ORIGINAL ARTICLE

Assessment of the role of gabapentin in patients with supratentorial tumours undergoing craniotomy under general anaesthesia: A double-blind randomised study

Rabie Soliman, Gomaa Zohry

Abstract

Background: Gabapentin attenuates the haemodynamics, decreases the catecholamine release and has a neuroprotective effect. The aim of the present study was to assess the effect of gabapentin in patients with supratentorial brain tumours undergoing craniotomy under general anaesthesia. **Methods:** A radial arterial line, central venous line and ventriculostomy catheters were inserted before surgery. Anaesthesia was induced with thiopental, fentanyl and atracurium and maintained with sevoflurane, fentanyl and atracurium infusion. The study included 160 patients classified randomly into two groups: Group G: The patients received gabapentin capsules 1200 mg orally 2 h before surgery. Group C: The patients received placebo capsules. **Results:** The heart rate, mean arterial blood pressure and intracranial pressure decreased significantly with gabapentin as compared to the control group ($P < 0.05$). The dose of fentanyl and end-tidal sevoflurane was lower with gabapentin than the control group ($P < 0.05$). The urine output was higher in the gabapentin group than the control group ($P < 0.05$). The Glasgow coma scale score was better in the gabapentin group as compared to the control group ($P < 0.05$). The incidence of nausea and vomiting was lower in the gabapentin group as compared to the control group ($P < 0.05$). **Conclusions:** Pre-operative administration of gabapentin in patients undergoing craniotomy under general anaesthesia minimised the fluctuations in haemodynamics, reduced the requirements for sevoflurane and fentanyl, decreased intracranial pressure and improved the outcomes. There were some side effects associated with gabapentin such as hypotension and bradycardia.

Key words: Gabapentin, Glasgow coma scale score, haemodynamics, intracranial pressure, supratentorial craniotomy

INTRODUCTION

The intense surgical stimuli associated with craniotomy frequently induce sympathetic activation and marked changes in systemic arterial pressure, cerebrospinal fluid and intracranial pressure. Cerebrovascular responses may result in elevated intracranial pressure and reduction in cerebral perfusion pressure, especially in patients with impaired auto-regulation and compromised cerebral compliance. Perioperative hypertension in neurosurgical patients is associated with intracranial bleeding and prolonged hospital stay.[1] Thus, the prevention and control of the haemodynamic responses to nociceptive stimuli are of utmost importance to preserve cerebral homoeostasis in neurosurgical patients.[2,3]

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Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA).[3] The mechanism of action of gabapentin on the central nervous system differs from that of GABA. Gabapentin acts by decreasing the synthesis of the neurotransmitter glutamate[4] and binding to the alpha 2 delta subunits of voltage-dependent calcium channels,[5] thus acting in the manner similar to calcium channel blockers.[6] The previous studies showed that gabapentin attenuates the haemodynamics[7-12] and neuroendocrine response to laryngoscopy and tracheal intubation.[13] Gabapentin has anticonvulsant, anti-nociceptive, anxiolytic and neuroprotective activities.[14-17] The aim of the present study was to assess the effects of gabapentin in patients with supratentorial brain tumours undergoing craniotomy under general anaesthesia.

MATERIALS AND METHODS

Patients

The study was done after obtaining informed consent and approval from the Local Ethics and Research Committee, in Kasr El-Aini Hospital, Cairo University, Egypt (2014–2016). The study was double-blind randomized and included 160 patients with computed tomography scanning proof of supratentorial brain tumour and scheduled for elective craniotomy under general anaesthesia. Exclusion criteria included patients with cardiac, renal or psychiatric diseases or pre-operative treatment with beta or calcium channel blockers, known allergy to gabapentin or emergency surgery (with midline shift). All patients were admitted to the Neurosurgical Intensive Care Unit (ICU) one night before surgery. The patients were classified randomly (by simple randomization through a process of coin-tossing) into two groups (each = 80), and the study medication was given blindly by the anaesthetic staff nurse: Group G: The patients received gabapentin capsules 1200 mg (Neurontin: capsules 400 mg, Pfizer, Goedecke, GmbH, Germany) orally 2 h (in the neurosurgical ICU) before surgery. Gabapentin 1200 mg was used as it is the most effective pre-operative dose for pre-medication.[18-21] Group C: The patients received placebo capsules (the placebo capsules were filled with sugar after the evacuation of the capsule of gabapentin).

