nausea and vomiting. **Material and methods:** 120 patients posted for caesarean section under spinal anaesthesia were enrolled for the study after clearance from institutional ethical committee. Patients of group I - received low dose IV ketamine in dose of 0.5 mg/kg in 5ml Normal Saline Group II - received IV ondansetron in dose of 4 mg in 5ml Normal Saline Group III - Received IV 5ml Normal Saline, slow IV over 5 mins. Incidence of nausea, vomiting and complete response, hemodynamic, sedation score and block characteristics were noted at fixed intervals. **Results:** group I (ketamine) had maximum percentage of complete response (82.5 %). The difference in complete response among the three groups was statistically significant (p value – 0.001), whereas incidence of nausea and vomiting among the three group was comparable (p value – 0.021, 0.037). Apgar score noted was of grade 9 with statistically insignificant difference among all the groups (p- value 0.52). **Conclusion:** patients undergoing elective caesarian section under spinal anaesthesia who have high risk of IONV; prophylactic therapy of low dose ketamine (0.5 mg/kg) just before giving spinal anaesthesia can be used for prevention of IONV without any adverse effect on neonates similar to IV ondansetron.

KEYWORDS : Intraoperative nausea vomiting, ketamine, cesarean section, spinal anaesthesia, ondansetron

INTRODUCTION:

Caesarean section (CS) with spinal anaesthesia (SA) has attracted much attention in recent years and is now a common surgical practice. Intra-operative nausea and vomiting (IONV) in parturient subjected to CS under spinal anaesthesia is a major drawback of the technique[1]. Intra- operative nausea and vomiting is an uncomfortable feeling for patients upsets obstetricians, distresses anaesthetists and may increases the risk of visceral injury during surgery because of the involuntary uncontrolled abdominal movements[2,3].

Various drugs have been found to be effective in decreasing IONV like anticholinergic drugs (scopolamine, atropine), dopamine receptor antagonist (prochlorperazine and metaclopramide), anti-histaminic drugs (diphenhydramine, promethazine and hydroxygene), 5HT3 receptor antagonists (ondansetron, granisetron, dolosetron) and steroids (dexamethasone) but have their own adverse effects varying from lethargy, restlessness, tachycardia, extrapyramidal symptoms, dystonic reactions increasing the incidence of delayed discharge and unwanted hospital re-admission[4]. Selective serotonin antagonist now forms the mainstay in the prevention and treatment of IONV, but even they have limited effects. None of the available anti-emetics is entirely effective, perhaps because most of them act through the blockade on one type of receptor. Hypotension can induce the emetic symptoms by leading to cerebral hypo perfusion in patients undergoing CS in spinal anaesthesia. There is a growing interest for searching of newer anti-emetic and also to look for anti-emetic effect of drugs already in use during anaesthesia.

Ketamine, an intravenous dissociative anaesthetic agent related to phencyclidine group works by antagonizing N-methyl D-aspartate (NMDA) receptors. It has unique central sympathomimetic, vagolytic and analgesic properties[5,6].

Ondansetron is a selective antagonist of the 5-hydroxytryptamine (5-HT3) receptors and is a very effective agent in the prevention and treatment of nausea and vomiting that is well tolerated by the patients[7].

This study is an attempt to evaluate the effect of low dose ketamine on the intraoperative nausea and vomiting in parturient subjected to elective CS under spinal anaesthesia

and compares the antiemetic efficacy of low dose ketamine as prophylactically with ondansetron to decrease the incidence of intra-operative nausea and vomiting during CS under spinal anaesthesia.

MATERIALS AND METHODS

This prospective randomised double blind controlled study was conducted on 120 pregnant female of 19-38 years of age undergoing elective caesarean section under spinal anaesthesia after clearance from institutional ethical committee. Patient of ASA III or more, with severe cardio respiratory, hepatic, renal neurological or endocrinal disease, with hypersensitivity to drug, obese patients wt more than 90 kg, emergency caesarean section were excluded from the study.

Assuming that 50% of the patients would experience intraoperative nausea and vomiting, if not receiving antiemetic prophylaxis, undergoing caesarian section under spinal anesthesia. A sample size of 40 patients in each group is determined by a priori power analysis with α error of 0.05 and β error of 80% to detect an absolute difference of 25% between the treatment groups (i.e. reduction from 50% to 25%) including 10% drop out rate, a total of 120 patients were taken as sample for the study.

Patients were randomly divided in three groups of 40 patients each by simple randomization technique of card method. A total number of 120 cards were prepared by principal investigator, after recruitment every patient was asked to draw one card and grouped accordingly. Group I - Received low dose IV ketamine in dose of 0.5 mg/kg in 5ml Normal Saline Group II - Received IV ondansetron in dose of 4 mg in 5ml Normal Saline. Group III - Received IV 5ml Normal Saline slow IV over 5 mins.

