Clinical evaluation of clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block

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ABSTRACT
BACKGROUND: To evaluate the efficacy and safety of clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus blockade in respect to onset, peak, duration of sensory-motor blockade, duration of effective analgesia, total dose and frequency of rescue analgesics, sedation, effect on hemodynamic variables.

METHODS AND MATERIAL: After institutional review board approval and informed written consent, present study was carried out in 120 patients of American society of anaesthesiology physical status I-II, aged 20–60 years of either sex scheduled for upper limb orthopaedic surgeries. Patients were randomized into two groups of 60 patients each. Group R received ropivacaine 0.5% 30ml + 0.6ml normal saline and group RC received ropivacaine 0.5% 30ml + 0.6ml (90μg) clonidine in supraclavicular brachial plexus block under guidance of nerve locator. Sensory-motor characteristics, post-operative analgesia, hemodynamic, sedation and complication were recorded. RESULTS: Sensory onset (11.16±02.30 vs 9.70±01.53), peak (18.18±03.47 vs 13.78±01.94), duration (475.50±31.105 vs 672.70±125.48) and motor onset (16.20±03.95 vs 14.51±02.30), peak (37.56±03.03 vs 22.85±03.94), duration (418.67±35.39 vs 548.00±34.43) minute was observed in group R and group RC respectively. (P<0.05) Duration of analgesia was (584.6±34.41 vs 801±80.46) minutes respectively in group R and RC. (P<0.05) Sedation score was significantly higher in group RC compared to group R. Except bradycardia in 3% patients in group RC, no other complication was noted in either group. (P<0.05) CONCLUSION: 90 μg clonidine added to ropivacaine in supraclavicular brachial plexus block is effective and safe in improving the quality of blockade, post-operative analgesia with adequate sedation as compared to ropivacaine.

Key-words: Clonidine, Ropivacaine, Supraclavicular brachial plexus block, Postoperative analgesia

INTRODUCTION
Brachial plexus block is a safe, reliable, economical technique, with the advantage of prolonged post-operative analgesia. It remains the choice of anaesthesia for upper limb orthopedic surgery. Ropivacaine has lower lipid solubility and have produced less central nervous system toxicity and cardiotoxicity than bupivacaine for which it is gaining popularity over bupivacaine for peripheral nerve blocks. Adjuvants like dexamethasone, tramadol, midazolam, clonidine, dexmedetomidine have been used in regional blocks to prolong the intraoperative as well as postoperative analgesia. Clonidine, an imidazole, α2 adrenergic agonist, provides a substantial antinociceptive effect by acting on α2 receptor and achieves effective prolongation of analgesia when used as an adjuvant to local anaesthetic agents. Clonidine is increasingly being used in the periooperative period because of its ability to reduce the requirements for anesthetic and analgesic agents. We evaluated the effect of clonidine as an adjuvant to ropivacaine on various characteristics of supraclavicular brachial plexus block.

MATERIAL AND METHODS
Ethics and study design: This prospective, randomized, double-blind, controlled study was conducted in 120 patients after the permission from Institutional Review Board (IRB) (IRB No. 443/2014), Govt. Medical College, Bhavnagar and obtaining written informed consent from the patient. The study was...
registered in Clinical Trial Registry of India (CTRI/2015/10/006321) and carried out as per guidelines of good clinical practice. Study was conducted in the Department of Anaesthesiology, Government Medical College and Sir Takhatshinhji General Hospital, Bhavnagar, Gujarat.

**Recruitment criteria:** This clinical trial was carried out in 120 patients aged 20 to 60 years of both gender, American society of anaesthesiology physical status (ASAPS) I and II, scheduled for elective upper limb orthopaedic surgery. After thorough preanaesthetic evaluation patients with any major systemic illness, peripheral neuromuscular disease, coagulation disorder, drug allergy, psychiatric illness, antenatal females, lactating mother, inadequate effect requiring supplementation were excluded. Patients were randomly allocated by sealed envelope method into two groups of 60 patients each. Each group received either 0.5% ropivacaine (30 ml) with 0.6 ml of normal saline (Group R) or 0.5% ropivacaine (30 ml) with 0.6 ml (90 μg) of clonidine (Group RC) for supraclavicular block.

