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A Prospective Randomized Controlled Study to Assess the Efficacy of Gabapentin in Attenuating the Haemodynamic Responses during Skull Pin Insertion in Patients Undergoing Elective Craniotomy

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Abstract: *Application of skull pins during craniotomy produces a significant haemodynamic response. We hypothesized that oral premedication of gabapentin would attenuate this response. Forty ASA I and II patients of age group 16 – 40 years, scheduled to undergo elective craniotomy for intracranial tumour resection were randomly divided into two groups. Group A received vitamin tablet and group B patients received 900 mg of gabapentin 2 hours before the induction of anaesthesia along with lignocaine scalp infiltrations. We assessed heart rate and blood pressure responses every 1 minute interval after pin insertion until the end of 10 minutes. Heart rate in gabapentin group (88.35 ± 12.11) at 3rd minute of skull pin insertion was statistically significant (p-0.017) in comparison to placebo group (97.50 ± 10.95) which continued upto 10 minutes. Systolic blood pressure in gabapentin group (130.75 ± 11.420) at the 2nd minute was statistically significant (p-0.009) when compared to the placebo group (139.15 ± 7.63) and significant attenuation continued upto10 minutes. The gabapentin group had a statistically significant attenuation of mean arterial pressure (p value 0.02) after 4th minute of skull pin placement. To conclude, 900 mg of gabapentin administered orally 2 hours prior to the induction of anaesthesia along with lignocaine scalp infiltration produced a delayed attenuation of haemodynamic response to skull pin insertion.*

Key words*: Gabapentin, Craniotomy, Skull Pin Response*

I. Introduction

The application of the skull-pin head-holder, used to stabilize the head during craniotomies, produces an intense nociceptive stimulus and results in abrupt increases in blood pressure, heart rate and intracranial pressure (ICP). Different methods including local anesthetic infiltrations [2,3,4], skull blocks[4], narcotics [5-9] and deepening of anesthesia with inhalation and intravenous anaesthetics [10] have been used to blunt this deleterious effect with variable success.

Gabapentin [11], a structural analogue of the neurotransmitter γ-aminobutyric acid (GABA) frequently used for preoperative anxiolysis, postoperative analgesia, attenuation of the haemodynamic response to intubation has been investigated for attenuation of pressor responses due to skull pin insertion [12]. Considering the perioperative uses of gabapentin and the absence of adequate number of studies, we decided to investigate and corroborate the role of gabapentin in maintaining haemodynamic stability during skull pin placement in elective craniotomies.

II. Methods

After obtaining approval from the Institutional Ethics Committee, with alpha error of 0.05% and power of 80, forty consecutive ASA I and II patients scheduled to undergo elective craniotomy for intracranial tumour resection were prospectively recruited into the study. Patient refusal, emergency craniotomy, patients with raised ICP, obesity, systemic comorbidities such as cardiac, renal, hepatic and endocrine, uncontrolled hypertension, patients planned for intracranial aneurysm clipping, patients with known or suspected pregnancy and lactating mothers, patients on multiple antiepileptic drug therapy including gabapentin for seizure prophylaxis, patients in whom May field clamp was applied more than once, patients undergoing tumour decompression in positions other than supine, American Society of Anaesthesiologist (ASA) Physical status III & above patients were excluded from the study.

The sample size was calculated based on the previous study [12]. By computer generated randomization, patients were assigned into two groups, Group A (Placebo, n = 20) and Group B (Gabapentin, n =20). The study drug that is, vitamin B complex (Group A) or gabapentin (Group B) order was written by an independent anaesthesiologist not participating in the study during the preoperative visit. The operating room anaesthesiologists, surgeons, nurses and recovery room staff were blinded to the study.

Group A patients were administered placebo (Vitamin B complex) orally 2 hrs before induction of anaesthesia followed by scalp infiltration with 2 ml of 2% lignocaine at each of the 3 pin sites 1 minute before application of skull pin. Group B patients were administered gabapentin 900 mg orally 2 hrs before induction of anaesthesia followed by scalp infiltration with 2 ml of 2% lignocaine at each of the 3 pin sites 1 minute before application of skull pin.

