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A Comparative Study between Ondansetron and Dexamethasone as Antiemetic during Elective Caesarean Section done Under Spinal Anaesthesia

Dr. Swagata Mondal[1], Dr. Usha Shukla[2], Dr. Surekha Saxena[3], Dr. Dheer Singh[4]

Abstract: ***Background**: Intra operative nausea and vomiting are frequently seen in parturients during caesarean section (CS) under regional anaesthesia. It is a major problem, not only for the patient but for the surgeon and the anaesthesiologist as well. **Objective**: To compare the antiemetic efficacy of Ondansetron and Dexamethasone combination with that of the single use of each agent to decrease the incidence of post-deliveryintra-operative nausea and vomiting (IONV) during CS under spinal anesthesia. **Method**: A randomized, prospective, double blind study was performed on total 90 ASA I & II full term parturients undergoing elective CS under spinal anaesthesia. Group A(n=30) received 4mg Ondansetron, Group B (n=30) received 8mg Dexamethasone, Group C (n=30) received 4mg Ondansetron plus 8mg Dexamethasone intravenously within 1-2 minutes after the umbilical cord was clamped. Frequency of post-delivery IONV episodes was recorded. **Results**: No statistically significant difference was seen between the groups in terms of baseline characteristics and intra-operative managements. In Group A 22 (73.33%) patients, in Group B 21 (70%) patients andin Group C 19 (63.33%) patients were free of emetic symptoms, Frequency of intra-operative nausea, retching and vomiting experiences were similar between the groups(p>0.05). **Conclusion**: Single dose 4 mg Ondansetron or 8mg Dexamethasone given intravenously are both effective agents for the control of post-delivery IONV in caesarean section under spinal anaesthesia, however, the combined use of these agents is no better than both used alone neither in terms of efficacy nor side effect profile.*

Keywords: Ondansetron, Dexamethasone, Antiemetic, Caesarean section, Spinal anaesthesia

1. Introduction

Caesarean section is the most frequently performed obstetric surgery now a days. Nausea and vomiting during regional anaesthesia for caesarean section still remains a major problem, not only for the patient but for the surgeon and the anaesthesiologist as well. The physiological and anatomical changes during pregnancy like high level of progesterone causing smooth muscle relaxation, increase in gastrin secretion, decrease in gastrointestinal motility and lower esophageal sphincter tone[1]make the pregnant women prone to nausea and vomiting.

Caesarean delivery performed under regional anaesthesia is associated with a relatively high incidence (50%-80%) of intra-operative, post-delivery nausea and vomiting, when no prophylactic antiemetic is given[2,3]. Ondansetron is a selective antagonist of the 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptors and is a very effective agent in the prevention and treatment of chemotherapy induced[4], intra-operative[3]and postoperative nausea and vomiting[5,6]. Dexamethasone is a corticosteroid used primarily as anti-allergic and anti-inflammatory drug. It is also effective alone, or in combination with other antiemetics, for preventing nausea and vomiting by causing a decrease in the release of endogenous opiates[7,8]. Since nausea and vomiting can occur by a variety of different mechanisms, combination of different antiemetics are used to prevent or treat these symptoms [9, 10]. With the help of these combinations, multiple pathways that can lead to nausea and vomiting can be blocked[11]. We hypothesized that intravenous Ondansetron 4 mg and Dexamethasone 8 mg, administered in combination to patients undergoing elective caesarean section under spinal anaesthesia would decrease the incidence of post-delivery intra-operative nausea and vomiting (IONV) when compared with either Inj. Ondansetron 4 mg or Inj. Dexamethasone 8 mg alone.

2. Materials and Method

After obtaining approval from the institutional clinical research ethics committee, the randomized controlled, prospective, double blind clinical studywas carried out on total 90 ASA physical status I & II parturients of 36 completed gestational week, aged between 19–40 years undergoing elective caesarean section under spinal anaesthesia. All participants were provided a written informed consent after explaining the study procedure in patient's own language. Patients with agastrointestinal disease, drug allergies, infection, diabetes, glaucoma, preeclampsia, eclampsia, h/o motion sickness, psychiatric disorder and those patients who took an opiates or antiemetic agent in the last 24 hours were excluded from the study.

In the operation theatre multichannel monitors that included electrocardiography, heart rate, non-invasive arterial blood pressure and pulse oxymetry were applied to all the patients. An intravenous access was established by 18G IV cannula and preloading was done with lactated Ringer's solution (10ml/kg)over 20 min prior to spinal anaesthesia. Under all aseptic precautions, with the patient in sitting position L_3–L_4 inter vertebral space (or alternatively the L_2–L_3 or L_4–L_5 interspace) was identified and lumber puncture was performed through midline approach using a disposable sterile 25G Quincke spinal needle and 2–2.5 ml of 0.5% Heavy Bupivacaine (Anawin Heavy %0.5, Neon Lab. Pvt. Ltd.) was administered to the subarachnoid space after free flow of CSF. Patients were then turned to supine position with a wedge placed under the right hip to avoid aorto-caval compression (until the delivery of the baby).After preloading, all patients were infused Ringer Lactate solution at a rate of 1.5 ml/kg/hr as maintenance fluid. Oxygen was delivered to all patients at a rate of 4–5 L/ min via a face mask. Before the surgical incision, the level of sensory

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blockade was assessed by pinprick test using hypodermic needle along the midclavicular line bilaterally and the highest level of blockade was noted down. Surgery was allowed only after sensory level of anaesthesia up to T_6 reached.A continuous monitoring was done for ECG, pulse rate, respiratory rate and peripheral oxygen saturation throughout the intra operative period. Non-invasive blood pressure was monitored at 3 min intervals, and in case of hypotension blood pressure measurement intervals were shortened to 1 min. Spinal induced hypotension was defined as a fall in systolic blood pressure of 20% from the baseline value or less than 90 mmHg. We treated hypotension by bolus infusion of 200ml of Ringer Lactate and 5 mg of intravenous Ephedrine (Efedrin Ampul 1 ml/50 mg, Osel) repeated as necessary until the blood pressure increased to acceptable levels. Within 1–2 minutes after the umbilical cord was clamped, the study drug was administered to the mother intravenously.

Antiemetic drugs were prepared as a 5ml solution diluted with normal saline in similar plastic syringes, by an independent anaesthesiologist who was not involved in the study. Two syringes, one filled with study drug and another filled with 5 ml normal saline were given by the anaesthesia technician to the anaesthesiologist performing the block who was unaware of the content of the syringe.

Group A (n = 30) received 4 mg Ondansetron (Ozotron 4mg/2ml, Ozone) diluted to 5ml by normal saline + 5ml normal saline ,

Group B(n = 30) received 8 mg Dexamethasone (Dexotara 8mg/2ml, Neclife) diluted to 5ml by normal saline + 5ml normal saline, or

Group C (n = 30) received 4 mg Ondansetron diluted to 5ml by normal saline + 8 mg Dexamethasone diluted to 5ml by normal saline.

Patients received the study drugs intravenously within 1–2 minutes after the umbilical cord was clamped.

After delivery of the fetus, 10 units of Inj. Oxytocin/500 ml 0.9% normal saline administered at a rate of 30 drops/min to increase the uterine contractility.

During the intra-operative post-delivery period, nausea, retching and vomiting episodes were recorded by the anaesthesiologist performing the block.

For the statistical analysis, SPSS software for Windows version 17.0 was used. Continuous data are presented as mean ± standard deviation (SD). One-way ANOVA test and paired t test were used for parametric data analysis; Kruskal-Wallis test and Chi-square tests were used to analyze non-parametric data. $P < 0.05$ was considered statistically significant.

3. Results

There were total 90 patients, with 30 patients in each of the three groups. The three groups were similar with regard to demographic characteristics (Table 1) and operative management (Table 2). All patients had an adequate level of surgical anaesthesia (T_6 to T_4) before incision. There were no statistically difference between the three groups in regard to blood pressure, heart rate and other vital parameters.Hypotension was experienced in patients with high sensory blockade ($\geq T_5$) and with or without associated intra-operative emetic symptoms (Table 3). In an intra-operative post delivery period, the episodes of emetic symptoms (nausea, retching and vomiting) was almost similar in patients of all the three groups (Table 4). Eight patients (26.67%) in Ondansetron group, nine patients (30%) in Dexamethasone group and eleven patients (36.67%) in Ondansetron &Dexamethasone combination group experienced nausea (p=0.696). The incidence of vomiting was seen in extrapyramidal reactions three patients (10%) in Ondansetron group, three patients (10%) in Dexamethasone group and two patients (6.67%) in the combination group (p=0.872). There was no observed instances of acute extrapyramidal reactions, excessive drowsiness or clinically significant respiratory depression in any of the study patients. Only 1 patient Ondansetron group and 2 patients in Ondansetron and Dexamethasone combination group experienced mild headache which was transient in nature and resolved spontaneously.