Anaesthetic technique

In the neurosurgical ICU under local anaesthesia, radial arterial catheter and central venous catheter in the sub-clavian vein were inserted for continuous monitoring of the heart rate, arterial blood pressure and central venous pressure. The ventriculostomy catheter was inserted under local anaesthesia by a neurosurgeon through a burr hole into the lateral ventricle of the brain for monitoring the intracranial pressure. In the operating room after fixing the monitors, the patients were pre-oxygenated, and then, intravenous thiopental (3–5 mg/kg) was given followed by fentanyl (3–5 mcg/kg) and atracurium 0.5 mg/kg as a bolus dose over 30 seconds, while controlled hyperventilation with 100% oxygen was started. Before the intubation, an additional bolus of thiopental (2–3 mg/kg) was given. After induction, controlled mechanical ventilation was adjusted to maintain $PaCO_2$ between 30 and 35 mmHg. The anaesthesia was maintained with sevoflurane 0.5%–3%, atracurium infusion of 0.5 mg/kg/h and fentanyl infusion (1 mcg/kg/h). Bolus doses of fentanyl (1–2 mcg/kg) were given to control the increased heart rate and systemic hypertension during surgery according to the need. Fluids resuscitation and maintenance were provided with glucose free iso-osmolar crystalloid solutions 2–3 ml/kg/h and replacement of blood loss and urine output. Drugs such as corticosteroids, furosemide (1–2 mg/kg) and mannitol (1 g/kg) were given according to the need. Esmolol was added if there was intraoperative tachycardia or hypertension before opening the dura mater. Nitroglycerine was added if needed to control intraoperative hypertension after opening the dura mater. Patients with a heart rate below 50 bpm were managed with a small dose of atropine 0.02 mg/kg. If the mean arterial blood pressure decreased below 60 mmHg, it was managed with fluids and a small dose of ephedrine (5–10 mg) if needed. At the end of surgery, all patients were transferred to the neurosurgical ICU for monitoring before extubated smoothly.

Monitoring

The monitoring included heart rate, mean arterial blood pressure, central venous pressure, arterial oxygen saturation, end-tidal carbon dioxide, core temperature from nasopharyngeal probe and intracranial pressure every 5 min. The end-tidal concentration of sevoflurane, total dose of fentanyl, urine output and arterial blood gases were recorded. Neurological assessment was done for all patients by Glasgow coma scale before induction of anaesthesia and after 2 h of extubation. The incidence of intraoperative awareness was evaluated after 2 h of extubation.

Data of the patients were collected at the following time points, T0: before administration of the study medication or placebo; T1: 5 min after induction of anaesthesia, T2: 30 min after induction; T3: 1 h after induction; T4: at the end of surgery; T5: on admission to the ICU; T6: before extubation and T7: 2 h after extubation.

Outcomes

The primary outcome was the stability of the haemodynamic status of the patients during surgery. Secondary outcomes were intracranial changes, total fentanyl dose, end-tidal sevoflurane concentration,

neurological outcome. The safety of the gabapentin was assessed by the occurrence of any adverse events.

Sample size calculation

Power analysis was performed using Chi-square (χ^2) test for independent samples on frequency of haemodynamic instability intraoperatively because it was the main outcome variable in the present study. A pilot study was done before starting this study because there are no available data in literature for the role of gabapentin in patients with supratentorial brain tumours undergoing craniotomy under general anaesthesia. The results of the pilot study showed the incidence of haemodynamic instability was 13.2% in the gabapentin group and 31.5% in the control group. Taking power of 0.8 and alpha error of 0.05, a minimum sample size of 80 patients was calculated for each group.

Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Mann–Whitney U-test for independent samples. For comparing categorical data, Chi-square test was performed. Fisher's exact test was used instead when the expected frequency is <5. A p-value less than 0.05 was considered as statistically significant. All statistical calculations were done using computer programs, Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Table 1: Preoperative data of patients (mean±SD, number)

Variable	Group G (*n*=78)	Group C (*n*=78)	*p*
Age (year)	43.52±15.26	45.18±16.34	0.513
Weight (kg)	85.63±12.27	83.18±13.79	0.242
Gender			
Male	49	45	0.744
Female	29	33	0.667
Hypertension	15	12	0.525
Diabetes mellitus	8	10	0.616

Group G: Gabapentin group, Group C: Control group

Table 2: Heart rate changes of patients (mean±SD)

Timepoints	Group G (*n*=78)	Group C (*n*=78)	*p*
T0	91.64±6.72	90.51±7.39	0.319
T1	87.18±6.60	90.94±8.33	0.002
T2	82.65±6.48	89.73±7.52	0.001
T3	80.42±5.47	87.68±8.32	0.001
T4	78.95±6.85	85.57±7.13	0.001
T5	79.64±6.44	86.51±5.75	0.001
T6	80.87±5.93	86.23±6.92	0.001
T7	80.30±6.82	87.39±6.85	0.001

T0=Before administration of the study medication,
T1=5 minutes after induction of anaesthesia, T2=30 minutes after induction, T3=One hour after induction, T4=At the of end surgery, T5=On admission to the ICU, T6=Before extubation and T7=2 Hours after extubation.
Group G: Gabapentin group, Group C: Control group

RESULTS

Figure 1 shows the CONSORT diagram for the flow of participants through each stage of the study. Two patients of each group were excluded from the analysis because of massive bleeding (either intraoperative or post-operative). There was no significant difference regarding the demographic data and pre-operative co-morbidities ($P > 0.05$) [Table 1].

The heart rate decreased "greatly" in patients of Group G compared to the baseline, but in Group C, the heart rate increased slightly compared with baseline and the comparison between the two groups was significant ($P < 0.05$) [Table 2 and Figure 2]. The decrease in heart rate below 50 bpm was in 12 patients of Group G and three patients of Group C and the comparison was significant ($P = 0.031$) [Table 3] and managed with incremental doses of atropine (0.02 mg/kg). There was sinus tachycardia in four patients of Group G and 18 patients of Group C and the patients were managed by increasing the sevoflurane concentration, bolus doses of fentanyl (50–100 mcg) or esmolol (incremental doses of 0.5 mg/kg over 30 s or infusion 50–200 mcg/kg/min if needed).

The mean arterial blood pressure decreased in patients of Group G more than patients of Group C with a significant statistical difference between the two groups ($P < 0.05$) [Table 4 and Figure 3]. The mean arterial blood pressure decreased below 60 mmHg in 13 patients of Group G and 4 patients of Group C ($P = 0.020$) and the hypotension was managed with incremental doses ephedrine (5 mg) [Table 3]. Six patients in Group G and 16 patients in Group C suffered from hypertension ($P = 0.036$) and they were managed by increasing the sevoflurane concentration, bolus doses of fentanyl (50–100 mcg) or esmolol, in addition to nitroglycerine infusion after opening of the dura mater [Table 3].

There was no significant difference in the central venous pressure of the patients between the two groups ($P > 0.05$) [Table 5]. The intracranial pressure

