Original Research Paper

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"COMPARATIVE CLINICAL STUDY OF THE EFFECT OF INTRAVENOUS ONDANSETRON AND GRANISETRON ON SPINAL INDUCED HEMODYNAMIC CHANGES AND SHIVERING IN PATIENTS UNDERGOING CESAREAN SECTION UNDER SPINAL ANESTHESIA."

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ABSTRACT **Background :** Spinal anesthesia in LSCS may result in different complications of which hypotension and bradycardia are of particular concern. Activation of Bezold Jarish Reflex (BJR) and increased baroreceptor activity may lead to bradycardia & hypotension. BJR can be attenuated by attenuating receptors involved in it i.e. 5-hydroxytryptamine3 (5-HT3,serotonin). Attenuation of serotonin receptors also helps in controlling post-anesthesia shivering.

AIM:

Material and Method: 90 patients of ASA grade I/II were randomized into 3 groups (n=30) as GroupA, B, C receiving Ondansetron 8 mg I/V, Granisetron 1 mg I/V & Normal Saline 10 ml I/V respectively, 5 minutes before spinal anesthesia. Hemodynamic data and shivering scores were recorded intraoperatively.

Result: Hemodynamic stability in the intraoperative period was better with granisetron as compared to ondansetron and control group. Hemodynamic stability was better with ondansetron as compared to control group. Granisetron was better than ondansetron in prevention of post anesthesia shivering after spinal anesthesia.

Conclusion: Our data suggested that although both Granisetron 1 mg I/V and Ondansetron 8 mg I/V were effective in controlling hypotension and shivering, Granisetron showed to have a better control over the hemodynamic stability and shivering as compared to ondansetron.

KEYWORDS : intravenous ondansetron and granisetron, hemodynamic changes, shivering, spinal anesthesia

INTRODUCTION:

Spinal anesthesia is the most practiced amongst all regional techniques. It may result in different complications, particularly hypotension and bradycardia which may be deleterious to both partiurent and baby[1,2]. Hypotension caused by subarachnoid block may result in nausea and vomiting in partiurent and apnea in baby, especially in patients reporting for emergency LSCS (60-100%)[3]. Relative dominance of parasympathetic system, activation of Bezold Jarish Reflex (BJR) and increased baroreceptor activity may lead to bradycardia and some degree of hypotension. Among them, BJR is predominantly responsible for profound drop in blood pressure and heart rate and it can be attenuated. The chemoreceptors involved in BJR respond to 5-hydroxytryptamine3 (5-HT3,serotonin),which are located peripherally as cardiac chemoreceptors on the intracardiac vagal afferents and centrally in the chemoreceptor trigger zone (CTZ)[4]. Ondansetron and Granisetron being selective 5-HT3 antagonists, by blocking the binding of 5HT3 to its receptors, blocks the BJR during and after surgery thereby attenuating bradycardia and further expansion of peripheral vessels leading to increased venous return to the heart, thereby prevents hypotension induced by spinal blockade[5,6].

Prolonged impairment of autonomic thermoregulatory control under anesthesia along with the cold environment of operating rooms and cold infusion fluids, contributes to a fall in core body temperature, and causes shivering. Post Anaesthesia Shivering (PAS) makes patient uncomfortable and produces artifacts in monitors such as ECG, NIBP and peripheral O_2 saturation (SpO_2) and increases heart rate, cardiac output, oxygen consumption by 5-fold , metabolic rate by 600% and post-operative pain[7,8,9]. Perioperative hypothermia and shivering are usually prevented by non pharmacological measures such as fluid warmers, maintaining ambient operating room temperature, warming blankets, surgical drapes, and active circulating water mattress. Pharmacological management includes opioids e.g.,pethidine, pentazocine and tramadol, alpha 2 agonist e.g.,clonidine, dexmedetomidine, ketamine and others such as doxapram, neostigmine and magnesium sulfate have been tried[10]. Ondansetron and granisetron are selective 5HT3 antagonists and they lower the human thermal set range, which reduces shivering and discomfort associated with postoperative hypothermia.

Present study evaluated the comparative effect of ondansetron and granisetron in prevention of spinal induced hemodynamic changes as a primary outcome and reduction in shivering as a secondary outcome.

MATERIAL AND METHOD:

The ethics committee approved the present prospective, double blinded, randomized controlled study which was carried out on 90 patients aged 20-40years of ASA grade I and II, scheduled for LSCS under spinal anesthesia in the Department of Anesthesiology, J.A Group of Hospitals of G.R. Medical College, Gwalior (M.P). Patients were excluded if they refused to participate, had any contraindications to subarachnoid block, hypertensives, hypersensitivity to study drugs or on Selective Serotonin Receptor Antagonists or migraine medications.

Well informed written consent was taken from eligible patients. Demographic information were collected, physical examination was performed and a standardized anesthesia regimen was followed.

