

# Comparison of intravenous labetalol and bupivacaine scalp block on the hemodynamic and entropy changes following skull pin application: A randomized, open label clinical trial

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## ABSTRACT

**Background:** The application of skull pins in neurosurgical procedures is a highly noxious stimulus that causes hemodynamic changes and a rise in spectral entropy levels. We designed a study to compare intravenous (IV) labetalol and bupivacaine scalp block in blunting these changes.

**Patients and Methods:** Sixty-six patients undergoing elective neurosurgical procedures were randomized into two groups, L (labetalol) and B (bupivacaine) of 33 each. After a standard induction sequence using fentanyl, propofol and vecuronium, patients were intubated. Baseline hemodynamic parameters and entropy levels were noted. Five minutes before, application of the pins, group L patients received IV labetalol 0.25 mg/kg and group B patients received scalp block with 30 ml of 0.25% bupivacaine. Following application of the pins, heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and response entropy (RE)/state entropy (SE) were noted at regular time points up to 5 min.

**Results:** The two groups were comparable with respect to their demographic characteristics. Baseline hemodynamic parameters and entropy levels were also similar. After pinning, the HR, SAP, DAP, MAP, and RE/SE all increased in both groups but were lower in the scalp block group patients. HR increased by 19.8% in group L and by 11% in group B. SAP increased by 11.9% in group L and remained unchanged in group B. DAP increased by 19.7% in group L and by 9.9% in group B, MAP increased by 15.6% in group L and 5% in group B ( $P < 0.05$ ). No adverse effects were noted.

**Conclusion:** Scalp block with bupivacaine is more effective than IV labetalol in attenuating the rise in hemodynamic parameters and entropy changes following skull pin application.

**Key words:** Entropy, labetalol, scalp block, skull pins

## Introduction

The use of head holders has become an essential aspect of neurosurgical procedures. Head holders or skull clamps

such as Mayfield and Sugita holders are employed to hold the head and neck in a steady position during the surgical procedure. Metallic pins are inserted through the scalp and the periosteum into the external lamina of the skull and are tightened. Although the application of skull pins is carried out after induction of general anesthesia, there always occurs a hemodynamic response to this stimulus in the form of tachycardia and hypertension.<sup>[1]</sup> The rise in cerebrospinal fluid pressure has also been noted.<sup>[2]</sup>

These hemodynamic changes can lead to adverse outcomes in patients with decreased intracranial compliance and impaired cerebral autoregulation. The increase in intracranial pressure in patients with intracranial pathology can increase morbidity.<sup>[3]</sup> Rupture of intracranial aneurysms and intracerebral hematomas can occur.<sup>[4]</sup>

Electroencephalographic (EEG) signals are analyzed under anesthesia to evaluate anesthetic depth. Among the

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EEG-derived indices, spectral entropy is most widely used to evaluate the depth of anesthesia. Spectral entropy is determined using raw EEG and frontal electromyography data, resulting in two indices, response entropy (RE) and state entropy (SE).<sup>[5]</sup> These reflect nociceptive and hypnotic levels respectively, during general anesthesia. Tracheal intubation, which is a highly noxious stimulus, has been shown to increase bispectral index (BIS) and entropy indices during anesthesia.<sup>[6]</sup> The increase in BIS has also been demonstrated following skull pin application.<sup>[7]</sup>

Different methods have been employed to blunt this hemodynamic response. They include: Local anesthetic infiltration of the pin sites on the scalp,<sup>[8]</sup> scalp block with local anesthetic,<sup>[9]</sup> deepening the plane of anesthesia,<sup>[10]</sup> opioids,<sup>[11-13]</sup> alpha agonists,<sup>[14,15]</sup> beta blockers,<sup>[16]</sup> and gamma-aminobutyric acid agonists.<sup>[17]</sup>

A scalp block is given to block the nerves supplying the scalp, with local anesthetic has been shown to control the hemodynamic response to skull pin placement.<sup>[9]</sup> Beta blockers have been widely used to attenuate the hemodynamic responses to tracheal intubation and other intraoperative stimuli. Recently, Landiolol, a short-acting beta blocker has been shown to control the increase in BIS and entropy values following laryngoscopy and intubation.<sup>[18]</sup> Intravenous (IV) labetalol has been used to blunt the hemodynamic response to laryngoscopy and intubation. The literature search did not reveal the use of labetalol for suppressing the hemodynamic response following skull pin application.