**Study procedure:** In preanaesthetic preparation Room, standard monitoring for Heart rate (ECG), Mean arterial blood pressure (NIBP), Peripheral oxygen saturation (SpO₂) were established and baseline vital parameters were recorded and sedation score was graded according to Ramsay sedation score. After establishing intravenous access, DNS infusion was started slowly. Ondansetron 0.08 mg/kg intravenously was given as premedication 15 minutes before induction. The doctor, performing the randomization, prepared the solution as per the group assigned. The patient, anaesthesiologist performing and assessing the block were unaware of the group and drug allocation. Supraclavicular brachial plexus block was performed in the operation theatre with the aid of nerve locator (B. BRAUN Company). After giving the position for supraclavicular brachial plexus block, a 22G short bevelled 1.5inch insulated needle was introduced just lateral to subclavian artery pulsation 1 cm above the mid-point of clavicle and advanced in backward, inward and downward direction. The current was initially set to deliver 0.5 milliampere (mA) at 2Hz stimulation frequency. The needle was advanced till we get contraction of forearm muscle. Once the contraction is seen, the current was reduced in 0.02 mA decrements with the advancement of the needle till we get maximum contraction with minimum possible current. At this point, the solution as per the group assigned, was injected after careful aspiration so as to avoid intravascular injection of drug.

**Outcome measures:** End point of the injection was taken as Time '0'. Immediately after the block, sensory and motor characteristics of blockade, hemodynamic variables, SpO₂ were assessed by the same doctor who performed the block at the time of 1, 3, 5, 10, 15, 30 minutes, then at 1 hour interval up to 4 hour, two hourly interval for 12 hour and four hourly interval up to 24 hour. Sensory blockade was assessed by pinprick test and graded 0- normal sensation to pinprick, grade 1- dull response to pinprick and grade 2- no response to pinprick. Motor blockade was assessed by thumb movement and graded 0- normal movement of thumb, grade 1- decreased movement of thumb and grade 2- no movement of thumb. The onset of sensory block was taken as time duration from end of injection to dull response to pin prick, peak was upto no response to pin prick and duration was till to pin prick sensation. The onset of motor block was taken as time duration from end of injection to decreased thumb movement, peak was complete abolition of thumb movement and duration as time duration from onset of motor block to reappearance of thumb movement. Duration of postoperative analgesia was defined as time duration from onset of sensory block to first rescue analgesic requested by the patient at Visual analogue scale (VAS) ≥ 5. Post operatively, the time of first rescue analgesic required at visual analog scale ≥ 5 and total doses of analgesic given in 24 hours was noted. Diclofenac sodium 75 mg intravenously was given as rescue
analgesic. Any complication or adverse event was also noted down. Bradycardia is defined as heart rate <60/min and was treated by atropine intravenously. Variation in Mean arterial pressure 20% on either side of baseline is considered significant and was treated accordingly.

**Statistical Analysis:** Considering the duration of analgesia as the main outcome measure of interest in this study with at least 10% efficacy shown by the treatment groups, minimum 33 patients were required per group with the permitted 0.05 α error and 0.2 β error. With permitted beta error of 0.2, the power of study stands out to be 80%. Data was summarized as mean ± standard deviation and as percentage wherever required. Statistical analysis was done by Graph pad Instat 3.0 software. Intra group comparison of the quantitative data was done using ANOVA (repeated measures) and inter group comparison among the different groups was done using the unpaired-t test with welch correction. Chi-square test was used for inter group comparison of qualitative data. P <0.05 was interpreted as statistically significant.

