Study Of Comparative Effects Of Oral Clonidine Vs Oral Diazepam Pre-Medication On The Extent And Duration Of Sensory Blockade In Patients Undergoing Vaginal Hysterectomy Under Spinal Anaesthesia

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Citation

Abstract
Clonidine stimulates alpha 2 adrenergic inhibitory neurons in medullary vasomotor centre which decreases sympathetic outflow. Decreased sympathetic nervous system activity is manifested as decreases in systemic blood pressure, heart rate and cardiac output. Our results show that there was significant difference in the time of onset of anaesthesia, which coincides with the study done by Herbhej singh, George, Y .Gaines and Paul .F.White, in which they concluded that oral Clonidine shortened the onset time of tetracaine’s sensory block & prolonged the duration of sensory & motor block. There are more studies, which also show that oral clonidine premedication prolong the sensory as well as motor blockade from Lignocaine & Tetracaine spinal anaesthesia. The antinociceptive effect produced by the orally administered α2- adrenergic agonist is mainly caused by direct spinal activation due to spread of the drug via the systemic circulation into the spinal cord. Neuraxial Clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimuli. Clonidine modifies function of K channels in the CNS causing cell membrane hyperpolarization which decreases anaesthetic requirements.

INTRODUCTION
Clonidine stimulates alpha 2 adrenergic inhibitory neurons in medullary vasomotor centre which decreases sympathetic outflow. Decreased sympathetic nervous system activity is manifested as decreases in systemic blood pressure, heart rate and cardiac output. Our results show that there was significant difference in the time of onset of anaesthesia, which coincides with the study done by Herbhej singh, George, Y .Gaines and Paul .F.White, in which they concluded that oral Clonidine shortened the onset time of tetracaine’s sensory block & prolonged the duration of sensory & motor block. There are more studies, which also show that oral clonidine premedication prolong the sensory as well as motor blockade from Lignocaine & Tetracaine spinal anaesthesia. The antinociceptive effect produced by the orally administered α2- adrenergic agonist is mainly caused by direct spinal activation due to spread of the drug via the systemic circulation into the spinal cord. Neuraxial Clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimuli. Clonidine modifies function of K channels in the CNS causing cell membrane hyperpolarization which decreases anaesthetic requirements.

METHODS
After obtaining approval from institutional ethics committee and written informed consent from all patients, this prospective and randomized study was carried out in 60 ASA grade I and II patients scheduled for vaginal hysterectomy in Dept of Anesthesiology, TNMC and Nair Hospital, Mumbai.

All Patients were assessed on the previous day of the surgery and patient satisfying the inclusion criteria were included in the study.

Procedure, its complications and alternative methods were explained to the patient in his own language and patients consent was taken.

Criteria for inclusion:
1. Age : 18-60 yrs
2. Weight : 40-70kg
3. ASA : Grade I & II
4. Conscious Co- operative patient

Criteria for exclusion:

1. Consent not available
2. Age <18 or >60 yrs
3. Weight < 40 or >70 kg
4. ASA grade III, IV, & V
5. Any contra – indication to spinal anaesthesia (Absolute or relative)
6. Non – co operative patient
7. Patients who are on antihypertensive or any sedative or on any antipsychotic drugs.

Base line record of pulse rate (by cardio scope), Blood pressure (by sphygmomanometer and NIBP), SpO\textsubscript{2} (by pulse oximetry) and respiratory rate were taken as Tbase.

In our study groups age and also physical parameters like weight and height were comparable among the two groups. There was no significant difference in preoperative parameters like pulse rate, respiratory rate and mean arterial pressure between the two groups.

The patients were randomly divided in two groups- Group C & Group D of 30 each. Patient in Group C received Clonidine 4-5mcg/kg oral premedication and patients in Group D received Diazepam 0.20-0.25mg/kg oral premedication 90 minutes before spinal anaesthesia.

Blinding was done by packing the three tablets of 100mcg each of clonidine and three tablets of 5mg each of Diazepam in silver foil, subsequently the packets were placed in small plastic pouches and were numbered randomly as per computer generated number. Person dispensed the drug and person observed did not know the content of the packet. Decoding of packets was done at the end of the study.

After preloading, under all aseptic precautions with patient in sitting position, spinal anaesthesia was given with 23 G Quincke needle in L3-4 interspace with 2.5 cc of 0.5 % Bupivacaine and 25mcg Fentanyl. Patient was made to sit for 2 minutes after subarachnoid block and then made supine. Onset, duration, height of sensory block, time taken to reach highest level, and the time taken for two segment regression, time taken for four segment regression and the time when patient asks for analgesia were monitored and noted sensory blocked were evaluated by pinprick sensation.

Onset of anaesthesia was considered as appearance of analgesia at L1.

Duration of analgesia was considered as the time between onset and the time when patient asked for analgesia.

After operation patient were observed till sensory level weaned upto L1 and patient remained in the Gynaec recovery till patient received first dose of analgesia and that time was noted.

RESULTS

The mean age in Group C was 50.93 years with standard deviation of 5.343 years and that in Group D was 50.93 years with standard deviation of 4.877 years. The groups were comparable according to age, weight and height.

