INTRODUCTION:
Neuroaxial (spinal or epidural) blockade remains the preferred choice for intra umbilical surgeries. Although spinal anesthesia has been considered the safer technique, it has many adverse effects, including hypotension, nausea, vomiting, bradycardia, and other dysrhythmias.[1] Large surveillance studies have observed the incidence of hypotension around 33% and bradycardia around 13% in nonobstetric population.[2,3] Bradycardia and hypotension are the result of altered cardiac autonomic balance and due to activation of Bezold-Jarisch reflex (BJR) [4] Animal studies have shown that the responsible receptors for the BJR are mechanoreceptors located in the heart walls which are 5HT3 in nature[5-8].

Previous studies have demonstrated that 4 mg of intravenous ondansetron can attenuate spinal anesthesia-induced reductions in systolic and mean arterial pressures[5,6]. Palonosetron, a second-generation 5-HT3 receptor antagonist has been reported to have superior anti-emetic properties and greater receptor binding affinity than classic 5-HT3 antagonists, such as ondansetron and granisetron.[6,7] Thus, we hypothesized that palonosetron might attenuate spinal anesthesia-induced hemodynamic changes differently than other classic 5-HT3 antagonists. The aim of our study was to evaluate the efficacy of pretreatment with i.v ondansetron and i.v palonosetron in attenuating the subarachnoid block induced hypotension.

MATERIALS AND METHODOLOGY:
After obtaining approval from the medical ethics committee and informed consent from all patients, this study was conducted in the department of Anaesthesiology of VSSIMSAR, Burla, from March 2015 to February 2016. The study was a randomized, double blinded, placebo controlled, prospective trial.

In a pilot study with total 30 patients, we found that to detect a mean inter-group difference of 6 mmHg in MAP after 10 mins of subarachnoid block, 23 patients per group were required for an type1-error of 0.05 and a power of study 80%. So we recruited 50 patients per group.

150 patients of ASA class I & II, between 25-50 years of age, 140-160 cm height and BMI 18.9 to 29.9 scheduled for abdominal hysterecomy under subarachnoid block, were included in the study. Patients with contraindications to subarachnoid block, with psychiatric disorders, with history of hypertension, chronic liver or kidney disease, hypersensitivity to the study drugs and local anaesthetics, taking selective serotonin reuptake inhibitors or migraine medications were excluded. Patients having surgical blood loss more than 10%, failure of subarachnoid block ( failure to achieve a MODIFIED BROMAGE SCALE 3 within 15 mins of SAB) were also excluded from the study. This nuber is 6,5 and 8 respectively for group – O, group – P and group – Respectively.

MODIFIED BROMAGE SCALE:
Grade 0 = no weakness
Grade 1 = inability to raise extended leg
Grade 2 = inability to flex knee
Grade 3 = inability to move any joint in legs.

All the studied drugs were diluted to a total volume of 10 ml with normal saline and supplied in similar syringes to the attendant anaesthesiologist (who was blinded to the studied medications) to inject them 10 min before starting the subarachnoid block over 5 mins. The same anaesthesiologist recorded the studied parameters.

The study drug was given as per the assigned group 10 mins before the spinal anaesthesia, they were infused with 500 ml of Ringer's Lactate.

Intraoperative fluid replacement was guided by “4 – 2 – 1” rule.
Intraoperative monitoring done by monitoring SBP,DBP,MAP by noninvasive oscillometric method at 5 mins interval, SPO2, heart rate with a 5lead ECG[Monitor used was STAR 55 Multipara monitor by Skanray Technologies Pvt.Ltd]

Reduction in MAP > 20% from baseline was treated with bolus of i.v ephedrine 6 mg, HR < 50/min was treated with i.v atropine 0.6mg>Total duration of surgery, total dose of ephedrine and atropine required were noted. Incidences of intraoperative QT interval prolongation(>0.4sec) and incidences of nausea, shivering in postoperative6

VARIABLES | “O” | “P” | “S” | P value |
--- | --- | --- | --- | --- |
AGE(years) | 43.45 ± 6.40 | 45.30 ± 5.88 | 44.38 ± 6.06 | 0.783 |
BMI (kg/m2) | 26.8± 2.80 | 28.06 ± 1.05 | 27.50 ± 4.29 | 0.484 |
ASA(1/I) | 26/18 | 31/15 | 27/15 | 0.903 |
observed at 5min (P=0.000) & 10 min (P=0.001). Comparing group "O" with group "P", a significant difference was 5min to 30 min in comparison with groups "P" & "O". While Group S had significantly lower MAP throughout at all interval from (mmHg)