Preoperative anaesthetic examination was done and witnessed written informed consent was obtained from all patients. Before shifting to the operating room, the secondary outcome of the study, the sedation level of the patients in the pre op holding area was assessed, using Ramsay Sedation Score (RSS) [13] (Table 1). Upon arrival in the operating room, monitoring was established with 6 lead electrocardiogram (Leads II and V5), pulse oximetry and non-invasive blood pressure cuff. The baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SpO_2) were recorded. Intravenous (IV) access was secured with a either 18G or 16G intravenous cannula preferably on the dorsum of right hand and Normal Saline (NS) was started. The radial artery was cannulated with a 20G arterial cannula and transduced to monitor invasive blood pressure.

Table1. Ramsay Sedation Score

Description	Score
Anxious or agitated or both	1
Co-operative, oriented & tranquil	2
Responds to commands only	3
Brisk response to a light glabellar tap	4
Sluggish response to a light glabellar tap	5
No response	6

The anaesthesia technique was standardized in both the groups. After preoxygenation for 3min with 100% oxygen, patients were induced with fentanyl (2mcg/kg) and thiopentone sodium (5 mg/kg). After mask ventilation was confirmed, the patient was paralyzed with vecuronium (0.1mg/kg). Preservative free 2% lignocaine (1.5 mg/kg) was administered 90 seconds prior to the intubation in both the groups. Patients were intubated 3 minutes after muscle relaxant was administered with appropriate sized flexometallic endotracheal tubes. Anaesthesia was maintained with air and oxygen in the ratio of 50:50 and sevoflurane titrated to minimum alveolar concentration (MAC) value of 1 by using monitoring MAC (Philips Intellivue GS- M1019A). Additional monitoring after induction of anaesthesia included end-tidal CO_2 ($ETCO_2$), temperature and urine output. Mechanical ventilation was adjusted to maintain $ETCO_2$ of 30 to 35mm Hg. A central venous access was obtained with a peripherally inserted central catheter device (PICC) through the basilic or cephalic vein.

Two ml of 2% lignocaine solution without adrenaline was infiltrated in all patients, at each of the 3 pin sites (total volume 6mL) with the last pin site infiltration ending 1 minute before application of the skull pin system. The skull pin insertion technique was standardized in all patients included in the study. At the end of surgery, neuromuscular blockade was adequately reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). After adequate neuromuscular recovery and stable hemodynamic status, patients were extubated. Postoperatively heart rate, blood pressure, O_2 saturation, pain and sedation scores were monitored in neurosurgery intensive care unit for next 24 hours.

The following parameters are the primary outcomes of the study and recorded before induction of anesthesia (Baseline), 1 minute after scalp infiltration but just before application of pin (Before PIN) and subsequently at every 1 minute interval after pin insertion until the end of 10 minutes (PIN 1 to PIN 10) :

1. Heart Rate (HR)
2. Systolic blood pressure (SBP)
3. Diastolic blood pressure (DAP)
4. Mean arterial pressure (MAP)

Hemodynamic parameters were considered 'critical' and treated immediately with propofol 30 mg IV bolus if heart rate and blood pressure values are more than 20% of baseline values. If HR < 50 beats per min, atropine 0.6 mg IV was given. If SBP < 90 mm Hg, phenylephrine IV bolus was given.

The statistical evaluation was done using the "Statistical Package for Social Sciences (SPSS) for Windows Release 15.0". Data were expressed as means ± standard deviation (SD), or as the number of patients. A P value of <0.05 was considered significant. Independent t test and Pearson chi square test were to analyze the data

III. Results

The mean age of patients in gabapentin group was 42.65 ± 12.04 yrs and in the placebo group was 38.65 ± 11.49 years (Fig 1). The data was analyzed using Independent t test with p value of 0.289 (Table 2). The difference between the two means was not statistically significant. Sex distribution between the two groups was

comparable (Fig 2). The data was analyzed using Pearson chi square test with p value of 0.741 (Table 2). There was no statistically significant difference in the distribution of patients according to the ASA physical status between the two groups (Fig 3). The data was analyzed using Pearson chi square test with p value of 0.523. (Table 3). The comparison of baseline haemodynamic parameters was statistically insignificant (p>0.05) between the two groups (Table 4).