Hence, we designed this study to compare the efficacy of IV labetalol and bupivacaine scalp block on the hemodynamic changes and to study their effect on spectral entropy changes following Mayfield skull pin application.

## Patients and Methods

The trial was registered in Clinical Trial Registry – India (CTRI/2015/03/005635). After obtaining Institute Ethics Committee approval and written informed consent from patients, 66 patients were enrolled for the study [Figure 1]. These patients were randomly divided into group L (labetalol) and group B (bupivacaine group) using a computer-generated randomization table (33 in each group). The sample size was estimated with an expected mean difference in increase in mean arterial pressure (MAP) between the two groups as 2.43 with a standard deviation (SD) of 3.5 (7% increase in bupivacaine group and 10% increase in labetalol group) at 5% level of significance and 80% power.

Patients aged 18–60 years, with the American Society of Anesthesiologists (ASA) physical status I and II, undergoing elective neurosurgical procedure under general anesthesia and requiring application of skull pins were included in the

study. Hypertensives, patients undergoing emergency surgery, intracranial aneurysm surgery, those having significant cardiac, pulmonary, renal or hepatic disease, those having contraindication to beta blockers, or taking treatment that can affect hemodynamic parameters were excluded.

## Anesthetic management

All the patients were premedicated with oral famotidine 20 mg and oral diazepam 5 mg. In the operating room, standard monitors such as electrocardiograph, noninvasive blood pressure, and pulse oximeter were attached and the baseline heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and MAP were noted.

After cleaning the skin with ether solution, entropy sensor was attached on the frontal region, according to the manufacturer's recommendation. All the patients were induced with 2 mcg/kg fentanyl, 2 mg/kg of propofol, and vecuronium 0.1 mg/kg was used for muscle relaxation. Anesthesia was maintained with nitrous oxide in oxygen mixture (60:40) with 1–1.2 minimum alveolar concentration of isoflurane to maintain SE values between 40 and 60. Postinduction radial artery was cannulated for the beat to beat monitoring of blood pressure. Ventilation was maintained with a tidal volume of 8–10 ml/kg and respiratory frequency of 12–15/min. IV vecuronium and IV fentanyl were used for maintenance of muscle relaxation and analgesia, respectively. The depth of anesthesia was maintained within 40–60 on entropy.

## Before pin application

The patients were allocated into one of two groups. Patients in group B received scalp block with 30 ml of 0.25% bupivacaine 10 min prior, and patients in group L received 0.25 mg/kg of labetalol IV 5 min prior to skull pin application.

## The scalp block

The supraorbital and supratrochlear nerves were blocked from the point where the supraorbital artery can be palpated above the eyebrow, to the medial end of the eyebrow. The auricular-temporal nerve was blocked 1.5 cm anterior to the ear at the level of the tragus. The lesser occipital and greater auricular nerves were blocked from a point 1.5 cm posterior to the ear at the level of the tragus in the direction of the occiput. The greater occipital nerves were infiltrated along the superior nuchal line approximately midway between the external occipital protuberance and the mastoid process.<sup>[8]</sup>

The following parameters were measured: HR, SAP, DAP, MAP, and SE and RE level. These parameters were noted at the following time points: just prior to the application of pins, and 30, 60, 90, 120, 180, and 300 s after application of pins. Any possible adverse effects of the study drugs were also noted. Any increase in HR and MAP > 20% of baseline was treated with 1 mcg/kg of fentanyl and increase in inhaled isoflurane concentration.

