Original Article

Effect of add-on Gabapentin premedication on hemodynamic response to skull pin insertion

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Abstract

Background and Aims: Effectiveness of oral gabapentin premedication in suppressing response to laryngoscopy and tracheal intubation suggests its potential for attenuating skull pin insertion response. The present study was therefore planned to evaluate the effect of add-on oral gabapentin premedication to local anesthetic injection at pin insertion site in obtunding hemodynamic response.

Material and Methods: Sixty adult patients posted for elective craniotomy were enrolled for a prospective, randomized and double-blinded study. Group I patients received gabapentin 900 mg orally as premedication whereas Group II patients received oral placebo. Both groups were administered subcutaneous (s.c.) injection (Inj) 2% lignocaine 2 mL at all four pin insertion sites. Mean arterial pressure (MAP) and heart rate (HR) were measured every 30 s for the initial 10 min. Increases in HR beyond 20% and MAP 30% above baseline were treated with bolus intravenous (IV) Inj propofol 30 mg. Quantitative data was compared using Student's t-test and Mann Whitney U test, while categorical data was compared using Chi-square (χ^2) test.

Results: The increase in HR and MAP from baseline was significantly greater and it remained above baseline levels longer in Group II as compared to Group I. Twenty-one patients (70%) received rescue boluses of propofol with a mean dose of 45.00 ± 39.98 mg in Group II as compared to nine (30%) patients receiving mean of 18.20 ± 29.04 mg in Group I. ($P = 0.015$). The mean emergence time and sedation scores in both the groups were statistically similar ($P = 0.060$).The incidence of adverse effects like hypotension, bradycardia, nausea/vomiting, sedation or dry mouth were similar in both the groups.

Conclusion: Add-on oral gabapentin premedication potentiates the effect of s.c. lignocaine Inj for suppression of skull pin insertion response.

Keywords: Craniotomy, gabapentin, hemodynamics, premedication

Introduction

Skull pins are frequently inserted for application of Mayfield or Sugita head-holder for patients undergoing craniotomy. Insertion of skull pins causes a brief but intense painful stimulus during which there can be sudden precipitous increases in the heart rate (HR), mean arterial pressure (MAP) and intracranial pressure (ICP).[1] Hypertensive patients and those having deranged cerebral auto-regulation are especially prone to the deleterious effects of these hemodynamic perturbations.[2]

Anesthesiologists attempt to attenuate these detrimental hemodynamic responses with measures like local anesthetic (LA) infiltration at pin sites, scalp blocks, additional doses of opioids, β-blockers, combined α and β blockers such as labetalol, α-2 agonists such as clonidine, dexmedetomidine and IV lignocaine.[3-5] Recently, oral

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gabapentin premedication has been successfully used for suppressing sympathetic response to laryngoscopy and tracheal intubation (LETI).[6] Since the pin site insertion response is similar to laryngoscopy-induced pressor response and is mediated via the same sympathoadrenal pathways, it was hypothesized that add-on oral gabapentin premedication may be effective in suppressing the scalp pin insertion response as well.[1,7] A single dose of gabapentin was chosen to be administered since skull pin insertion produces a brief, one-time stimulus obviating the need for repeated doses. Misra *et al.*[7] also reported blunting of skull pin insertion response with oral gabapentin premedication in patients undergoing craniotomy. The study, however, was performed in only a small number of patients and a need for a larger study was expressed by the authors. Thus, the present study was designed to evaluate the effect of add-on oral gabapentin premedication on hemodynamic response to skull pin insertion and emergence characteristics when administered along with pin site injection of LA in patients undergoing craniotomy.

Material and Methods

This study was conducted on 60 adult patients belonging to American society of Anesthesiologists (ASA) class I and II of either sex between ages 18 and 60 years, undergoing elective craniotomy for intracranial tumor surgery in supine position after approval from Institutional Ethics Committee (IEC). Written informed consent was taken from all patients (CTRI number: CTRI/2018/03/012809).

Exclusion criteria included obese patients having body mass index (BMI) ≥30 kg/m^2, uncontrolled hypertension, those suffering from significant co-morbidities like acute or chronic renal failure, ischemic heart disease, cirrhosis of liver, uncontrolled hypertension, diabetes mellitus or other endocrinopathies, patients with clinical features suggestive of raised intra-cranial pressure (ICP) like altered sensorium, hypertension, bradycardia or dilated pupils or those with a known history of drug allergy to either gabapentin or lignocaine. Pregnant patients, those taking anti-psychotic medications, patients undergoing emergency craniotomy or intracranial aneurysm clipping and those in whom skull pins were inserted more than once were excluded.