4. Discussion

Vomiting is a complex co-ordinated motor reflex. The neural pool lies in the lateral gray reticular formation of the medulla which coordinates the various components of vomiting[12]. Vomiting may be incited by direct stimulation of CTZ in the floor of the fourth ventricle. Vagal and sympathetic afferent nerve fibres transmit the effects of emetics acting locally on the bowel and carry other types of impulses from the thorax and abdomen. Thus, the medulla is the integrative area but vomiting may be initiated from almost any part of the body[12]. Severe pain whether produced in the viscera or parieties, may cause vomiting and does not necessarily connote a gastrointestinal disturbance[13]. The parietal peritoneum is innervated by cerebrospinal somatic nerve fibres and the visceral peritoneum by visceral affarents[14]. Stretch of the wall of the stomach, esophagus, or duodenum stimulates the same nerve endings as those carry visceral pain. The etiology of intra-operative nausea and vomiting is complex and may be attributed to different factors like-psychogenic(anxiety),surgical procedure itself, abrupt visceral movements, traction on the visceral peritoneum, medullary hypoperfusion, administration of opioid and uterotonic agents, and high sensory blockade[15] above T5. Patient demographic data and anaesthetic technique also have a role[16].

There is a higher predisposition to intra-operative nausea and vomiting among patients at the end of their pregnancies, as a consequence of raised intra-abdominal pressure[17].In this study, we focused on intra-operative post-delivery antiemetic efficacy of prophylactic Ondansetron and Dexamethasone in caesarean section patients under regionalanaesthesia.

Hypotension is probably the most important causeof IONV that occurs during CS under spinalanaesthesia. Hypotension can induce the emetic symptoms by leading to medullary hypoperfusion[8].Carpenter et al[18]concluded that hypotension leads to a two-fold increase in the relative risk of IONV.In our study we tried to take the necessary measures for the prevention and/or early treatment of maternal hypotension

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like - adequate preloading with Ringer Lactate solution, left uterine displacement to prevent aorto-caval compression, fluid bolus infusion and administration of Inj. Ephedrine 5 mg IV in repeated doses when there was maternal hypotension.

Kang et al[19] (1982) and Datta et al[20](1982) found that incidence of emetic complications during spinal anaesthesia for caesarean section correlated with the presence of arterial hypotension. In our study all patients developing hypotension also showed emetic symptoms sequentially, which resolved within a short time with correction of hypotension (Table 3).

In our study (Table 3), 2 patients in Group A, 2 patients in Group B and 1 patient in Group C experienced IONV even in the absence of high sensory blockade and hypotension. So, these patients are more relevant to assess the efficacy of study drugs rather than patients who experienced IONV along with high level ($\geq T_5$) of sensory blockade, as these emetic symptoms in such patients can be controlled by managing the hypotension.

In our study 73.33% patients in Group A (receiving Ondansetron 4 mg) were free of emetic symptoms.Similarly, 70% patients in Group B (receiving Dexamethasone 8 mg), and 63.33% patients in Group C (receiving Ondansetron & Dexamethasone combination) were symptom free (Table 12).There was no statistically significant difference between the groups (p=0.696) in prevention of IONV.FazalWadood et al[21] (2014) while comparing the efficacy of Ondansetron alone and Ondansetron plus Dexamethasone for prevention of PONV found no statistically significant difference (p=0.09) between patients receiving Ondansetron 4mg and Ondansetron 4mg + Dexamethasone 8 mg which is in corroboration with our study. DemirhanA et al[22] also found no significant difference between the antiemetic efficacy of Ondansetron, Dexamethasone and the combination of both agents.

Olaondo et al[23], Ashwani Kumar et al[24] and Shahryar Sane et al[25] found that combined use of Dexamethasone and Ondansetron seems to increase the antiemetic efficacy than the single agent used alone, although they have not given any specific reason for their findings.But in our study there was no statistically significant difference between the groups as the incidence of emetic symptoms in Group A was 26.67%, in Group B was 30% and in Group C was 36.67%(p=0.696).