## Statistical analysis

SPSS Inc., 233 South Wacker Drive, 11<sup>th</sup> Floor, Chicago, IL was used for statistical analysis. The data for the continuous variables such as age, HR, SAP, DAP, MAP, and entropy were expressed as mean with SD. The comparison of changes over time between the groups was carried out by using two-way repeated measures of ANOVA. A comparison of overall difference in SAP, DAP, MAP, HR, and entropy between the groups was carried out by using independent Student's *t*-test or Mann-Whitney U-test. All statistical analyses were carried out at 5% level of significance, and  $P < 0.05$  was considered as significant.

## Results

### Demographic characteristics

Patient demographics such as age, gender, and weight were comparable in both groups [Table 1]. The mean age of the patients in group L was  $40.58 \pm 8.57$  as compared to  $42.24 \pm 8.76$  in group B ( $P = 0.437$ ).

### Changes in heart rate

In group L, the mean baseline HR was  $73.55 \pm 7.04$  beats per min (bpm) while in group B, the mean baseline HR was  $73.85 \pm 7.26$  bpm ( $P = 0.864$ ). Following labetalol administration, HR decreased to  $72.45 \pm 7.53$  bpm. After pin application, it increased to a maximum of  $88.12 \pm 9.64$  bpm at 60 s (increase by 19.8%), after which a downward trend was seen. In group B, on the other hand, HR increased to  $76.36 \pm 6.48$  bpm after scalp block and then pinning to a maximum of  $82.18 \pm 7.13$  bpm at 60 s (a 11% increase), after which it decreased [Table 2]. Statistically, a significant difference was found between the two groups ( $P < 0.05$ ) [Figure 2].

### Changes in mean arterial pressure

The baseline MAP was  $85.76 \pm 7.67$  mm Hg in group L and  $86.39 \pm 6.30$  mm Hg in group B ( $P = 0.714$ ). Significant reduction in MAP was noticed in group L ( $P < 0.001$ ) [Table 3]. Following skull pin application, MAP increased to a maximum of  $99.21 \pm 5.93$  mm Hg in group L at 60 s (a 15.6% increase) and to  $91.30 \pm 5.19$  mm Hg in group B at 30 s (5% increase), after which a downward trend was observed in both the groups ( $P < 0.001$ ) [Figure 3]. SAP increased by 11.9% in group L, and remained unchanged in group B. DAP increased by 19.7% in group L, and by 9.9% in group B. Twelve patients in group L required additional supplementation of fentanyl as compared with one patient in group B ( $P < 0.05$ ).

### Changes in spectral entropy

The RE and SE values were comparable between the two groups at baseline ( $P > 0.05$ ). Following skull pin application, there was a significant increase in RE and SE values in group L as compared to group B ( $P < 0.001$ ) at 30 s. There was a gradual reduction in SE and RE values in both the groups over next 5 min [Figures 4 and 5].

**Table 1: Demographic characteristics among the two groups**

Demographics	Group L (n=33)	Group B (n=33)	P
Age (mean±SD)	40.58±8.57	42.24±8.76	0.437
Male:female	14:19	13:20	0.802
Weight (mean±SD)	61.78±6.06	60.21±6.06	0.296

SD – Standard deviation

**Table 2: Changes in HR in the two groups**

HR (bpm)	Mean±SD (n=33)		P
	Group L	Group B	
Baseline	73.55±7.04	73.85±7.26	0.864
Before pins	72.45±7.53	76.36±6.48	0.027*
30 s	87.00±9.52	82.06±6.97	0.019*
60 s	88.12±9.64	82.18±7.13	0.006*
90 s	86.30±9.65	79.58±7.05	0.002*
120 s	84.64±9.76	78.24±7.43	0.004*
180 s	82.09±9.17	75.73±6.92	0.002*
300 s	79.91±9.49	73.45±6.84	0.002*

\* $P < 0.05$ . HR – Heart rate; SD – Standard deviation

**Table 3: Changes in MAP in the two groups**

MAP (mm Hg)	Mean±SD (n=33)		P
	Group L	Group B	
Baseline	85.76±7.67	86.39±6.30	0.714
Before pins	78.58±5.61	85.09±5.21	<0.001*
30 s	97.97±5.68	91.30±5.19	<0.001*
60 s	99.21±5.93	91.12±5.10	<0.001*
90 s	96.61±5.60	89.48±5.43	<0.001*
120 s	94.70±5.73	87.76±5.39	<0.001*
180 s	92.55±5.86	85.79±5.21	<0.001*
300 s	89.76±5.85	84.61±4.97	<0.001*

\* $P < 0.05$ . MAP – Mean arterial pressure; SD – Standard deviation

## Adverse effects

No treatment-related adverse effects were noted in both groups.