All patients underwent a thorough pre-anesthetic check-up a day prior to surgery, which included detailed history, clinical examination and investigations comprising a complete hemogram, electrocardiogram (ECG), chest X-ray, renal function tests, pro-thrombin time (PT) and internationalized normal ratio (INR). Patients were advised nil per oral (NPO) for8h for solid foods and 2h for clear fluids prior to surgery and were administered tablet (Tab) Alprazolam 0.5 mg and Tab Ranitidine 150mg after dinner on the night prior to surgery.

The patients were randomly allocated to either of the two groups based on computer-generated random numbers which were kept in a sealed envelope and opened at the end of study. On the day of surgery, 2 hours prior to shifting to operating room (OR), patients were administered premedication by a resident doctor who did not participate in further management of the patients.

Group I patients were premedicated with three capsules of gabapentin 300 mg each, whereas, Group II patients were administered oral placebo in the form of three sugar-filled capsules (visibly similar to gabapentin capsules).

On arrival to the OR, standard monitoring which includes five lead ECG, pulse oximetry and non-invasive blood pressure (NIBP) were applied. An IV line was secured using an 18 G cannula preferably on the left dorsum of the hand and IV fluids started. Sedation level of the patient was recorded using modified Wilson's sedation score.[8] After performing modified Allen's test and local skin infiltration with 2% lidocaine, a 20 G cannula was inserted in the radial artery, preferably of left hand and arterial blood pressure monitoring started. Baseline hemodynamic parameters which included HR, systolic blood pressure (SBP), diastolic blood pressure (DBP) and MAP were recorded at this stage. Patients were administered Inj glycopyrrolate 0.2 mg IV and metoclopramide 10mg IV. Anesthesia was induced with fentanyl 2 μg/kg IV and propofol 1.5-2 mg/kg IV titrated to loss of consciousness followed by muscle relaxant atracurium 0.5 mg/kg IV. Trachea was intubated with appropriate-sized cuffed endotracheal tube passed orally after administering an additional dose of 0.5 mg/kg propofol.

Anesthesia was maintained using O_2:Air (1:2) on closed circuit using total fresh gas flow of 2 L/minute and infusion of propofol titrated according to HR and blood pressure. Inj atracurium in increments of 5 mg was administered as guided by neuromuscular monitoring maintaining a train of four (TOF) count of 0. The patients were ventilated with tidal volume of 6-8 mL/kg and respiratory rate of 12-14 per minute to maintain an end-tidal CO_2 concentration of 30-35 mmHg. A total volume of 500mL of normal saline was infused in all the patients from induction until skull pin insertion. Additional doses of fentanyl were avoided until skull pin placement. In both the groups, 60s prior to application of head holder and skull site pin insertion, 2 mL of 2% solution of lignocaine was injected subcutaneously at each of the four pin insertion sites.

HR, SBP, DBP and MAP were recorded just before administration of pin site local anesthetic (LA) injection, just before application of pin (before PIN) and subsequently at every 30 s interval after pin insertion until the end of 10 min (PIN 1 to PIN 20).

Any episode of tachycardia (defined as HR >20% of baseline value) and hypertension (defined as MAP >30% of baseline value) during this 10-minute interval was recorded and managed with a bolus of propofol administered in 30 mg IV aliquots. The number of propofol aliquots, total dose of rescue propofol administered and the number of patients requiring rescue therapy was recorded. Hypotension (defined as MAP <30% of baseline values) was treated by administering Inj ephedrine 3mg IV bolus which was repeated after 2 min if hypotension was not corrected. Bradycardia (defined as HR <60/min) was treated by administering Inj. atropine 0.6mg IV. After the initial 10 min, anesthesia was supplemented with sevoflurane and maintained at the discretion of the anesthesiologist conducting the case.

At the end of surgery, all patients were administered infusion Inj paracetamol 1g IV and ondansetron 8 mg IV at the beginning of the skin closure. The infusion of propofol was stopped on starting of skin closure and sevoflurane was stopped once dressing of the incision site was complete. After wound dressing, the patient was made supine and fresh gas flow was changed to 4 L min^{-1} of oxygen. The residual neuromuscular block was reversed with Inj. Neostigmine 2.5 mg IV and Inj. glycopyrrolate 0.4 mg IV and tracheal extubation was performed. Emergence time defined as the time elapsing from discontinuation of anesthetics to the time when the patient was able to recall his/her name and date of birth (on verbal prompting every 2 min after extubation) was measured in all patients.[9] Wilson's sedation score was noted again after shifting the patient to post-anesthesia care unit (PACU).The duration of study was from the administration of pin site LA till shifting the patient to PACU.

Sample size calculation was performed by post-hoc power analysis using the software package, G*Power version 3.1.9.2 (Franz Faul, University Kiel, Germany). Based on a study by Misra *et al.*,[7] taking HR changes at 1 minute interval due to gabapentin premedication into account, a sample size of 30 per group was obtained from an effect size of 4.7, a power of 99%, an α of 0.05 to detect the mean difference of 20 in HR at 1 minute between two groups.

Data was described in terms of range; mean ± standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using Student's t-test and Mann Whitney U test for independent samples for parametric and non-parametric data, respectively. For comparing categorical data, Chi-square (χ^2) test was performed and exact test was used when the expected frequency was less than 5. A probability value (*P* value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) 21 version statistical program for Microsoft Windows.

Results

Out of the 66 patients enrolled for the study, 6 were excluded and 60 completed the study [Figure 1]. Both groups were comparable with regards to demographic profile like mean age, weight, height, BMI, sex distribution and ASA classification. [Table 1]. The mean modified Wilson's sedation scores recorded after shifting the patients to OR were statistically similar in both the groups. The mean anesthesia time and surgery time were also statistically similar [Table 2]. Twenty-one patients (70%) in Group II received propofol boluses as compared to 9 (30%) in Group I ($P = 0.002$). The mean propofol bolus dose of 45.00 ± 39.98mg administered in Group II was significantly greater than 18.20 ± 29.04 mg in Group I. ($P = 0.001$). Similarly, mean requirement of fentanyl was significantly greater in Group II [Table 2].

The mean baseline HR at the time of skull pin site LA injection was statistically similar. HR increased in both groups after application of skull pins. The mean percentage change in HR from baseline was significantly greater in Group II as compared to Group I at all time intervals [Figure 2]. The mean HR returned to near baseline values at about a 6-minute interval after skull pin insertion in Group I whereas it remained higher in Group II even at the end of the study period [Figure 2]. Both groups had similar MAP at baseline and at the time of LA injection. Similar to HR response, MAP increased in both groups after pin insertion but the increase was greater in Group II at most time intervals [Figure 3]. The difference in mean percentage change of MAP from baseline was statistically significant for 3.5 min only.

Table 1: Demographic data

	Group I (Mean±SD)	Group II (Mean±SD)	*P*
Mean Age (years)	41.87±12.38	48.10±13.25	0.065
Mean Weight (kg)	65.50±8.61	68.03±12.83	0.589
Mean Height (cm)	167.03±7.48	169.27±7.67	0.258
Mean BMI	25.05±3.91	25.29±3.69	0.806
Sex distribution Male:Female	13:17	9:21	0.284
ASA physical status I: II	18:12	18:12	1.00

Table 2: Intra-operative variables

	Group I (Mean±SD)	Group II (Mean±SD)	*P*
Pre-operative mean modified Wilson's sedation score	1.03±0.18	1.00±0.00	0.321
Duration of surgery (min)	226.17±42.68	235.83±49.34	0.420
Duration of Anesthesia (min)	282.33±45.84	287.67±49.74	0.667
Mean Propofol bolus administered in initial 10 min (mg)	18.00±29.04	45.00±39.98	0.001
Number of patients who received propofol boluses	9 (30%)	21 (70%)	0.002
Mean number of propofol boluses administered	0.60±1.04	1.5±1.33	0.005
Mean total intra-operative fentanyl administered	241.50±41.71	286.67±39.51	<0.001
Post-operative mean modified Wilson's sedation score	2.00±0.91	1.82±0.75	0.441
Mean emergence time (min)	23.10±6.84	20.13±5.00	0.060