**Fig 1:** The greatest in the S group decrease in MAP was seen in all groups compared with their basal MAP. After establishment of spinal anesthesia significant difference between the given time and the basal MAP in each group. *Significant between the given time and the basal MAP in each group; †Significant compared with the control group; NOTE:

**TABLE 2 : COMPARISON OF MEAN ARTERIAL BLOOD PRESSURE (mmHg)**

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>&quot;O&quot;</th>
<th>&quot;P&quot;</th>
<th>&quot;S&quot;</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASAL</td>
<td>93.40 ± 4.806</td>
<td>92.8 ± 5.284</td>
<td>92.15 ± 5.779</td>
<td>0.771</td>
</tr>
<tr>
<td>5min</td>
<td>90.45 ± 2.564*#</td>
<td>80.55±2.564*##</td>
<td>75.35 ± 3.884#</td>
<td>0.000</td>
</tr>
<tr>
<td>10 min</td>
<td>85.50±5.405*#</td>
<td>78.55±5.326*##</td>
<td>73.05 ± 6.320#</td>
<td>0.001</td>
</tr>
<tr>
<td>15min</td>
<td>82.45 ± 5.137*#</td>
<td>76.70±4.105*##</td>
<td>73.35 ± 6.055#</td>
<td>0.032</td>
</tr>
<tr>
<td>20 min</td>
<td>81.75±3.420*##</td>
<td>79.55 ± 2.982*#</td>
<td>76.30 ± 4.889#</td>
<td>0.000</td>
</tr>
<tr>
<td>25 min</td>
<td>82.25±3.127*##</td>
<td>81.25 ± 2.489*#</td>
<td>77.25 ± 4.701#</td>
<td>0.000</td>
</tr>
<tr>
<td>30 min</td>
<td>85.05±3.677*#</td>
<td>83.25 ± 2.124*##</td>
<td>80.70 ± 3.570#</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**NOTE:**
- *Significant compared with the control group;
- †Significant compared with group O;
- #Significant between the given time and the basal MAP in each group.

There was no significant difference between the groups regarding their basal MAP. After establishment of spinal anesthesia significant decrease in MAP was seen in all groups compared with their respective basal MAP, the least decrease occurring in the O group and the greatest in the S group (Table 2, Fig 1).

**Fig 1: COMPARISON OF MEAN ARTERIAL BLOOD PRESSURE (mmHg)**

Group S had significantly lower MAP throughout at all interval from 5min to 30 min in comparison with groups "P" & "O". While comparing group "O" with group "P", a significant difference was observed at 5min (P<0.000) & 10 min (P<0.001).

**TABLE 3: COMPARISON OF VASOPRESSOR NEED AND SIDE EFFECTS**

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>&quot;O&quot; GROUP</th>
<th>&quot;P&quot; GROUP</th>
<th>&quot;S&quot; GROUP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose of Ephedrine (mg)</td>
<td>6.11 ± 1.22*</td>
<td>9.67 ± 4.38*#</td>
<td>13.71 ± 10.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Time for 1st rescue vasopressor (mins)</td>
<td>8.7±3.52*</td>
<td>6.1 ±2.51*</td>
<td>3.42 ± 2.12</td>
<td>0.013</td>
</tr>
<tr>
<td>Nausea</td>
<td>3(6.81)*</td>
<td>0(0)*</td>
<td>20(47.61)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Shivering</td>
<td>15(34.09)*</td>
<td>13(28.88)*</td>
<td>19(45.23)</td>
<td>0.039</td>
</tr>
<tr>
<td>QTc interval</td>
<td>8(18.18)*</td>
<td>1(2.22)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Difference in heart rate among three groups at no time was significant (Fig2). Significant difference for ephedrine as a rescue vasopressor was seen among the groups, with the greatest number of patients being in group S and the smallest in group O. The time to first ephedrine requirement was statistically higher in group S but no statistical difference was observed among group O and group P (P=0.09). The incidence of postoperative nausea and shivering was highest in S group, followed by O group and least in group P (Table 3).