## Discussion

The use of skull pins during neurosurgical procedures is a highly noxious stimulus. It leads to a significant hemodynamic response in the form of a rise in HR and blood pressure. An increase in depth of anesthesia parameters such as the BIS index has also been demonstrated.<sup>[7]</sup> These hemodynamic changes may be tolerated in young, healthy patients, but can be detrimental or even fatal in patients with coronary artery disease and patients with reduced intracranial compliance.

Many methods and drugs have been used for attenuation of these hemodynamic changes. Drugs such as beta blockers,<sup>[16]</sup> opioids,<sup>[11-13,19]</sup> local anesthetics,<sup>[8]</sup> and alpha agonists<sup>[14,15]</sup> have been shown to be effective. Some methods can cause hypotension and possibly lead to cerebral ischemia.

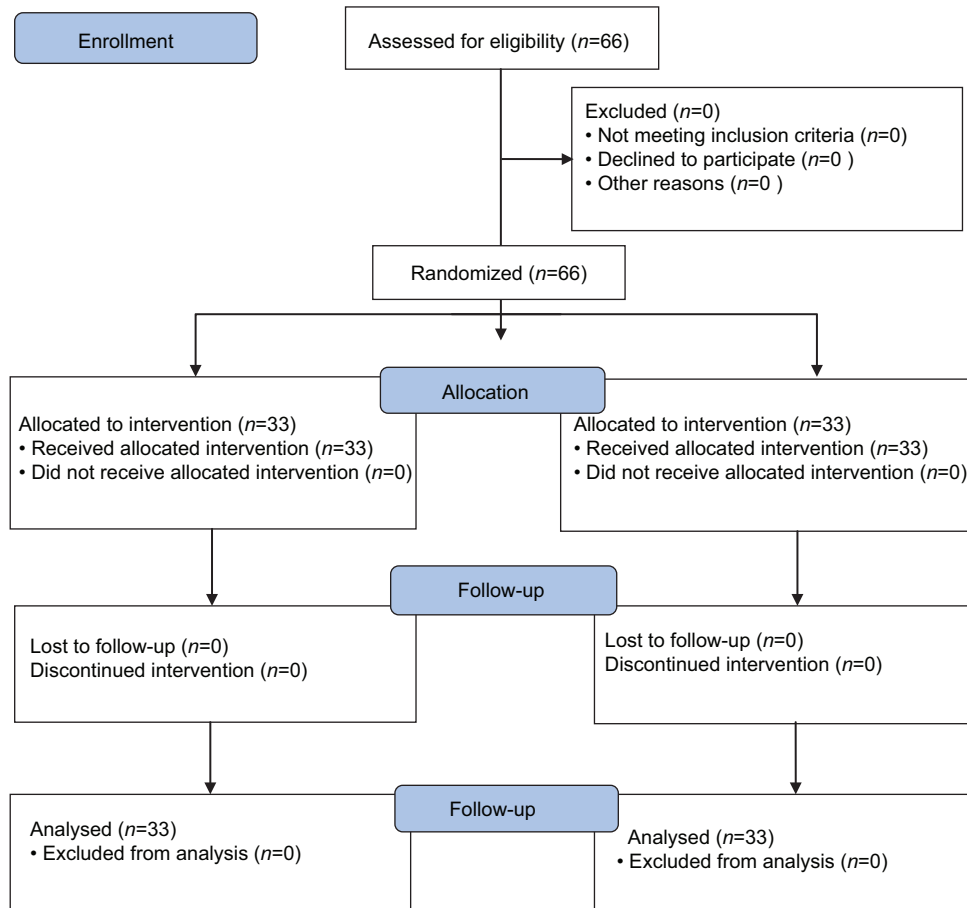


Figure 1: CONSORT figure representing enrollment data

In our study, 66 ASA classes I and II normotensive adult patients undergoing elective neurosurgery under general anesthesia were enrolled. The patients were randomized into two groups of 33 each. The two groups were similar with respect to age, sex, and weight. The study groups designated as groups B and L received scalp block with 30 ml of 0.25% bupivacaine and IV labetalol 0.25 mg/kg respectively, 5 min before application of the Mayfield skull pins. A vasoconstrictor like adrenaline was not included in the local anesthetic solution as inadvertent intravascular injection or systemic absorption would cause tachycardia and hypertension. Vitals were recorded just before pinning, and 30, 60, 90, 120, 180, and 300 s following skull pinning and 30, 60, 90, 120, 180, and 300 s following skull pinning. The depth of anesthesia was also monitored using spectral entropy.