Table 2. Comparison of age (in years) and sex between the two groups

Demographic Characteristics	**Mean ± SD- Standard Deviation**		**p value**
	Group A	**Group B**	
Age in years	38.65 ± 11.49	42.65 ± 12.04	0.289
Sex	Male = 14 (70%) Female = 6(30%)	Male = 12(60%) Female = 8(40%)	0.741

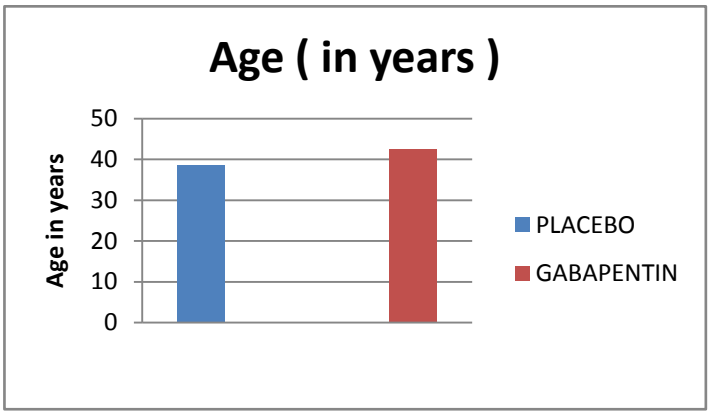

Fig 1. Distribution of patients by age

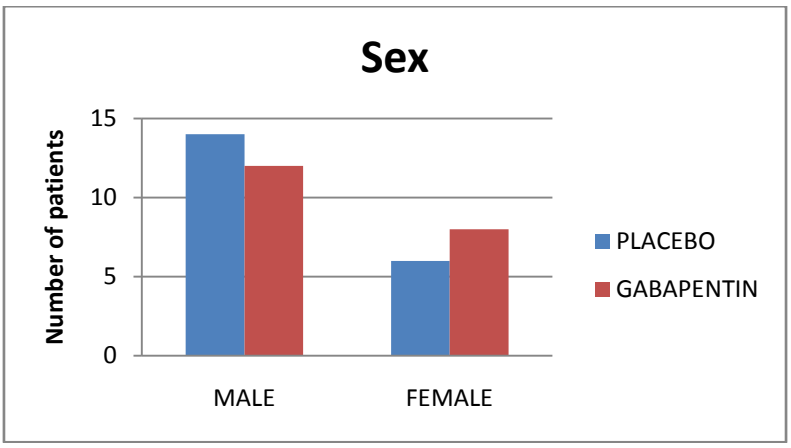

Fig 2. Distribution of patients by sex

Table3. Classification of patients according to the ASA physical status with percentage distribution within and between the two groups

ASA	**Placebo**		**Gabapentin**		**Total**		**p value**
	N	%	N	%	N	%	
I	10	50	7	35	17	42.5	0.523
II	10	50	13	65	23	57.5	
TOTAL	20	100	20	100	40	100	