The study medication was given intravenously by anesthesiologist who was not aware of the study and data was collected by resident who was blinded about the group allocation. Even patient was also not aware about the group allocation. Anaesthesia technique was standardized. Patients were kept fasting for 8 hours prior to surgery. On arrival to operation theatre, routine monitoring was done heart rate, NIBP, SpO2, ECG. An intravenous line was established in non dominant arm and Ringer lactate infusion was started. The study drug was given to patient slow IV over 5 mins just before the lumbar puncture**.** Then patient were placed in lateral position under all aseptic precautions, Lumber puncture was performed at L3-L4 intervertebral space with a 25G Quincke's spinal needle through mid-line approach. 2 ml 0.5% hyperbaric Bupivacaine was injected slowly into the subarachnoid space. The surgical anaesthesia was considered to be achieved when at least T6 dermatome level of maximum cephalic dermatome was anaesthetized. Hemodynamic parameter were recorded every min from 0- 5 minutes then at every 5 minutes interval till 30 minutes followed by at 10 minutes of interval during intraoperative period till the end of surgery and in postoperative room, also haemodynamics were recorded. **Nausea** was defined as an unpleasant sensation associated with the awareness of vomiting. Vomiting was defined as forceful expulsion of gastric contents from the mouth. **Retching** was defined as an active attempt to vomit without expulsion of gastric contents. Retching was included in vomiting. Rescue anti emetic (metaclopromide10 mg IV) was given to patients who experience persisting nausea for more than 5 min, had one or more episodes of vomiting/retching or who demanded treatment for their emetic symptoms.

Sedation score was evaluated intraoperatively at every 30 minutes interval by Ramsay Sedation Scale. Fetal well being (assessed with Apgar score) was recorded. All data was tabulated and presented as Mean ± SD, in absolute numbers and percentages. The data was analyzed using Microsoft excel 2000 (Microsoft corporation, Redmond, WA, USA). Statistical analysis was performed using SPSS (Version 23) software. Pearson Chi-Square Test was used for analysis of categorical data and one way analysis of variance (ANOVA) test was used for analysis of Numerical data. A p- value of <0.05 was considered statistically significant and that of <0.001 was considered statistically highly significant.

RESULTS

The demographic profile of patients between the two groups was comparable. (Table 1)

Table 1: Demographic profile among the study groups

Variables	Ketamine (Group I)	Ondansetron (Group II)	Control (Group III)	P-Value
Age (years)	25.15±2.31	26.05±3.29	27.23±4.43	0.053
Weight (kg)	64.9±6.75	64.85±6.22	63.93±5.97	0.74
Height (Cm)	162.25±4.82	161.95±5.92	162.55±6.55	0.90
BMI (kg/m2)	24.53±2.70	24.78±2.58	24.21±2.06	0.85

Total cumulative data of nausea, vomiting and rescue antiemetic over 0-60 minutes shows that group I (ketamine) had maximum percentage of complete response (82.5 %) and group III(control) had minimum percentage of complete response (45%) and group II (ondansetron) had(77.5%). The difference in complete response among the three groups was statistically significant (p value – 0.001). The incidence of nausea and vomiting among the three groups was also statistically significant (p value – 0.021, 0.037). Percentage of rescue anti emetic usage was the highest in group III (control) and was statistically significant (p value- 0.031).(table 2)

Table 2: Comparison of nausea, vomiting, rescue medication and complete response among the study groups at different intervals between (0-60 mins)

Interval- Intraop	Ketamine (Group I)		Ondansetron (Group II)		Control (Group III)		P value
	N	%	N	%	N	%	
0-60 mins							
Nausea	3	7.5	3	7.5	14	35	0.021*
Vomiting	4	10	6	15	19	47.5	0.037*
Rescue Medication	4	10	6	15	19	47.5	0.031*
Compete Response	33	82.5	31	77.5	18	45	<0.01*

MAP was statistically significantly higher in ketamine and ondansetron group in comparison to control group though difference in heart rate was statistically comparable. (Table 3)

Table 3: Comparison of mean MAP (mmHg) among the groups

Interval (in Min)	Ketamine (Group I)	Ondansetron (Group II)	Control (Group III)	P Value
Baseline	91.26±5.59	89.77±5.78	89.75±6.09	0.574
3rd	93.09±6.72	91.33±5.83	77.88±5.82	0.02*
5th	88.93±5.19	87.00±7.0	76.13±6.39	0.034*
15th	87.73±6.85	85.20±7.24	78.03±8.72	0.038*
30th	87.60±6.75	83.76±7.11	82.08±7.27	0.521
45th	86.18±4.18	83.26±6.16	84.22±5.51	0.472
60th	85.67±5.15	84.06±6.57	85.53±5.54	0.383

Sedation score of the patients were recorded during various time intervals in among groups was compared. In ketamine group maximum number of patient had Grade 2 Sedation (87.5%) and 2.5% had Grade 1 sedation and 10% also had grade 3 sedation while in group ondansetron maximum number of patient had Grade 1 Sedation (62.5%) and 37.5% patients had Grade 2 sedation. In group 3 (control) maximum number of patient had Grade 1 sedation (57.5%) and 42.5% patient had Grade 2 sedation which was statistically significant (p-value <0.003). Side Effects like Headache and dry mouth were noted in ketamine group and group II (ondansetron) only. They were statistically non-significant (p-

value 0.361, 0.461). Shivering was found in 30%, 17.5% and 10% of the subjects in group III (control) II (ondansetron) and group I (ketamine) respectively. It was statistically significant among the groups (p-value 0.03). There was only one patient in ketamine group which had nystagmus. There was no statistically significant difference among the groups. (Table 4)

Table 4: Comparison of side effects among the study groups.