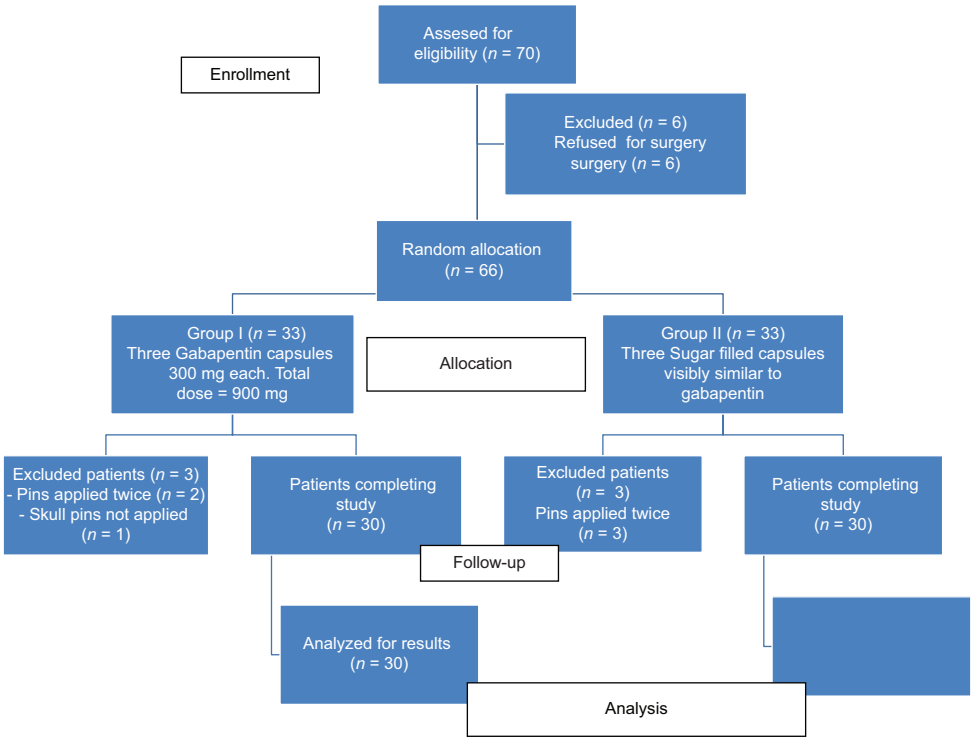

Figure 1: Consort diagram

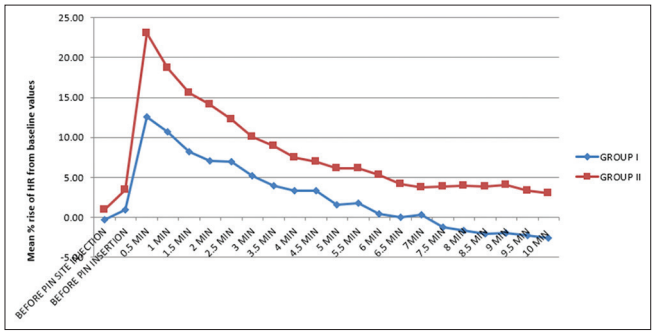

Figure 2: Mean percentage change in heart rate from baseline values

The mean emergence time of 23.10 ± 6.84 min in Group I was statistically similar to 20.13 ± 5.00 min in Group II.(P = 0.060) Both groups had similar mean pre-operative and post-operative sedation scores [Table 2]. The incidence of hypertension was 50% in Group II as compared to 20% in Group I and the difference was statistically significant (P = 0.015). Similarly, the incidence of tachycardia in group II was significantly greater at 43.3% as compared to 16.7% in Group I.(P = 0.023) There was no difference in the incidence of other adverse effects like hypotension, bradycardia, nausea/vomiting, sedation or dry mouth [Table 3].

Discussion

Oral gabapentin was administered in addition to pin site injection of local anesthetic lignocaine, as pin site LA injection is a standard technique at our institute. A single oral dose of 900 mg gabapentin was chosen as this dose has been observed to be effective in suppressing hypertensive response to noxious stimuli with minimal adverse effects.[10] Various researchers have administered oral gabapentin in doses

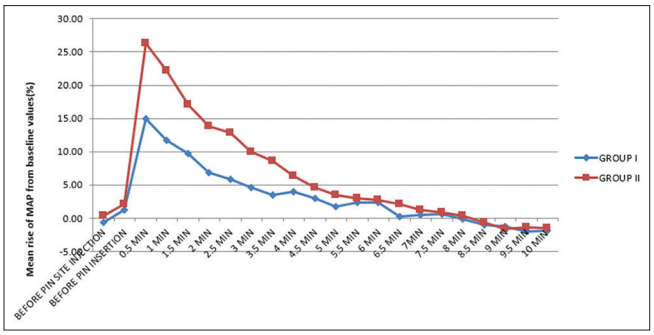

Figure 3: Mean percentage change in MAP from baseline values

Table 3: Adverse effects in the initial 10 min and after extubation

	Group I	Group II	*P*
Initial 10 min			
Hypertension	20.0%	50.0%	0.015
Tachycardia	16.7%	43.3%	0.024
Hypotension	0%	3.3%	0.313
Bradycardia	0%	0%	-
After Extubation			
Dry mouth	3.3%	3.3%	1.000
Nausea/Vomiting	23.3%	13.3%	0.253
Sedation	33.3%	20.0%	0.243
Nausea/VomitSing score	2.00±1.08	1.67±1.03	0.226

ranging from 400 to 1600 mg.[11] The effective single dose of oral gabapentin is between 800 and 1000mg.[12,13] The elimination $t_{1/2}$ of gabapentin is 5-9 h, and 2-3 h is the optimal time for attainment of its peak plasma concentration.[14] The administration of gabapentin premedication was, therefore, timed so that pin application could be around the time of its peak plasma levels.[14]

We observed that the increase in MAP and HR occurred to a significantly lesser extent and the increase lasted for much shorter duration in Group I. These findings are similar to those of Misra *et al.*,[7] who observed blunting of hypertensive response to skull pin insertion with combination of gabapentin premedication and subcutaneous infiltration of LA at the site of skull pin insertion. Similarly, Neogi[10] reported significantly reduced pressor response to LETI in patients administered with gabapentin premedication. Fassoulaki *et al.*[6] and Bhandari *et al.*,[13] however, observed that gabapentin premedication could only prevent increases in blood pressure while increases in HR could not be prevented. This difference could be due to lesser dose administered by Fassoulaki *et al.*[6] (400mg) and Bhandari *et al.*[13] (600 mg). The assertion is supported by a study which reported 800 mg gabapentin being more effective than 400 mg for suppression of LETI.[15] In addition, both Fassoulaki *et al.*[6] and Bhandari *et al.*[13] used gabapentin alone, whereas, we administered gabapentin premedication as an add-on therapy to pin site LA injection. Bafna *et al.*[11] have also reported that gabapentin blunts the hypertensive response to intubation and highlighted that this effect seems to be dose-dependent.

The exact site and mechanism of action of gabapentin is still not clear. Though gabapentin has selective agonist action on GABAB receptors, it also blocks cell membrane voltage-gated calcium channels in a manner similar to other calcium channel blockers. This has been postulated to be responsible for suppression of response to LETI and other similar stimuli.[16,17]

Propofol bolus administered as a rescue therapy to control increased HR or MAP was also required less often and in significantly reduced doses in Group I. This further supports the role of oral gabapentin premedication in blunting sympathetic response to skull pin insertion in Group I. Doleman also highlighted the efficacy of gabapentin in suppressing the pressor response to LETI and equated the efficacy of gabapentin with that of clonidine for this purpose.[18] Total intra-operative fentanyl requirement in Group I was also reduced as compared to Group II. This is not surprising as oral gabapentin is known to have opioid sparing effects both intra-operatively and post-operatively.[19]

Gabapentin is known to cause dose-related adverse effects like dizziness, drowsiness, dry mouth, bradycardia and hypotension. However, the incidence of these adverse effects was negligible in our study. Neogi *et al.*[10] also didnot observe any significant adverse effects with 900 mg gabapentin administration.The Wilson sedation score was also similar in both the groups, both before induction of anesthesia and at the end of surgery.

The present study has certain limitations worth mentioning. First of all, depth of anesthesia was not monitored during surgery. Monitoring depth of anesthesia could have provided greater insights to our results. However, placing electrodes for depth of anesthesia monitoring for craniotomy patients is extremely challenging. Second, only a single dose of gabapentin was studied. Third, we did not measure plasma levels of catecholamines at the time of skull pin insertion, limiting ourselves to monitoring hemodynamic parameters only. Future studies can be undertaken to find out the optimal dose of gabapentin for obtunding the skull pin insertion response.

Conclusion

Add-on oral gabapentin premedication potentiates the effect of s.c. lignocaine Inj for suppression of skull pin insertion response.

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Conflicts of interest
There are no conflicts of interest.

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