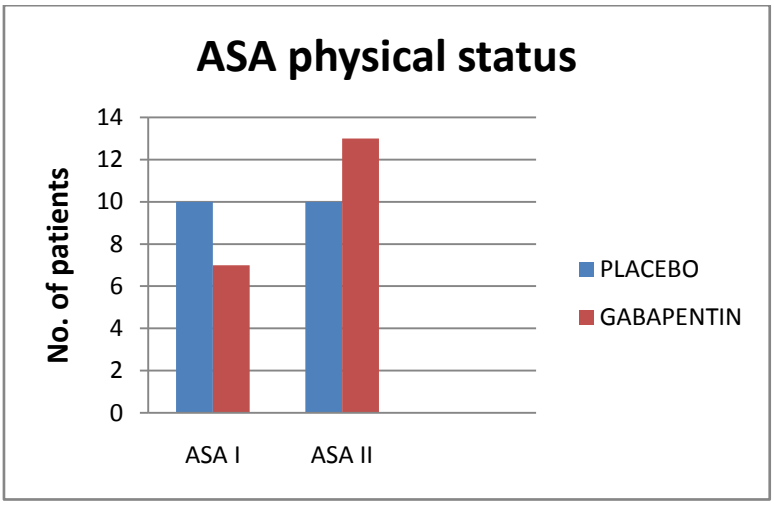

Fig 3. Distribution of patients by ASA physical status

Table 4. Comparison of baseline parameters between the groups

Baseline Parameters	Mean		p value
	Group A	Group B	
Mean HR (b /min) ± SD	76.60 ± 9.827	83.30 ± 15.685	0.114
Mean SBP (mmHg) ± SD	123.10 ± 9.380	125.45 ± 7.564	0.389
Mean DBP (mmHg) ± SD	72.10 ± 7.867	76.410 ± 9.179	0.120
Mean MAP (mmHg) ± SD	89.25 ± 7.405	92.65 ± 7.485	0.157

SD- standard deviation; HR–heart rate; SBP-systolic blood pressure; DBP-diastolic blood pressure; MAP-mean arterial pressure

Heart rate in gabapentin group (88.35 ± 12.11) at 3rd minute of post skull pin insertion was statistically significant (p-0.017) when compared to the placebo group (97.50 ± 10.952) (Table 5). This statistically significant difference in heart rate was observed upto 10 minutes post skull pin placement in the gabapentin group (Fig 4).

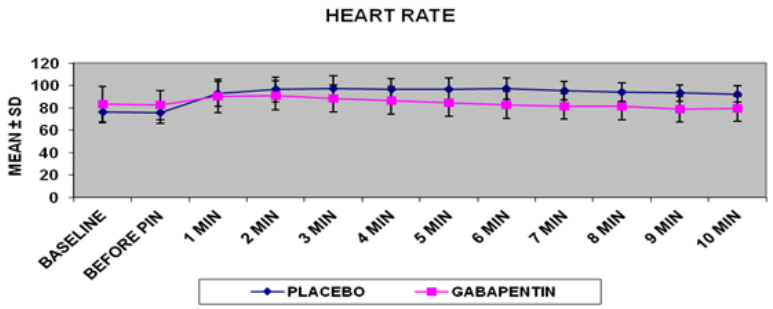

Fig 4. Comparison of Heart Rate (HR) between the two groups

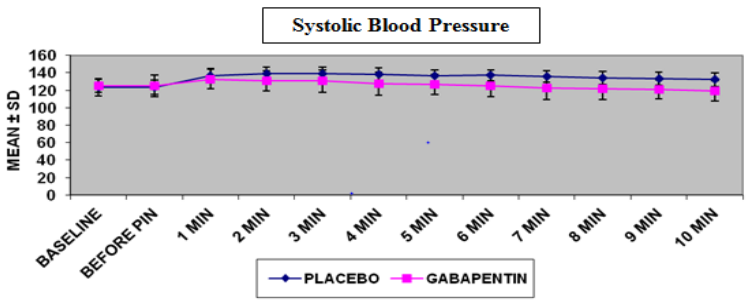

Fig 5. Comparison of Systolic Blood Pressure (SBP) between the two groups

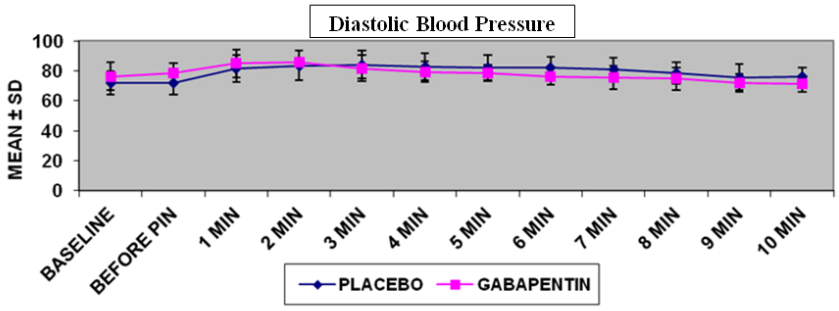

Fig 6. Comparison of Diastolic Blood Pressure (DBP) between the two groups

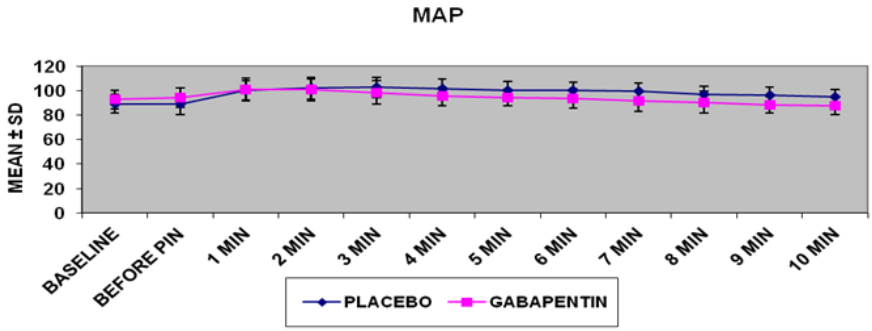

Fig 7. Comparison of Mean Arterial Pressure (MAP) between the two groups

Systolic blood pressure in gabapentin group (130.75 ± 11.420) in the 2nd minute post skull pin placement was statistically significant (p value - 0.009) when compared to the placebo group (139.15 ± 7.63) (Table 6). This statistically significant difference in systolic blood pressure was observed upto10 minutes post skull pin placement in the gabapentin group (Fig 5). The Diastolic Blood Pressure (DBP) in the gabapentin group just before pin placement was significantly lower when compared to the placebo group (p value 0.011) (Table 7). The later measurements after pin placement were variable in comparison to the placebo group (Fig.6). The gabapentin group had a statistically significant attenuation mean arterial pressure response (p- 0.02) after 4th minute of skull pin placement when compared to the placebo group (Table 8). This trend continued till the 10th minute post pin placement (Fig. 7).

Table 5. Comparison of Heart Rate (HR) between the two groups

Heart Rate (bpm)	Group	N	Mean ± SD	P value
HR Baseline	Group A Group B	20 20	76.60 ± 9.827 83.30 ± 15.685	0.114
HR Before pin	Group A Group B	20 20	76.00 ± 10.042 82.40 ± 13.216	0.093
HR 1 MIN	Group A Group B	20 20	92.65 ± 10.917 90.55 ± 14.767	0.612
HR 2 MIN	Group A Group B	20 20	96.65 ± 11.127 91.25 ± 12.908	0.165
HR 3 MIN	Group A Group B	20 20	97.50 ± 10.952 88.35 ± 12.115	0.017
HR 4 MIN	Group A Group B	20 20	96.60 ± 9.561 86.80 ± 12.138	0.007
HR 5 MIN	Group A Group B	20 20	96.90 ± 10.094 84.80 ± 12.404	0.002
HR 6 MIN	Group A Group B	20 20	97.20 ± 9.350 82.55 ± 12.172	0.000
HR 7 MIN	Group A Group B	20 20	95.35 ± 8.242 81.40 ± 11.255	0.000
HR 8 MIN	Group A Group B	20 20	94.00 ± 8.375 81.45 ± 12.163	0.001
HR 9 MIN	Group A Group B	20 20	93.35 ± 7.191 78.95 ± 11.619	0.000
HR 10 MIN	Group A Group B	20 20	92.50 ± 7.473 79.35 ± 11.198	0.000