Although previous studies[26,27] reported many adverse effects of the study drugs, we observed transient headachein 1 patient from Group A (Ondansetron group) and in 2 patients from Group C (Ondansetron & Dexamethasone combination group), while it did not occur in any of the patients in Dexamethasone group (group B). This was an indicator that neither single dose use of Dexamethasone or Ondansetron did cause an increase in the side effect profile nor their combined use increased the side effects of each drug and was well tolerated by the patients.

In our study, we tried to avoid the potential adverse effects of the study drugs on the fetus by administering study drugs IV immediately, after clamping of the umbilical cord, though it was also a limiting factor of the present study and probably explains the occurrence of IONV in considerable percentage of cases in each group.

Another limiting factor may be the insufficient intra operative observation period to identify the difference between the antiemetic efficacy of Ondansetron and Dexamethasone alone with that of the combination of the two drugs.

5. Conclusion

Single dose 4 mg Ondansetron or 8mg Dexamethasone given intravenously are both effective agents for the control of post-delivery IONV in caesarean section under spinal anaesthesia, however, the combined use of these agents is no better than both used alone neither in terms of efficacy nor side effect profile. Further randomized, controlled trials with a larger sample size and longer study duration extending to postoperative period are needed to clarify the efficacy of these agents in the control of post-delivery IONV.

Table 1: Demographic data of the patients

	Ondansetron Group (Group A)	Dexamethasone Group (Group B)	Combination Group (Group C)
Age (years)	27.97±5.86	28.50±5.49	28.76±5.11
Weight (Kg)	61.23±5.26	61.97±3.79	62.90±3.83
Height (cm)	147.03±13.78	148.13±14.07	150.26±11.45
ASA I : ASA II	26:4	26:4	25:5
Gestational age (wks)	37.6±6.34	37.65±9.24	37.87±8.10
Multiparous (%)	3(10%)	4 (13.3%)	3(10%)

Values are expressed as mean ± SD, numbers or numbers (%) of patients.

Table 2: Operative management

	Ondansetron Group (Group A)	*Dexamethasone Group (Group B)*	*Combination Group (Group C)*
Total Operation time (min)	48.73±3.28	48.07±3.27	48.63±3.25
I-D time (min)	3.48±0.75	3.43±0.79	3.53±0.95
U-D time (sec)	35.00±7.19	35.27±7.38	34.67±8.80
No. of patients that had hypotension who required Ephedrine (%)	4(13.3%)	3 (10%)	2 (6.7%)
Peak sensory block height T_4 (%)	16 (53.3%)	19 (63.4%)	20 (66.6%)

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Values are expressed as mean ± SD, numbers (%) of patients.
I-D time: time from skin incision to delivery of fetus, U-D time: time from uterine incision to delivery of fetus.

Table 3: Association of hypotension and peak sensory block height with IONV

		Ondansetron Group (Group A)	*Dexamethasone Group (Group B)*	*Combination Group (Group C)*
IONV associated with Hypotension		4	3	2
IONV without Hypotension		4	6	9
IONV associated with high sensory blockade	With hypotension	4	3	2
	Without hypotension	2	4	8
IONV even in absence of high sensory blockade and hypotension		2	2	1

Values are expressed as numbers of patients.

Table 4: Incidence of intra-operativeemetic symptoms

	Ondansetron Group (Group A)	*Dexamethasone Group (Group B)*	*Combination Group (Group C)*	*Chi square*	
				χ2	*P value*
No symptoms	22 (73.33%)	21(70%)	19 (63.33%)	0.726	0.696
Incidence of nausea	8 (26.67%)	9 (30%)	11 (36.67%)	0.726	0.696
Incidence of retching	7 (23.33%)	5 (16.67%)	6 (20%)	0.417	0.812
Incidence of vomiting	3 (10%)	3 (10%)	2 (6.67%)	0.274	0.872

Values are expressed as numbers (%) of patients.