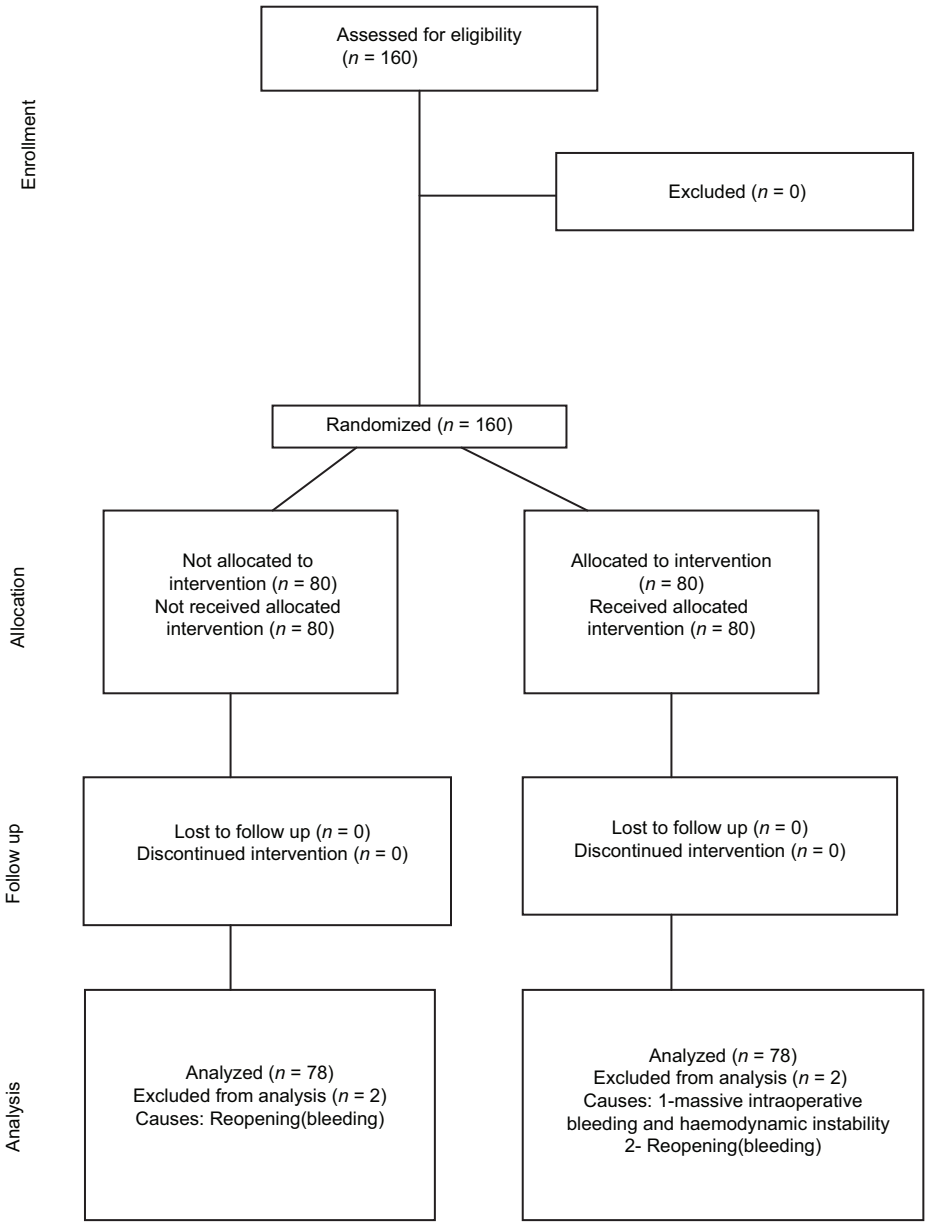

Figure 1: CONSORT diagram for the flow of participants through each stage of the present study

decreased in patients of Group G more than Group C, with a significant difference between the two groups ($P < 0.05$).

Table 6 shows the intra- and post-operative data of patients. There was no difference regarding the temperature, duration of the procedures and types of supratentorial brain tumours ($P > 0.05$). The total fentanyl requirements during the procedures were lower in Group G than in patients of Group C, with a significant statistical difference between the two groups ($P < 0.05$). The end-tidal sevoflurane concentration was lower in Group G than in patients of Group C, with a significant difference between the two groups ($P < 0.05$). The urine output was higher in Group G more than the Group C, with a significant difference between the two groups ($P < 0.001$). The recovery time (time from the end of anaesthesia to the time of opening the eyes spontaneously or the response to verbal commands) between the two groups was shorter in Group G ($P < 0.001$). The extubation time (duration from the end of anaesthesia until the patients become fully awake and removal of endotracheal tube) was shorter in patients of Group G than Group C ($P < 0.001$). The incidence of nausea and vomiting was lower in Group G compared to the Group C ($P = 0.009$); therefore, the requirement for antiemetic medications (metoclopramide and