Side Effects	Ketamine (Group I)		Ondansetron (Group II)		Control (Group III)		p-value
	N	%	N	%	N	%	
Headache	2	5	2	5	0	0	0.361
Dry Mouth	2	5	2	5	0	0	0.461
Nystagmus	1	2.5	0	0	0	0	0.37
Shivering	4	10	6	17.5	12	30	0.03*

Apgar score of the baby were recorded in group I (ketamine), group II (ondansetron),and group III(control) maximum Apgar score noted was of grade 9 with statistically insignificant difference among all the groups (p- value 0.52).

DISCUSSION

Current literature indicates a high incidence of intraoperative nausea and vomiting during caesarean section under spinal anaesthesia. The incidence of IONV is greatly increased during cesarean section because of triggering of vagal afferents on the bowel and peritoneum which in turn induces emesis by activating the vomiting centre. The unavoidable manipulation of the uterus and peritoneum as well as the exteriorization of the uterus during surgery can cause nausea and vomiting by activating afferent vagal fibres.[8]Depending on the parturient's cardiac output and other circulatory variables, compensating huge blood loss can take several minutes. Meanwhile, the blood pressure may further decrease. These events cause a reduced perfusion of the brain. This ischemia may activate the vomiting center in the medulla oblongata. As a result, patients can be affected by nausea and – in worst case – vomiting. Prevention of hypotension is therefore important for the prevention of intraoperative nausea and vomiting.

Ketamine, an intravenous dissociative anaesthetic agent related to phencyclidine group works by antagonizing N-methyl D-aspartate (NMDA) receptors. It has unique central sympathomimetic, vagolytic and analgesic properties. These properties of ketamine are assumed to reduce the incidence of spinal induced hypotension and consequently nausea and vomiting.[5,6] Placental perfusion as indicated by umbilical venous and arterial blood gases and acid base level is well maintained with the use of ketamine and compares favorably with results published by other workers using established methods of anaesthesia. Ketamine has no effect on Apgar score at 1 min & at 5 min intervals after delivery of baby.[9]

Shabana A et al. (2012) conducted a study to evaluate the effect of ketamine (0.5 mg/kg) on IONV during elective CS under SAB. 290 patients were randomly allocated into two equal groups: the ketamine group; in which it was infused intravenously in 20 min and the placebo group; in which normal saline was infused. They observed that IV infusion of ketamine was associated with a significant reduction in the incidence of IONV and hypotensive episodes. Sedation scores and Apgar scores were also comparable.[10]

Ondansetron is a selective antagonist of the 5-hydro xytryptamine (5-HT3) receptors and it exhibits an anti emetic action by antagonizing vomiting signals in the afferent pathway from the stomach or small intestine and solitary tract nucleus and is effective at preventing IONV. The 5HT3 receptor antagonist forms the first line of management of IONV. It is used in surgeries which may be accompanied by nausea and vomiting without many severe adverse side effects.[11]

Nazir O et al. (2018) conducted a study to compare the effects of ondansetron and low dose Ketamine (0.25 mg/ kg), for prevention of IONV during CS under SAB. Both ketamine and ondansetron were effective for reduction of IONV during CS under SAB without any significant adverse effect. They found that both drugs are comparable in terms of hemodynamic stability, Apgar scores and sedation scores. Though in present study also we found similar Apgar and sedation scores but MAP were significantly higher in ketamine group than ondansetron group this probably because higher dose of ketamine used in present study.[12]

Song J W et al (2013) conducted a study effect of ketamine (0.3 mg/kg) as an adjunct to intravenous patient controlled analgesia, in patient at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery in 50 patients. Ketamine was infused intravenously over 20 min and placebo group normal saline was infused. They concluded that low dose ketamine did not reduce the incidence of PONV. The difference results could be probably due to lower dose of ketamine and smaller sample size.[13]

Hassanein A et al. (2015)has compared antiemetic effect of ketamine with dexamethasone in patients undergoing caesarean section and conclude comparable effect of the two drugs[14], similarly **Haque M et al. (2019)** also conducted randomized control study and concluded that ketamine is effective as antiemetic in patient undergoing Caesarean section.[15]

Most of the studies have concluded that ketamine is effective as antiemetic in patients undergoing CS under spinal anaesthesia due to its sympathomimetic action. Since most of the studies are done in patients undergoing Caesarean sections, there is a further need of randomized control trials on evaluation of antiemetic action of ketamine on patients undergoing other kind of surgeries also.

CONCLUSION

The present study concludes that in patients undergoing elective caesarian section under spinal anaesthesia who have high risk of **IONV**, both low dose **ketamine** and **ondansetron** are effective in prevention of IONV. Thus, prophylactic therapy of **low dose ketamine (0.5 mg/kg)** just before giving spinal anaesthesia can be used for prevention of IONV without any adverse effect on neonates.

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