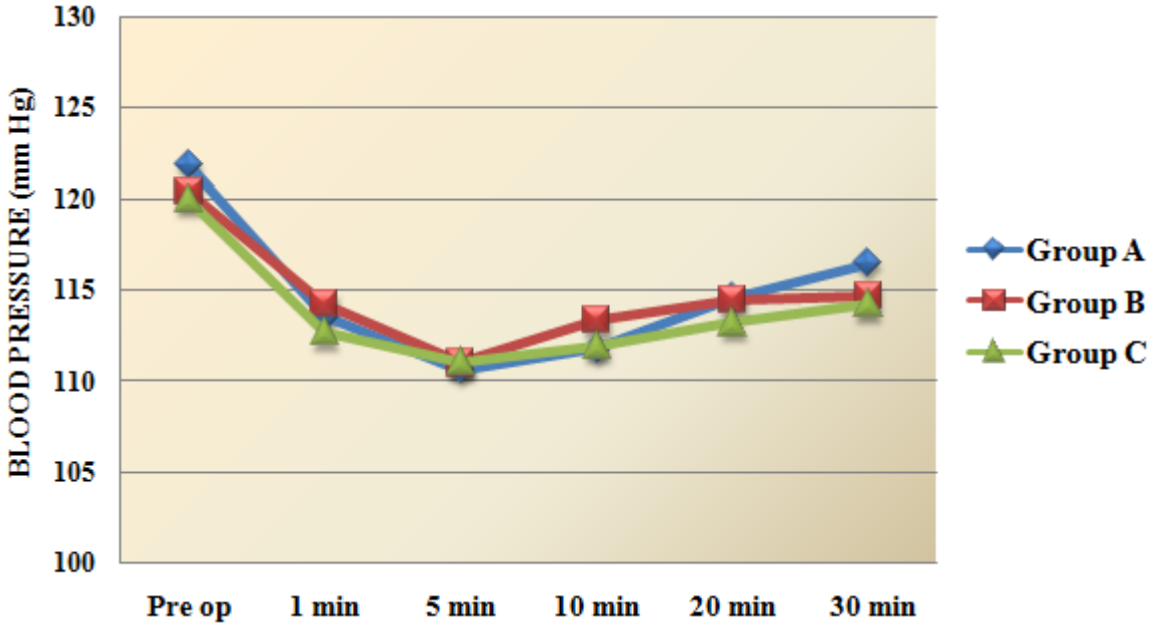

Figure 1: Diagram showing changes in average SBP with time in different groups

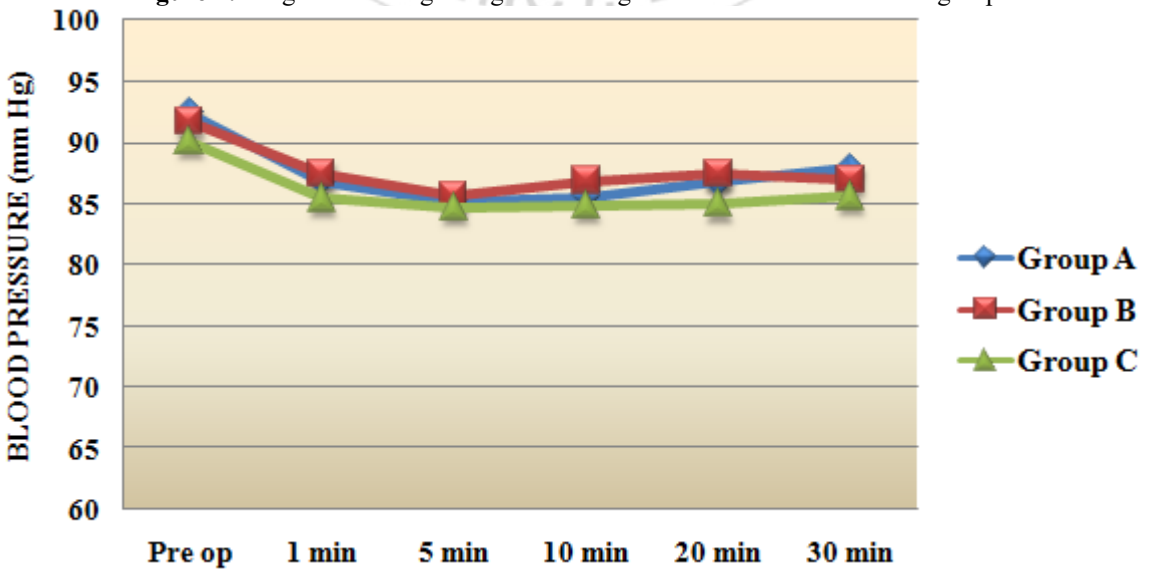

Figure 2: Diagram showing changes in average MAP with time in differentgroups

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