SD- standard deviation; HR– heart rate; bpm-beats per minute

Table 6. Comparison of Systolic Blood Pressure (SBP) between the groups

SBP (mmHg)	Group	N	Mean	Standard Deviation	P value
SBP Baseline	Group A Group B	20 20	123.10 125.45	9.380 7.564	0.389
SBP Before pin	Group A Group B	20 20	123.50 125.10	8.495 12.143	0.632
SBP 1 MIN	Group A Group B	20 20	137.00 132.90	8.265 10.853	0.187
SBP 2 MIN	Group A Group B	20 20	139.15 130.75	7.631 11.420	0.009
SBP 3 MIN	Group A Group B	20 20	139.20 130.60	7.157 12.886	0.013
SBP 4 MIN	Group A Group B	20 20	138.55 127.25	7.134 13.166	0.002
SBP 5 MIN	Group A Group B	20 20	136.50 126.60	6.565 11.546	0.002
SBP 6 MIN	Group A Group B	20 20	137.15 125.25	6.401 12.341	0.000
SBP 7 MIN	Group A Group B	20 20	136.15 122.80	6.667 13.813	0.000
SBP 8 MIN	Group A Group B	20 20	134.15 122.20	7.162 13.193	0.001
SBP 9 MIN	Group A Group B	20 20	133.65 120.95	7.343 11.062	0.000
SBP 10 MIN	Group A Group B	20 20	132.35 119.10	7.721 11.466	0.000

Table 7. Comparison of Diastolic Blood Pressure (DBP) between the groups

DBP (mmHg)	Group	N	Mean	Standard Deviation	P value
DBP Baseline	Group A Group B	20 20	72.10 76.40	7.867 9.179	0.120
DBP before pin	Group A Group B	20 20	72.20 78.35	7.885 6.643	0.011
DBP 1 MIN	Group A Group B	20 20	81.85 85.00	8.999 9.257	0.282
DBP 2 MIN	Group A Group B	20 20	83.70 85.75	10.173 9.101	0.506
DBP 3 MIN	Group A Group B	20 20	84.30 81.85	9.376 8.549	0.393
DBP 4 MIN	Group A Group B	20 20	82.90 79.50	8.985 6.825	0.186
DBP 5 MIN	Group A Group B	20 20	82.20 78.45	8.575 5.463	0.107
DBP 6 MIN	Group A Group B	20 20	82.05 76.45	7.294 5.735	0.010
DBP 7 MIN	Group A Group B	20 20	80.95 75.65	7.776 7.534	0.035
DBP 8 MIN	Group A Group B	20 20	78.70 74.85	7.183 7.506	0.106
DBP 9 MIN	Group A Group B	20 20	75.85 72.25	80792 6.008	0.139
DBP 10 MIN	Group A Group B	20 20	75.95 71.40	6.557 5.605	0.024

Table 8. Comparison of Mean Arterial Pressure (MAP) between the groups

MAP (mmHg)	Group	N	Mean	Standard Deviation	P value
MAP Baseline	Group A Group B	20 20	89.25 92.65	7.405 7.485	0.157
MAP Before pin	Group A Group B	20 20	88.70 94.00	8.086 7.974	0.044
MAP 1 MIN	Group A Group B	20 20	100.20 101.05	8.186 9.162	0.759
MAP 2 MIN	Group A Group B	20 20	102.10 100.85	8.837 8.970	0.659
MAP 3 MIN	Group A Group B	20 20	102.60 98.05	8.172 9.456	0.112
DBP 4 MIN	Group A Group B	20 20	101.35 95.40	7.949 7.549	0.020
MAP 5 MIN	Group A Group B	20 20	100.20 94.60	7.374 6.652	0.016

MAP 6 MIN	Group A Group B	20 20	100.40 93.05	6.411 7.810	0.002
MAP 7 MIN	Group A Group B	20 20	99.45 91.45	6.817 8.709	0.003
MAP 8 MIN	Group A Group B	20 20	97.15 90.55	6.714 8.841	0.011
MAP 9 MIN	Group A Group B	20 20	96.10 88.55	6.735 6.621	0.001
MAP 10 MIN	Group A Group B	20 20	94.85 87.35	6.277 6.815	0.001

The gabapentin group had a significantly sedation score (p value < 0.000) when compared to the placebo group (Table 9). The Ramsay sedation scores (RSS) were observed to be 3 or less in all the patients in the study. 85% of the patients in the gabapentin group had RSS of 2 and were co-operative, oriented and tranquil before induction of anaesthesia, providing adequate anxiolysis to the patients.