Local anesthetic infiltration and scalp block are the two regional anesthetic methods used to blunt the response to skull pinning. A scalp block can be easily performed after induction and has the advantage that the pin sites can be changed if required. It also has the advantage of avoiding any significant systemic effects and reducing the need for an additional anesthetic agent or vasoactive drugs. A possible

disadvantage is that it may increase the risk of needle stick injury due to the multiple injections needed.

Previous studies have also explored these potential benefits of local infiltration and scalp blocks and have found that the hemodynamic response is blunted more efficiently than deepening the level of anesthesia. Pinosky *et al.*<sup>[9]</sup> studied scalp block with 0.5% bupivacaine. They found increases in SAP of  $40 \pm 6$  mm Hg, DAP of  $30 \pm 5$  mm Hg, MAP of  $32 \pm 6$  mm Hg, and HR of  $22 \pm 5$  bpm in the control group while no increases occurred in patients who received scalp block. Levin *et al.*<sup>[20]</sup> used Mepivacaine infiltration at pin sites to control the hemodynamic response. Significant increases in MAP by 43% and HR by 15% were seen in the control group while no significant changes occurred in the study group. Arshad *et al.*<sup>[8]</sup> used lignocaine with adrenaline infiltration at the sites of skull pinning. The MAP and HR at 60 s after pinning were significantly higher in the control group ( $104.03 \pm 12.95$  mm Hg and  $103.07 \pm 6.98$  bpm) as compared to the study group ( $86.13 \pm 9.73$  mm Hg and  $78.23 \pm 7.19$  bpm). Similarly, in our study we found significant increases in HR, SAP, DAP, and MAP in patients who received IV Labetalol as compared to scalp block with 0.25% bupivacaine.