**RESULTS**

Both the groups were comparable for their demographic data of age, sex, height, weight and ASA physical status and duration of surgery. [Table 1]

**Table 1: Demographic profile of patients**

<table>
<thead>
<tr>
<th>Data/Groups</th>
<th>Group R</th>
<th>Group RC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>35.68±4.67</td>
<td>36.45±6.81</td>
<td>0.6158</td>
</tr>
<tr>
<td>Gender (Male / Female)</td>
<td>39/21</td>
<td>43/17</td>
<td>0.556</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.76±6.99</td>
<td>58.45±6.08</td>
<td>0.3209</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.23±4.26</td>
<td>158.30±4.57</td>
<td>0.7968</td>
</tr>
<tr>
<td>ASA Physical Status (I/II)</td>
<td>47/13</td>
<td>49/11</td>
<td>0.8195</td>
</tr>
<tr>
<td>Duration of Surgery (min)</td>
<td>103.00±29.24</td>
<td>103.33±22.97</td>
<td>0.8715</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or absolute numbers

ASA = American Society of Anaesthesiologist

The onset of sensory blockade was significantly earlier in group RC (9.70±1.53 min) as compared to group R (11.16±2.30 min). (P<0.0001) Mean time to achieve peak of sensory blockade was 18.18±3.47 and 13.78±1.94 minutes respectively in group R and RC. (P<0.0001) Mean duration of sensory blockade was significantly prolonged in group RC (672.70±125.48 min) as compared to group R (475.50±31.105 min). (P<0.0001) [Table 2]

Mean time of onset was 16.20±3.95 and 14.51±2.30 min respectively in group R and group RC (p=0.0054), peak was 37.56±3.03 and 22.85±3.94 min respectively in group R and group RC (p<0.0001) and duration of motor blockade was 418.67±35.39 and 548.00±34.43 min respectively in group R and group RC which was statistically significant. (P<0.0001) Henceforth, the onset and peak of motor blockade was significantly earlier and duration was significantly prolonged in groups RC as compared to group R. [Table 2]

**Table 2: Sensory and motor blockade characteristics**

<table>
<thead>
<tr>
<th>Parameter/Groups</th>
<th>Group R</th>
<th>Group RC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory block Onset (min)</td>
<td>11.16±2.30</td>
<td>9.70±1.53</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peak (min)</td>
<td>18.18±3.47</td>
<td>13.78±1.94</td>
<td>0.0001</td>
</tr>
<tr>
<td>Motor block Onset (min)</td>
<td>16.20±3.95</td>
<td>14.51±2.30</td>
<td>0.0054</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>37.56±3.03</td>
<td>22.85±3.94</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation

The duration of analgesia was prolonged with addition of clonidine to ropivacaine. Mean duration of analgesia was 584.17±36.0 min in groups R and 799.00±78.88 min in groups RC. (P<0.0001) [Table 2] In group R, majority of the patients required first dose of rescue analgesics between 8-10 hours of brachial plexus blockade. In group RC, 97% patients required first dose of rescue analgesics after 14 hours. In group R, majority of patients needed minimum of two analgesic doses during 24 hour study period while in group RC, majority of patients needed only one analgesic dose.

**Table 3: Doses of rescue analgesics required in 24 hours**

<table>
<thead>
<tr>
<th>Analgesic Doses</th>
<th>Group R</th>
<th>Group RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>%</td>
<td>Number of patients</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1.66</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>81.66</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>16.66</td>
</tr>
</tbody>
</table>
Data are presented in numbers and percentage (%).

In this study, sedation score was higher in group RC (score 2 - Asleep but reusable) as compared to group R (score 0) without any adverse consequences. (P<0.05)

On comparison of haemodynamic amongst the two groups, there was statistically significant decrease in heart rate and blood pressure in group RC as compared to group R. (P<0.05) Two patients developed bradycardia in group RC, which responded to atropine and was not clinically significant. [Figure 1 and 2]

**Figure 1:** Diagram showing heart rate (HR) at various time intervals

[Image of heart rate graph]

**Figure 2:** Diagram showing mean arterial blood pressure (MAP) at various time intervals

[Image of blood pressure graph]

SpO₂ remained stable and comparable in both groups throughout the study period. (P>0.05)

Except bradycardia (3% in group RC), no other complication was observed in two groups.

**DISCUSSION**

We observed that clonidine 90 μg in of 0.5% ropivacaine enhanced the characteristics of supraclavicular brachial plexus block by significantly faster onset, prolonged sensory-motor duration and significant reduction in the post-operative analgesic consumption. These benefits were without any clinically significant hemodynamic changes or adverse events. Regional anaesthesia in orthopaedic surgery provides excellent post-operative analgesia without undue sedation thus facilitating early mobilization and discharge. Supraclavicular brachial plexus block is performed at the level of the trunk in the brachial plexus. Trunk carries almost the entire sensory, motor and sympathetic innervation of the upper limb and it consists just three nerve structures in a very small compartment. As a result, brachial plexus blockade by supraclavicular route provides very dense anaesthesia along with higher success rate. Clonidine, α₂ agonist, reduces heart rate and blood pressure. So it has been used as an antihypertensive agent. Clonidine impairs the peripheral adrenergic neurotransmission and increases parasympathetic nervous system activity by activation of inhibitory presynaptic α₂ receptors. The outflow of sympathetic nervous system involving the endogenous opioid system is also reduced. Clonidine blocks the conduction of Aδ and C fibers, increases the potassium conductance in isolated neurons in vitro and intensifies the conduction block of local anaesthetics. It enhances sensory and motor blockade of neuraxial and peripheral nerves. The clonidine has been used as an adjuvant to local anaesthetics in peripheral nerve blocks in different doses ranging from 30 μg to 300 μg. The clonidine in the doses upto 150 μg being associated with minimal side effects. As such, no single study has been done with 90 μg of clonidine as an adjuvant with ropivacaine in brachial plexus block. Which prompted us to use clonidine in the dose of 90 μg as an adjuvant to ropivacaine. In this study, statistically significant improved onset and duration of sensory and motor blockade in the group RC was observed as compared to group R. We also observed significant prolonged duration of analgesia of 799.00 ± 78.88 min in the study group as compared to the control group where it was 584.17 ± 36.0 min. El Saied A.H et al. evaluated the effects of clonidine in the dose of 150 μg with 40 ml 0.75% ropivacaine in brachial plexus block and found that the duration of analgesia was significantly prolonged in the clonidine group (828 ± 35 min) as compared to control group (587 ± 40 min). Sidharth S Routray et al. studied 150 μg clonidine with 35 ml 0.5% ropivacaine in supraclavicular brachial plexus block and...
found that the duration of analgesia was 586 ± 56.8 min in the clonidine group as compared to 465.8 ± 62.5 min in the control group. Finding of present study suggest that there is no need of using higher doses of clonidine above 90 μg as there is no improvement in duration of analgesia with higher doses. There was significant lower VAS score and significant reduction in total dose of rescue analgesics required in 24 hours in clonidine group as compared to control group, indicating good postoperative analgesic effect. In this study, significant level of sedation was observed with 90 μg clonidine in group RC as against no sedation observed in control group R. Maximum sedation score achieved was score 2, none of the patient developed respiratory depression. Gaumann et al. found significant level of sedation with the use of 150 μg clonidine added to 40 ml of 1% lignocaine in the brachial plexus block which was similar to present study. We found that the sedation produced by clonidine was desirable as all the patients remained calm and quite in intraoperative and postoperative periods. 3% patients in the group RC developed bradycardia, which responded to atropine intravenously and was not clinically significant. α2 adrenergic agonists are known to cause bradycardia. Mechanism of bradycardia is presynaptic feedback inhibition of norepinephrine release and possible vagomimetic effect on nucleus tractus solitarius by α2 agonist. Though, there was statistically significant reduction in MAP in group RC, it was not clinically significant as none of the patients developed more than 20% fall in MAP from baseline. From this study, it is concluded that addition of 90 μg of clonidine to ropivacaine in supraclavicular brachial plexus blockade is safe and effective in improving the quality of blockade, prolongs the duration and provides effective analgesia with adequate sedation well extending into the postoperative period without any adverse events. We recommend the routine use of 90 μg of clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block for upper limb orthopaedic surgery.

REFERENCES
11. El Saied AH, Steyn MP, Ansermino JH. Clonidine prolongs the effect of ropivacaine for axillary brachial plexus