Table 9. Comparison of preoperative sedation scores between the groups

Ramsay sedation score	**Groups**		**Total**	**P value**
	Group A	**Group B**		
1	20 (100%)	0 (0%)	20 (50%)	0.000
2	0 (0%)	17 (85%)	17 (42.5%)	
3	0 (0%)	3 (15%)	3 (7.5%)	
Total	20 (100%)	20 (100%)	40 (100%)	

IV. Discussion

Most neurosurgical cases involve the placement of skull pins when a rigid fixation is required for craniotomy. Most commonly used instrument for skull fixation is the Mayfield Headrest and Skull Clamp System, a C-shaped metal clamp with 3 sharpened metal pins arranged triangularly. Tightening of the pins into the periosteum produces approximately 80 pounds of pressure [14]. Thus, it produces a reproducible source of intense stimulus each time the pins are applied resulting in brief but undesirable increases in HR, BP, and ICP [1]. This increase in heart rate and blood pressure is undesirable in patients with coronary heart disease in whom the myocardium is vulnerable to hemodynamic stressors and may end up in myocardial ischemia, pulmonary edema. [1,15] But in a patient undergoing craniotomy, either for an intracranial mass or aneurysm the primary concern is the increase in ICP associated with the hemodynamic alterations due to pinning. In patients with intracranial mass lesions or aneurysms there is abnormal autoregulation of cerebral blood flow and hence increase in the arterial pressure, can lead to increase in ICP.[1]Moreover uncontrolled increase in blood pressure can precipitate cerebral edema and herniation. [16]

Hence, it is clear that the hemodynamic response to skull pin response needs to be attenuated. So there has been a multitude of attempts in finding an ideal technique/drug to attenuate the noxious stimuli and thereby the accompanying sympathetic stimulation without altering the dynamics of intracranial milieu or at the least with minimal alteration. Various modalities have been in vogue for the suppression of the haemodynamic response secondary to skull pin placement. Systemic drugs such as subanaesthetic doses of ketamine17, alpha 2 agonist such as dexmedetomidine [18], clonidine[14], opioids such as Fentanyl [5-7], sufentanil [7], and beta blocker like esmolol[19] have been tried in various studies.

Local anaesthetic agents are infiltrated into the skull before application of pins to attenuate the haemodynamic responses either alone or in combination with other drugs. [2,3,4] Hence we used it in both the groups as the patients in placebo group should not be denied of this advantage and to standardize the study protocol. Although the proposed benefits of local anaesthetic infiltration include use of small volume of the drug, rapid onset of analgesia, no additional increase in depth of anaesthesia and attenuation of haemodynamic perturbations, the true advantage can be obtained if the local anaesthetic is infiltrated into the scalp at least 1 to 2 minutes before the insertion of the pins. Secondly, the infiltrated dose may be inadequate and the area infiltrated may not match the exact pin site.

A study by Misra et al [12] found that systemic administration of gabapentin prior to the induction of the anaesthesia caused a significant decrease in haemodynamic response to skull pin placement. Its use has been documented for preoperative anxiolysis, postoperative analgesia, attenuation of the haemodynamic response to intubation, chronic post-surgical pain, postoperative nausea and vomiting and delirium.

Gabapentin (1-aminomethyl-cyclohexaneacetic acid) is an amino acid that has the structure similar to neurotransmitter GABA without any significant interaction with any other neurotransmitter [20, 21]. It is an anti-convulsant with tolerable side effects. The absorption rate is good after oral administration with maximal plasma concentration noted after two to three hours [21]. It is widely distributed (volume of distribution of 58 liters) with protein binding capacity of 3 to 5% [21]. There is no enzymatic induction and it readily crosses the

blood-brain barrier. It excreted unchanged through the kidneys, but a small proportion is eliminated in the faeces, with an elimination half-life of 5 to 9 hours [22].