**DISCUSSION:**

Sympathetic blockade from spinal anaesthesia decreases systemic vascular resistance and induces peripheral pooling of blood leading to hypotension. Mechanoreceptors in the heart wall that trigger the Bezold-Jarisch Reflex, participate in systemic responses to hyper and hypo-volaemia(9,10). In response to hypovolaemia due to decreased venous return following subarachnoid block, stimulation of cardiac mechanosensory receptors in the left ventricle induces this Bezold-Jarisch reflex which results in bradycardia, vaasodilation and hypotension(9-11). Another proposed mechanism is activation of chemoreceptors located in the vagal nerve ending, in response to decreased blood volume by serotonin(10,12), which is released from activated thrombocytes in a scenario of increased venous stasis after subarachnoid block(12,13,14). These receptors are 5-HT3 in nature and structurally G protein coupled, ligand-gated fast-ion channels and stimulation results in increased efferent vagal nerve activity(10), frequently producing bradycardia and hypotension(15). Several studies have confirmed the efficacy of first generation serotonin antagonists like Ondansetron(5), Granisetron (16) and Ramosetron (17) for attenuation of spinal induced hypotension.

Ondansetron, a carbazole derivative, is a competitive antagonist at 5-HT3 receptors. It also has affinity for other 5-HT receptors, adrenergic, histaminic, dopaminergic or opioid receptors(18,19). Palanosetron, an isoquinoline derivative, has allosteric binding to the 5HT3 receptors and unlike ondansetron has no affinity for other receptors. These functional and structural differences contribute to its longer duration of action and also the different effect of palanosetron, on haemodynamic changes after spinal anesthesia in comparison to classic 5-HT3 antagonists (20).

Owczuk et al. in a mixed group of patients aged 20–70 years, found that ondansetron 8 mg decreased the incidence of bradycardia and hypotension after spinal anaesthesia(21). Sahoo et al. observed i.v.
ondansetron 4 mg given before spinal anaesthesia can attenuate decreases in blood pressure in parturients undergoing elective caesarean section (5). So, we choose the lower effective dose of ondansetron, i.e., 4 mg i.v. for our study. Jung Ju Choi et al. also studied role of Palanosetron 75 microgram i.v for attenuation of spinal induced hypotension given 10 mins before the subarachnoid block, which is similar to our study.

Many of us to administer ondansetron as a bolus peripheratively without knowing that ondansetron 4 to 8 mg iv should be administered over 2 to 5 min and certainly not as a bolus or in less than 30 sec(9). So, we administered all of our study drugs as a slow i.v injection over 5 mins.

G.Hocking et al. stated that in most circumstances, 3ml of intrathecal hyperbaric bupivacaine 0.5% appears to stop spreading 20–25 min after injection. However, marked changes in patient posture up to 2 h after injection can lead to significant changes in extent of the block and probably represents bulk movement of CSF still containing significant concentrations of local anaesthetics(23). As we included patients undergoing surgery throughout in supine position only, we observed MAP and HR upto 30 mins.

Sahoo et al. (5) found ondansetron to be effective for attenuation of spinal induced hypotension in parturients undergoing caesarean section, which is consistent with our study finding. But, we found palanosetron also to be effective for this purpose as compared to the placebo group, as opposed by Jung Ju Choi et al.(22), who found that palanosetron might be ineffective in attenuating spinal induced hypotension during orthopedic surgery. We also found that ondansetron is more effective than palanosetron for the attenuation of hypotension following subarachnoid block.

In our study, there was no significant difference in heart rate among the three groups. Shrestha et al. (16) also observed the same while comparing ondansetron and granisetron for attenuation of spinal induced hypotension.

Jabalalemi et al. (24) concluded that the most effective method for prevention of hypotension was administration of crystalloid preload plus ephedrine. Rout et al. (25) showed that incidence of hypotension after spinal anaesthesia was reduced in patients who received crystalloid preload with 20ml/kg crystalloids infused 30 mins before. Adigun et al. (26) found that ephedrine at 6 mg effectively restored both the systolic and the diastolic blood pressure during elective caesarean section under spinal anaesthesia. So, we preloaded every patient with 500ml of Ringer’s Lactate 30 mins before subarachnoid block and choose ephedrine 6mg i.v bolus as rescue vasopressor.

Our study found that both the studied drugs reduced the ephedrine requirement as shown by Rashad et al. (27) who compared ondansetron and granisetron for attenuation of spinal induced hypotension. We also found that time for first dose of ephedrine as well as total dose of ephedrine was less in patients receiving premedication with these drugs. Ondansetron was found to be superior to Palanosetron for attenuation of spinal induced hypotension.

The limitations of the study included the result of this study may not be extrapolated to patients with high risk group, obstetric patients, emergency surgeries or upper abdominal surgeries under subarachnoid block. In addition to that, we also did not studied the effect of these drugs on sensory and motor block and postoperative pain.

REFERENCES: