Evaluation of the Hemodynamic Response of Intravenous Clonidine versus Ropivacaine Scalp Block to Insertion of Scalp Pins in Neurosurgical Patients

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Abstract

Background: The application of the skull-pin head-holder, used to stabilize the head during neurosurgical procedures, produces an intense nociceptive stimulus and results in abrupt increases in blood pressure and cerebral blood flow under general anesthesia. Different anesthetic and pharmacologic techniques, including local anesthetics, narcotics, antihypertensives, and deepening of anesthesia with inhalation anesthetics, have been used to blunt this deleterious effect with variable success. Aim: To compare the analgesic and hemodynamic effects of ropivacaine scalp block, and intravenous (IV) clonidine in attenuating the hemodynamic response to the scalp pin insertion in neurosurgical patients. Settings and Design: A comparative two group’s clinical study of 64 patients undergoing elective craniotomy in Department of Anaesthesiology, Bangalore Medical College and Research Institute. Methodology: Sixty-four patients were allocated into any one of two groups of 32 patients each, by means of computer-generated randomization: (1) Group S: Patients receiving scalp block with injected ropivacaine 0.25% 30 ml. (2) Group C: Patients receiving 2 µg/kg IV clonidine. Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean ± standard deviation (minimum–maximum) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Results: Increase in heart rate and blood pressure during pin insertion was attenuated by clonidine hydrochloride (P < 0.001). The number of patients who required more fentanyl and propofol to stabilize the hypertensive response were more in control group than clonidine group. Conclusion: IV clonidine maximally attenuated the hemodynamic response to application of head pins in a dose of 2 µg/kg compared to ropivacaine scalp block, thus maintaining intracranial pressure for neurosurgical anesthesia.

Keywords: α2-agonists, clonidine hydrochloride, craniotomy, hemodynamic response, scalp blocks

INTRODUCTION

Anesthesia for craniotomy requires special considerations. The brain is enclosed in a rigid skull and at the same time, being a vascular organ presents potential for massive perioperative hemorrhage and increased intracranial pressure (ICP). Maintenance of adequate blood flow to the brain is of fundamental importance in neuroanesthesia[1] because of tolerance of the brain to interruption of substrate delivery is minimal. Increased ICP in patients with mass lesions is due to poor volume compensation and intracranial compliance. As the ICP depends on mean arterial pressure (MAP), it is important to maintain the ICP throughout the surgery by controlling the MAP. Not only the arterial blood pressure rises but also the cerebrospinal fluid pressure[2-4] These changes can be deleterious in patients with compromised intracranial compliance. Different methods including local anesthetic infiltrations[5-8] skull blocks, and narcotics and deepening of anesthesia with inhalation and intravenous (IV) anesthetics have been used to blunt this deleterious effect with variable success.[9] Although the onset of analgesia is rapid, no additional increase in the depth of anesthesia and effective attenuation of hemodynamic perturbations and small volume of the drug required are claimed as the advantages for the infiltration

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**Methodology**

The study design was a prospective, double-blinded, randomized trial on patients undergoing elective craniotomy in Bangalore Medical College and Research Institute conducted over 1 year. Witnessed informed consent was obtained from all patients before surgery by the anesthesiologist, 64 patients were included in the study. They were allocated into any one of two groups of 32 patients each, by means of computer-generated randomization:

- **Group S**: Patients received scalp block with injection ropivacaine 0.25% 30 ml
- **Group C**: Patients received 2 µg/kg IV clonidine.

Before induction of general anesthesia, standard monitors such as electrocardiography and pulse oximetry probe were connected. The radial artery on the nondominant hand was cannulated under local anesthesia with a 20-gauge cannula for continuous blood pressure monitoring. The baseline heart rate (HR) and arterial blood pressure were recorded. Patient in the Group C (clonidine group) was given a bolus dose of clonidine (2 µg/kg) as an infusion over a period of 10 min, before induction of anesthesia. Induction of anesthesia was achieved with a standard induction protocol for all patients with propofol (2 mg/kg), fentanyl (2 µg/kg), and vecuronium (0.15 mg/kg). After endotracheal intubation, anesthesia was maintained with 0.8 minimal alveolar concentration of isoflurane in 50% O₂:air. In the patients assigned to Group S (scalp block group), bilateral ropivacaine skull block was performed with 30 ml of 0.5% ropivacaine - 15 ml on each side by the principal investigator, as described by Pinosky et al. under sterile precautions.[13] Bradycardia was defined as HR <50 bpm, tachycardia as a >20% increase from baseline in HR, hypertension as a >20% increase from baseline in MAP, and hypotension as <20% decrease from baseline in MAP. Bradycardia was treated by administration of atropine 0.6 mg.

The person who monitored the patients was blinded for both the techniques. Hypotension was treated by administration of 5 mg of ephedrine. Refractory or persistent hypotension was defined as hypotension requiring more than three boluses of ephedrine and more than 500 ml of crystalloid. In both the groups, any rise in the HR or MAP, more than 20% of baseline was treated immediately in two successive steps. The second step was followed only if the first step failed to control the rise in MAP and HR, respectively.

- **Step 1**: Single bolus administration of fentanyl 1 µg/kg
- **Step 2**: Bolus injections of propofol, 1 mg/kg.

**Statistical software**

The statistical software, namely, SAS 9.2 (SAS Institute, Cary, NC, USA), SPSS 15.0 (SPSS version 15.0 IBM Corp, Armonk, NY), Stata 10.1 (StataCorp LP, 4905 Lakeway Drive, College Station, Texas, USA), MedCalc 9.0.1 (American Statistical Association, Aacaiaan 22, 8400 Ostend, Belgium), Systat 12.0 (Systat Software, San Jose, CA 95131, USA), and R environment version 2.11.1 were used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs, tables, etc.

Student’s t-test (two-tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (intergroup analysis) on metric parameters. Chi-square/Fisher’s exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

**Results**

The two groups were comparable to each other as regards age, gender, and weight [Table 1 and Figure 1]. The comparison of baseline hemodynamic parameters was statistically insignificant ($P > 0.05$) between the two groups. During pin

| Table 1: Baseline information of patients in two groups studied |
|---------------------------------------------------------------|
| **Age in years** | **Weight (kg)** | **Height (cm)** |
| 42.2±11.07 | 64.38±9.15 | 159.72±5.02 |
| 39.59±10.17 | 62.81±10.64 | 159.06±4.57 |

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Clonidine is an antihypertensive agent that reduces sympathetic outflow via α2-adrenergic receptor stimulation.[9,10] α₂ adrenergic receptors are distributed widely within and outside the central nervous system (CNS), mostly in the region of pons and medulla which regulates the transmission of sympathetic nervous system stimulation from higher centers to the periphery. Presynaptic α2-receptors activation inhibits the release of norepinephrine. Whereas α₂-adrenoceptors situated postsynaptic in the dorsal horn and on vascular smooth muscle when stimulated prevents nociceptive signal transmission and causes vasoconstriction, respectively.[11-13] Stimulation of α2 receptors by clonidine in the CNS has a role on sedation for which clonidine is widely used as an adjunct to anesthesia and pain medicine.[14] Clonidine reduces sympathetic tone and the release of norepinephrine from nerve terminals.[15] During general anesthesia, clonidine reportedly enhances intraoperative circulatory stability by reducing catecholamine levels.[16] Therefore, the use of clonidine during surgery has been proposed as a way of improving hemodynamics, decreasing both the ICP and anesthetic requirements. We conducted this trial to compare the analgesic and hemodynamic effects of ropivacaine and IV clonidine in attenuating the hemodynamic response to the scalp pin insertion in neurosurgical patients.
application, i.e., 0 min (0.001) and after application of pins at 1 min (<0.001), 2 min (0.011), and 3 min (0.036), there was a significant increase in HR in both groups relative to before-pin values; the rise was significantly higher in the scalp block group ($P < 0.001$) relative to the clonidine group. Significant rise ($P < 0.001$) in systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP in scalp block during 0, 1, 2, 3, 4, and 5 min compared to clonidine group. Five minutes after pin insertion, HR, SBP, DBP, and MAP returned to near before-pin values in the clonidine group while they remained significantly higher in the scalp block group [Tables 2, 3 and Figure 2], reflecting that the analgesia obtained with clonidine was of better quality than that achieved with scalp block.

Additional bolus of fentanyl was required more for scalp block group (18.8) compared to clonidine group (6.3) and combined fentanyl, and propofol requirement was also greater in the control group (28.1) compared to clonidine group (0). Only one case in control scalp group had reapplication of pins, which required additional injection fentanyl 2 $\mu$g/kg [Figure 3].

**DISCUSSION**

Clonidine appears to possess many properties that make it an appealing adjunct to the intraoperative management of neurosurgical patients.[3] $\alpha_2$-agonists are a novel class of drugs with mechanisms of action that differ from other commonly used anesthetic drugs. They have neuroprotective, cardioprotective, and sedative effects. These unique characteristics make them potentially useful during neuroanesthesia.[1,9] Clonidine prevents fluctuation of hemodynamics throughout the entire perioperative period, which is very important in neurosurgical patients.[31] By stimulating $\alpha_2$-receptors, clonidine decreases total peripheral resistance, renal vascular resistance, HR, and blood pressure.[1,9,10] This agent also decreases cerebral electrical activity and the cortical response to sensory input, which may partially explain the decrease in anesthetic requirements associated with clonidine administration. In

**Table 2: Comparison of Heart rate (beats/min) of patients in two groups studied**

| Heart rate (beats/min) | Scalp Block | Clonidine | $P$ |
|------------------------|-------------|-----------|-----|
| Baseline               | 83.53±12.27 | 87.27±11.66 | 0.215 |
| Before Induction       | 79.81±12.40 | 86.50±14.14 | 0.049* |
| After intubation       | 76.50±9.60  | 79.94±14.03 | 0.257 |
| Before pinning         | 77.44±8.08  | 78.28±15.78 | 0.789 |
| 0 min                  | 96.88±12.83 | 84.41±15.68 | 0.001** |
| 1 min                  | 95.81±10.92 | 84.47±13.55 | <0.001** |
| 2 mins                 | 89.91±11.37 | 81.41±14.49 | 0.011*  |
| 3 mins                 | 86.84±12.37 | 79.34±15.46 | 0.060+  |
| 4 mins                 | 82.63±12.55 | 77.22±14.01 | 0.109   |
| 5 mins                 | 81.34±12.34 | 77.06±14.48 | 0.208   |

**Table 3: Comparison of MAP (mm Hg) of patients in two groups studied**

| MAP (mm Hg) | Scalp Block | Clonidine | $P$ |
|-------------|-------------|-----------|-----|
| Baseline    | 104.09±16.46| 100.00±12.20| 0.263 |
| Before Induction | 100.00±20.08 | 92.84±14.93 | 0.111 |
| After intubation | 95.63±16.55 | 86.03±12.41 | 0.011* |
| Before pinning | 87.88±17.41 | 80.44±13.44 | 0.060+ |
| 0 min       | 104.69±19.21| 90.28±15.50 | 0.002** |
| 1 min       | 102.13±16.95| 88.72±12.57 | 0.001** |
| 2 mins      | 96.22±14.41 | 84.88±10.65 | 0.001** |
| 3 mins      | 94.53±12.61 | 81.63±11.09 | <0.001** |
| 4 mins      | 91.56±13.29 | 80.63±11.89 | 0.001** |
| 5 mins      | 89.63±11.12 | 77.94±10.95 | <0.001** |

**Figure 1: Gender distribution**

**Figure 2: Comparison of MAP (mmHg) of patients in two groups studied**

**Figure 3: Percentage of requirement of drugs**
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The present randomized, double-blind study demonstrated that hemodynamic changes associated with pin insertion in patients undergoing cranioectomy can be ameliorated more efficiently when clonidine was used as IV premedication. Both the groups did not differ with respect to age, weight, and sex. All preoperative baseline hemodynamic variables were almost identical in both groups \( (P > 0.05) \). Gaumann et al. noted that patients treated with clonidine had lower values of MAP than patients with placebo.\(^{[17]}\) Oral clonidine premedication in cranioectomy, a study conducted by Traill and Gillies noted that in clonidine group lower SBP on arrival in the operative room, preinduction, and postintubation than control group.\(^{[18]}\) IV route was chosen to provide exact drug dosing and a gap of 10–15 min between administration of drug and induction of patients was chosen because onset of action of IV clonidine is 2–28 min and an average of 15 min was taken.

Favre et al.\(^{[4]}\) administered clonidine 3 µg/kg 10 min before surgery. The dose, route of administration, and time interval were similar to our study. In our study, the MAP showed an increase during pin head-holder application in control group which was highly significant \( (0.001) \). On comparison between the two groups at various intervals, we found that there was a significant difference in HR between the two groups. The difference in HR between the two groups was highly significant \( (P < 0.001) \) at P1. There were no cases of bradycardia reported in either group. Jellish et al. in their study show that baseline HR was lower in patients who received clonidine.\(^{[10]}\) Endotracheal intubation is associated with significant increases of arterial pressure, HR; clonidine attenuates the sympathoadrenal stimulation during tracheal intubation effectively. This was observed in our study also as the decrease in HR was maintained after induction in the Group C, but not in the Group S. Costello and Cormack suggested that oral clonidine (3 µg/kg, 90 min before induction) is effective in controlling the increase in MAP \( (P = 0.03) \) resulting from pin head-holder application.\(^{[19]}\)

There have been studies using dexmedetomidine, the other potent \( \alpha_2 \)-agonist. Uyar et al. have shown that single bolus of dexmedetomidine before induction of anesthesia attenuated the hemodynamic and neuroendocrinal response to skull pin insertion as compared to that of placebo.\(^{[20]}\) Dawlatly et al. showed that the use of a small dose of dexmedetomidine (0.25 mcg/kg by infusion) has resulted in obtunding the hemodynamic responses to skull pin placement similar to lidocaine infiltration.\(^{[21]}\)

Duration of action of dexmedetomidine being less than clonidine, we chose to study the latter drug to extend its hemodynamic obtunding effect into the intraoperative period. Clonidine appears to possess many properties that make it an appealing adjunct to the intraoperative management of neurosurgical patients.\(^{[10]}\)

Our study showed that those patients with only scalp block required another drug to stabilize the hypertensive response during pin head-holder application, also scalp block procedure involves multiple injection and increase in operating room (OR) time.

**Limitations**

1. No patients with Glasgow Coma Scale below 15 were included in this study, and hence whether either of these techniques could have had a distinct advantage over the other in those with severely raised ICP could not be addressed in our study
2. Direct estimation of ICP or the increase in ICP as a response to pinning which would probably be the gold standard was not measured. Only the hemodynamic responses were studied
3. Difficult to monitor postoperative sedation score in clonidine group in craniotomy patients
4. Future research direction would be interesting to compare the hemodynamic response to pin insertion in patients with borderline cardiovascular function, elderly patients, and those with severely elevated ICP with both the techniques. It would also be interesting to follow-up these patients throughout the procedure to compare the analgesic requirement, hemodynamic stability, and time taken for emergence among both the groups.

**Conclusion**

We can state that during craniotomy clonidine maximally attenuated the hemodynamic response to application of head pins compared to ropivacaine scalp block in neurosurgical patients. Clonidine also reduced mean propofol and fentanyl...
requirements intraoperatively. There were no adverse effects observed in both the groups.

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Conflicts of interest
There are no conflicts of interest.

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