**Figure 1**

Table 1: Comparison of Mean Age, Weight and Height

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE(yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>30</td>
<td>50.93</td>
<td>4.877</td>
</tr>
<tr>
<td>CLONIDINE</td>
<td>30</td>
<td>50.93</td>
<td>4.343</td>
</tr>
<tr>
<td>WT(kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>30</td>
<td>53.30</td>
<td>6.804</td>
</tr>
<tr>
<td>CLONIDINE</td>
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<td>53.97</td>
<td>5.852</td>
</tr>
<tr>
<td>HEIGHT (cm)</td>
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<td>159.93</td>
<td>5.959</td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>30</td>
<td>157.40</td>
<td>4.256</td>
</tr>
</tbody>
</table>

Mean arterial pressure (MAP) was significantly lower in Group C as compared to Group D. Similar trends in falling Mean and Diastolic blood pressure are seen as with systolic blood pressure and the results were significant with lower blood pressure with Clonidine as compared to Diazepam.
There was also a significant difference in time taken to reach highest sensory level in Group C and D. The mean time taken to reach highest level for Group C was 18.97 min with standard deviation of 6.239 min and that for Group D was 24.40 min with standard deviation of 6.026 min. (p value 0.001).

The mean time taken for two segment regressions in Group C was 103.87 min with standard deviation of 12.754 min and that with Group D was 90.53 mins with standard deviation of 17.419 min. (p value 0.001)

The mean time taken for four segment regressions in Group C was 140.67 min with standard deviation of 27.753 min and that with Group D was 122.83 min with standard deviation of 24.589 min. (p value 0.001)

The mean time when patient asks for analgesia in Group C was 286.67 min with standard deviation of 79.017 min and that with Group D was 114.30 min with standard deviation of 15.234 min. The difference was significant. (p value 0.001)

The time for surgery with Group C was 95.00 min with standard deviation of 6.823 min and that for Group D was 96.17 min with standard deviation of 7.391. The difference was non-significant. (p value 0.528)

**DISCUSSION**

Clonidine is rapidly absorbed after oral administration. Peak plasma concentration is rapidly achieved in 60-90 mins is highly lipid soluble, easily crosses blood–brain barrier and therefore may interact with alpha–adrenergic receptors at spinal and supraspinal sites within the central nervous system. In addition previous studies suggest that clonidine may also affect peripheral sensory nerves as a sole agent or in combination with local anaesthetics.

Clonidine has been demonstrated to inhibit neurotransmission in both A-delta and C nerve fiber which are theorized to mediate pin-prick, surgical pain. Finally Clonidine has been demonstrated to potentiate inhibitory effects of local anaesthetics on C fiber activity. Therefore Clonidine may exert its effects within the central nervous system at peripheral nerve roots by potentiation of effects of local anaesthetics.

We have compared our results with previous study which also showed the same results. The primary mechanism of Clonidine analgesia is via a non–opoid spinal action on central alpha 2 adrenergic receptor in the dorsal horn of...
spinal cord.

The analgesic effect of clonidine is mediated by the same central alpha2 adrenoreceptors that mediate its hypotensive effects. Clonidine added to local anaesthetics enhances the effects of local anaesthetics on C fiber action potentials.

We have also studies showing that prolongation of sensory anaesthesia when clonidine and fentanyl was combined was solely due to clonidine 1.

Our results showed that premedication with 4-5 μgm/ kg oral clonidine premedication prolongs the duration of sensory blockade by Bupivacaine and Fentanyl spinal anaesthesia as compared to that of 0.20-0.25mg/kg Diazepam oral premedication, and this results agree with the study done in 1992, by Kouechi Ota, Akiyoshi Namiki, Yoshihito Ujike & Ikuko Takahashi 3. They concluded that prolongation of tetracaine sensory analgesia may be produced by premedication with oral clonidine premedication may have a distinct advantage because of its capacity to prolong sensory blockade & its potent sedating properties.

We added fentanyl to bupivacaine to determine its effect on anesthesia quality, and sensory block. The administration of intrathecal opioids may provide benefits in augmenting sensory level, but also carries a risk of respiratory depression but we had taken care of it by watching respiratory rate and saturation.

Our results showed that there was significant difference in the time of onset of anaesthesia, which coincides with the study done by Herbshej singh, George, Y. Gaines and Paul .F. White 1, in which they concluded that oral clonidine shortened the onset time of tetracaine’s sensory block & prolonged the duration of sensory & motor block.

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The dose of clonidine (4-5μgm/ kg) & time Interval (90min before spinal anaesthesia) were decided according to previous studies regarding safety of clonidine premedication in elderly & dose response studies of oral clonidine for tetracaine spinal anaesthesia.

Thus in the end as per results from our comparative study of effect of oral clonidine versus oral diazepam premedication on sensory blockade by intrathecal bupivacaine 0.5%(2.5ml) and fentanyl 25mcg, showed that clonidine hastens the onset of action, and reduces the time taken to reach highest sensory level. Clonidine also prolongs the total duration of sensory block by increasing the time for 2 and 4 segment sensory regression, also there was significant extension of analgesia.

Although few incidences of hypotension, bradycardia, nausea, vomiting and pruritus (Diazepam) were noted with both the groups, the difference was not statistically significant.

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