In the preoperative room, nearly 500ml crystalloid (Ringer's lactate) was infused intravenously after insertion of intravenous 18 gauge cannula in non-dominant hand. On arrival in the operating room, standard monitoring ECG,NIBP,spO2 connected and baseline vital parameters were recorded.

Patients were randomly assigned into three equal groups; Group A received 4 ml (8 mg) Inj. Ondansetron diluted upto 5 ml with normal saline, Group B received 1 ml (1 mg) Inj. Granisetron diluted upto 5 ml with normal saline and Group C received 5 ml normal saline (NS), all the study medications were given slowly intravenously over 10 seconds, 5 minutes before spinal anaesthesia. Under all aseptic precautions, cleaning, painting and draping was done in left lateral position. Subarachnoid block was induced with 23 gauge Quincke spinal needle in L3-L4 intervertebral space. After confirming free flow of cerebrospinal fluid 2.5ml (12.5mg) of Inj. hyperbaric bupivacaine (0.5%) was injected intrathecally. Patient was made supine and level was checked. Close watch was kept on all vitals.

Supplemental oxygen was administered via facemask at 4L/min. Maintenance fluids (10ml/kg in first hour and 5 ml/kg in subsequent hours) was given at room temperature. Oxytocin was given following delivery of the fetus.

Haemodynamic data (SBP, DBP, MAP,heart rate, oxygen saturation SpO2) were recorded at 5 minutes interval in the first 30 minutes and then every 10 minutes until the end of procedure. Nausea, vomiting and shivering were recorded if present.

Rescue intravenous bolus doses of mephentermine was given if the patient becomes hypotensive (hypotension is defined as a decrease in MAP more than 20% from the baseline). Decrease in heart rate to less than 50 beats/min was treated with 0.6mg atropine intravenously.

No shivering was graded as 1, fasciculations in head and neck that was just visible as artifacts on ECG as grade 2, obvious tremors on head, neck and limbs as grade 3 and generalized tremors throughout the body as grade 4, and has been studied at different time intervals in the intraoperative period.

Vomiting episodes were treated with metoclopramide 10mg intravenously and shivering was treated with tramadol 3mg/kg intravenously.

STATISTICALANALYSIS:

The observations recorded in the three groups were tabulated using EXCEL. Statistical analysis was carried out using ANOVA test, paired t-test, unpaired t-test and chi-square test by SPSS 20.0 software. p value >0.05 was taken to be statistically insignificant and p value <0.05 was taken as statistically significant.

OBSERVATION AND RESULTS:

A total of 90 patients were enrolled in this study, and were divided into three equal groups. The three groups were comparable with respect to age, weight, height, ASA grade and duration of surgery.

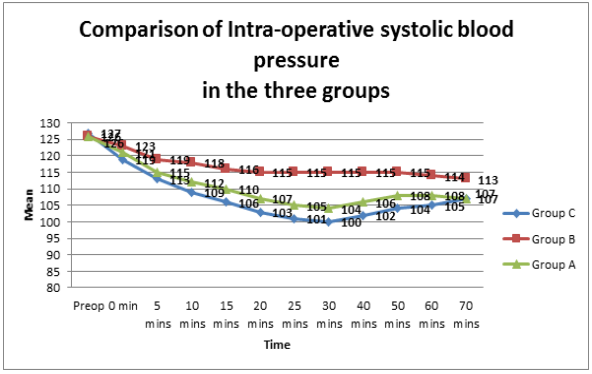
In all the groups, there were significant fall in SBP,DBP and MAP from the pre-op basal value ($p < 0.05$) at all time intervals, with significant less fall in SBP, DBP and MAP in group B and A as compared to group C at most of the time intervals, with group B having least fall in SBP,DBP and MAP.

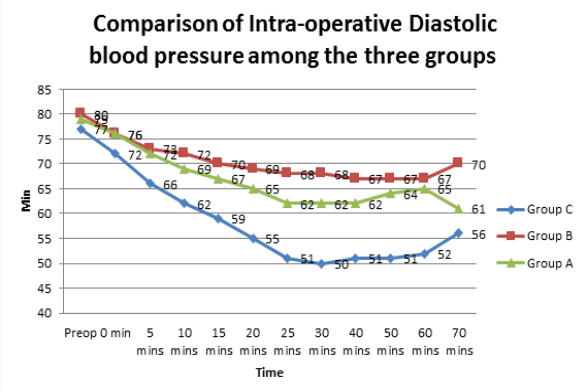
In group C 28 patients experienced shivering, in group B 9 patients experienced shivering while in group A 18 patients experienced shivering showing that granisetron and ondansetron are effective in prevention of post anaesthesia shivering than normal saline with grainsetron being more effective.