Considering the perioperative advantages of gabapentin and the absence of adequate number of randomized control studies in evaluating the efficacy of gabapentin in suppression of haemodynamic response to skull pin placement, we initiated a randomized control study to reaffirm the role of gabapentin in maintaining haemodynamic stability during skull pin placement. Based on study by Mishra et al [12], we have chosen a dose of gabapentin 900 mg which was administered 1 to 2 hours prior to the induction [11].

In our study, demographic profile was comparable between the two groups. All forty patients recruited into the study were included without any drop outs. There were no critical responses in any of the hemodynamic parameters during the study. The baseline heart rate values in our study showed no statistical significance (p - 0.114) between the groups despite the adequate favourable sedation scores in gabapentin group which is comparable to the previous study by Mishra et al [12] where p value is 0.1 between similar groups. In contrast to study by Mishra et al[12], there were no statistically significant attenuation of heart rate response during the initial 3 minutes of post skull pin placement in patients who received gabapentin. Although the maximal HR after pinning was noted at 3rd minute, which was 97.50 ± 10.952 beats/min in group A (Placebo), 88.35 ± 12.11 beats/min in group B (Gabapentin), increase in HR in both the groups were not more than 20% of baseline preinduction values (Group A – 76.60 ± 9.82, Group B – 83.20 ± 15.68) (Table.5). The probable reason behind these variations may be due to the differences in patient age groups included in the study.

Baseline Systolic blood pressures (SBP) between the two groups were comparable. But there were no statistically significant increase in systolic blood pressure (SBP) after 2 minutes of skull pin placement in patients who received gabapentin when compared to the placebo group. In contrast to previous study (p value<0.001), the first minute post pinning systolic blood pressure was statistically insignificant (p – 0.187) between the groups, eventhough the rise in SBP was not critical (Table.6). Although the statistical significance was not found between the groups while analysing diastolic BP, the rise in diastolic pressures were not more than the 30% of baseline values (Table.7)

In our study we also found that there were no statistically significant increases in mean arterial pressures (MAP) between the groups, during the initial 3 minutes of pinning (Group A - 102.60 ± 8.172 mm Hg, Group B - 98.05 ± 9.456 mm Hg). Later at 4th minute there was control in rise of MAP in Gabapentin group (95.40 ± 7.549 mm Hg) compared to placebo group (101.35 ± 7.949 mm Hg), which continued till at the end of 10th minute suggesting a lower pressor response. (Table 8)

Preoperative sedation score were observed to be less than 3 in both groups. Patients were calm and cooperative in the gabapentin group (Table 9) when compared to the placebo group, reaffirming the anxiolytic properties of gabapentin. Tu re et al, [23] found that in patients undergoing supratentorial tumor resection, premedication with gabapentin was associated with delayed extubation and increased postoperative sedation. In their study, patients received higher dose of gabapentin (1200mg in divided doses starting 1 week before surgery) as compared to the single dose of 900mg in our patients which might have been the reason for the differences in sedation and recovery in our patients.

Our study had several limitations. The major one is, patients with Glasgow Coma Scale (GCS) below 15 were not included in this study and either of these groups could have had a distinct advantage over the other in those with raised ICP, which could not be addressed in our study. Direct estimation of ICP was not measured, which would probably be the gold standard. Only the hemodynamic responses were studied in our study. Plasma catecholamine levels were not measured to assess the comparability between the two groups in attenuating the sympatho-adrenal response. Phenytoin could have interacted with gabapentin to attenuate the hemodynamic response to pinning because of its analgesic effects; however, as it was impossible to exclude antiepileptic therapy preoperatively, we therefore excluded patients on multiple antiepileptic drugs and included the patients receiving only phenytoin.

We can thus conclude from the present study that in patients posted for elective craniotomy for intracranial tumour resection, gabapentin 900 mg given orally 2 hours prior to the induction of anaesthesia along with lignocaine scalp infiltration produced a delayed attenuation of haemodynamic responses to skull pin insertion. Larger meta-analysis is required to strengthen the evidences for future gabapentin usage.

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