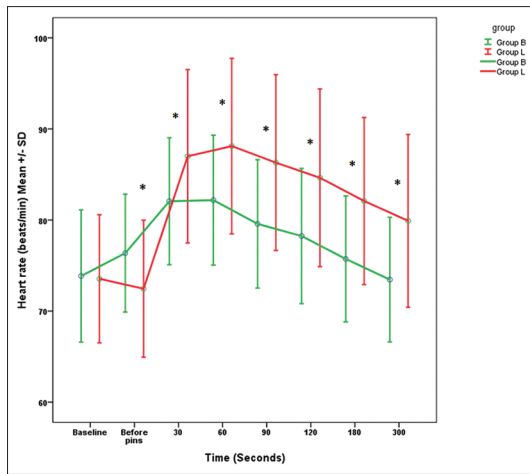


Figure 2: Changes in heart rate in two groups. \* $P < 0.05$

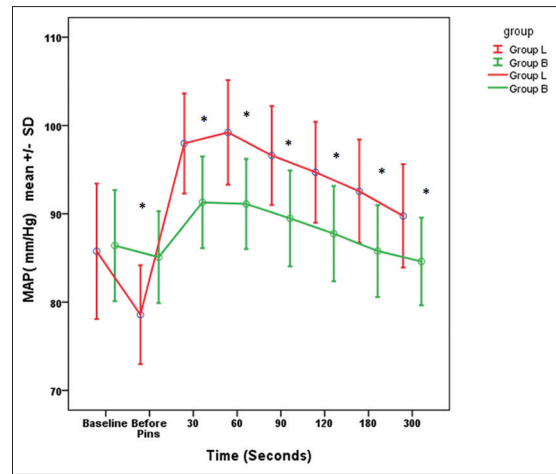


Figure 3: Changes in mean arterial pressure in two groups. \* $P < 0.05$

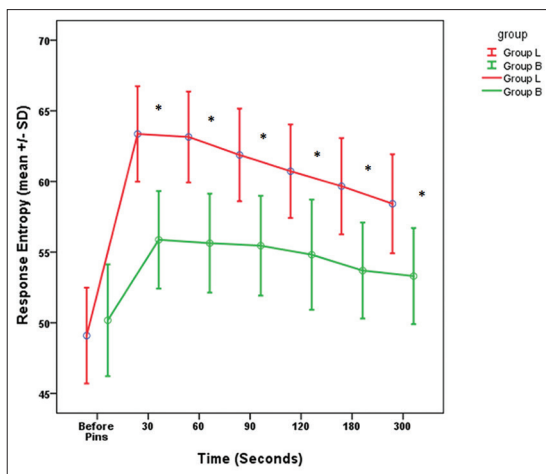


Figure 4: Response entropy changes in the two groups. \* $P < 0.05$

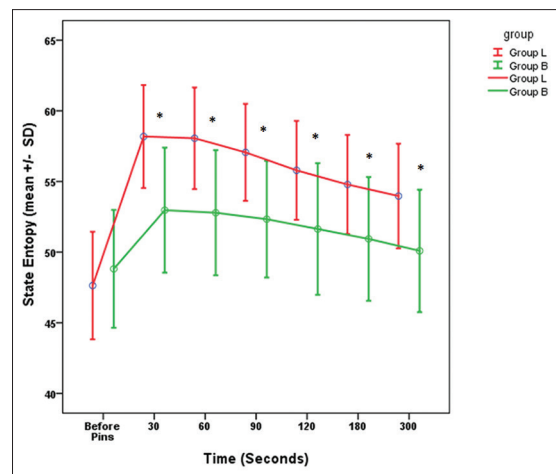


Figure 5: State entropy changes in two groups. \* $P < 0.05$

Labetalol is an adrenergic receptor blocker with mild alpha-1 and prominent beta-adrenergic receptor blocking actions. The onset of action when administered IV is 5 min. Labetalol has been used previously to blunt hemodynamic changes to laryngoscopy and intubation,<sup>[21]</sup> and has been shown to be effective. In our study, there was a significant increase in HR, MAP, and spectral entropy values following skull pin application as compared to scalp block. Possible adverse effects include bradycardia and hypotension. We did not, however, notice any adverse effects in the labetalol group in our study.

Bithal *et al.*<sup>[7]</sup> studied the changes in BIS index after skull pin application, and they observed that lignocaine infiltration at the pin application site, effectively prevented the rise in BIS index values. Similarly, spectral entropy has been routinely used for monitoring of the depth of anesthesia in neurosurgical patients.<sup>[22]</sup> We used spectral entropy to measure the depth of anesthesia during the study period. In our study, we noted that there is a statistically significant increase in SE and RE values in patients who received IV labetalol and a only marginal increase in patients with scalp block with bupivacaine. RE increased

by 14 and SE by 11 in group L while in group B, increases by 5 and 4 respectively, were seen.

These results demonstrate that a scalp block with bupivacaine is more effective than a bolus of IV labetalol in blunting the hemodynamic and entropy changes following skull pin application.

## Conclusion

Scalp block with bupivacaine and IV labetalol are both effective in attenuating the rise in HR, systolic, diastolic and MAP, and spectral entropy following the application of Mayfield skull pins. However, scalp block is more effective than labetalol.

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