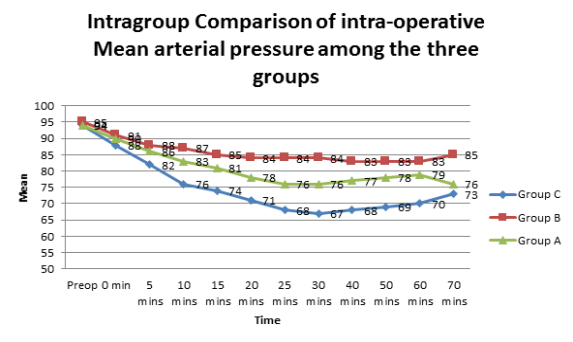
In group C 28 patients experienced nausea, in group B none of the patient experienced nausea while in group A 3 patients experienced nausea showing that although granisetron and ondansetron are effective in prevention of nausea, grainsetron is more effective in preventing nausea.

There were no episodes of vomiting in group A and B while 13 patients experienced vomiting in control group which shows that granisetron and ondansetron are equally effective in controlling vomiting.

None of the patient in either group experienced any adverse effects.







DISCUSSION:

Spinal anesthesia has emerged as a fast, reliable and cost effective technique of choice for lower limb surgeries. Although it prevents the risks associated with general anesthesia, but is encountered with some untowards effects, the most common being hypotension due to sympathetic block resulting in marked decrease in systemic vascular resistance.

Systemic vasodilatation, hypotension and bradycardia after spinal anesthesia also occurs as a consequence of Bezold Jarish Reflex. Mechanoreceptors of this reflex which are located in the left ventricle are activated by the decrease in the ventricular blood volume induced by spinal anesthesia.

Serotonin can activate Bezold Jarish response. 5HT3 receptors located in infracardiac vagal afferents and sympathetic neurons mediate the cardiovascular effect of serotonin – the Bezold Jarish Reflex.

Several trials were done to abolish this reflex to prevent undesired cardiovascular effects of spinal anesthesia such as hypotension. Present study is undertaken to compare the effectiveness of 5HT3 antagonists, Ondansetron and Granisetron for thr prevention of spinal induced hypotension and bradycardia due to Bezold Jarish Reflex

In our study there is significant decrease in fall in blood pressure among the groups with least fall in Granisetron group, followed by Ondansetron group and then placebo group.

Previous studies also showed similar results with Granisetron and Ondansetron.

In contrast to present study, studies conducted by **Suraj L et al[11], Battu K et al[12] and Mowafi et al[13]** observed that prophylactic administration of Granisetron had little effect on spinal induced hypotension as compared to control group.

Shekoufeh B et al[14] observed similar findings with granisetron 3 mg I/V but he recommended that regarding the results of his study and other similar studies on the effect of granisetron and ondansetron in prevention of spinal anesthesia induced hypotension in cesarean section as well as different findings for ondansetron effect, and very few studies about the effect of granisetron, it seems that further studies are required before a definite statement can be made.

Prophylactic intravenous administration of Ondansetron 4mg and Granisetron 1 mg, 5 minutes before spinal anesthesia significantly reduced severity of spinal induced hypotension in study conducted by **Mostafa et al[15]** but significant difference was not observed regarding MAP.

Although both Ondansetron and Granisetron are from the same category and have same mechanism of action but better results with Granisetron in our study may be due to difference in pharmacodynamics of the two drugs. Selectivity of granisetron on 5HT3 receptors with minimal or no affinity for other 5HT receptors and the action of Ondansetron on mixed receptors may be the reason for this difference observed.

The number of patients free from shivering at different time intervals were highest in granisetron group followed by ondansetron group.

These findings were in accordance with studies conducted by **S.P. Sharma et al[16]** and **Srinivasa R et al[17]** which showed that prophylactic

administration of ondansetron 8 mg significantly reduced shivering in patients undergoing spinal anesthesia for various surgeries.

Joseph et al[18] found out that prophylactic administration of dexmedetomidine or ondansetron effectively decreased incidence and severity of shivering after spinal anesthesia without any significant difference in their efficacies in comparison to placebo group.

Savitri et al[19] concluded that prophylactic administration of granisetron 40 μ/kg I/V is as effective as pethidine 0.4 mg/kg I/V in prevention of perioperative shivering following spinal anesthesia and it also reduces the need of antiemetics.

Limitations: We used oscillatory method for non invasive blood pressure measurements. Invasive blood pressure monitoring would have been used for more precise assessment of hemodynamic changes. Amount of blood loss was not recorded in the study. This can influence the hemodynamic profile of the patients. In our study, single dose of ondansetron and granisetron were compared. Results may vary if different doses of drugs were used. In addition, we cannot comment on the effect of ondansetron and granisetron on the incidence of bradycardia, as no patient experienced this complication in our study. Also, we did not monitor core body temperature intraoperatively.

CONCLUSION:

Both granisetron and ondansetron are safe and effective in prevention of spinal induced hypotension, when given 5 minutes before spinal anesthesia in patients undergoing lower segment cesarean section, with Granisetron 1 mg being better than ondansetron 8 mg. Granisetron is better than ondansetron in prevention of post anesthesia shivering after spinal anesthesia. Both granisetron and ondansetron are effective in reducing the incidence of nausea and vomiting with granisetron being more effective.

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