Table 3: Intracranial pressure changes of patients (mean±SD)

Timepoints	Group G (*n*=78)	Group C (*n*=78)	*p*
T0	22.53±3.25	21.82±3.69	0.204
T1	21.65 ±2.90	21.63±3.13	0.967
T2	16.35±1.34	18.88±2.44	0.011
T3	14.80±1.22	17.92±2.26	0.001
T4	12.22 ± 1.06	15.38±1.98	0.001
T5	12.56±1.03	14.76±1.86	0.001
T6	11.92±0.95	14.58±1.37	0.001
T7	10.54±0.87	13.29±1.43	0.001

T0=before administration of the study medication,
T1=5 minutes after induction of anaesthesia, T2=30 minutes after induction, T3=one hour after induction, T4=at the of end surgery, T5=on admission to the ICU, T6=before extubation and T7=2 hours after extubation. Group G: Gabapentin group, Group C: Control group

Table 4: Mean arterial blood pressure of patients (mean±SD)

Timepoints	Group G (*n*=78)	Group C (*n*=78)	*p*
T0	95.45±8.67	96.62±7.80	0.377
T1	90.59±5.80	94.87±6.74	0.001
T2	86.64±5.75	97.42±6.22	0.001
T3	84.53±6.44	93.86±5.19	0.001
T4	82.60±5.79	92.90±6.73	0.001
T5	83.58±4.87	90.43±5.66	0.001
T6	85.49±5.80	92.64±5.18	0.001
T7	86.56±5.38	94.74±6.77	0.001

T0=Before administration of the study medication,
T1=5 minutes after induction of anaesthesia,
T2=30 minutes after induction, T3=One hour after induction, T4=At the of end surgery, T5=On admission to the ICU, T6=Before extubation and T7=The reading 2 hours after extubation. Group G: Gabapentin group,Group C: Control group

Table 5: Central venous pressure changes of patients (mean±SD)

Timepoints	Group G (*n*=78)	Group C (*n*=78)	*p*
T0	13.12±1.08	13.15±1.13	0.865
T1	11.33±1.46	11.18±1.39	0.512
T2	11.30±1.10	11.25±1.28	0.794
T3	10.89±1.20	11.04±1.08	0.413
T4	10.40±1.17	10.72±1.25	0.101
T5	9.81±1.02	9.55± 1.11	0.129
T6	9.36±1.03	9.40± 1.09	0.814
T7	9.12± 1.35	9.25±1.24	0.532

T0=Before administration of the study medication,
T1=5 minutes after induction of anaesthesia, T2=30 minutes after induction, T3=One hour after induction, T4=At the of end surgery, T5=On admission to the ICU, T6=Before extubation and T7=2 hours after extubation. Group G: Gabapentin group, Group C: Control group

ondansetron) was lower in Group G than the Group C (P = 0.043, P = 0.034, respectively). GCS at baseline was comparable but it was significantly higher in group G after surgery with a significant difference between the two groups (P = 0.002). There was no intraoperative awareness.

DISCUSSION

Many articles were reviewed to compare the results of the present study, but there were few studies that assessed only some effects of gabapentin and there were no data about the other effects of gabapentin in patients undergoing craniotomy for supratentorial tumours.

The present study showed that the gabapentin attenuated significantly the haemodynamic responses to laryngoscopy, intubation, Mayfield three-pin head holder application surgical stimulation, during the surgery and extubation in patients undergoing supratentorial surgery. To control the haemodynamic responses in patients of the control group, higher doses of sevoflurane, fentanyl and esmolol were used before the opening of the dura in addition to nitroglycerine after opening of the dura. These findings correlate with the results of Misra *et al*.[22] They evaluated the effect of 900 mg gabapentin given 2 h before elective craniotomy in 47 patients, and they found that gabapentin alone abolished the increases in the heart rate and arterial blood pressure after skull pin insertion as compared to placebo or lidocaine infiltration. There were two studies which found that the gabapentin decreased significantly the heart rate and mean arterial blood pressure during and through 10 min after the intubation,[8,23] and the same result was documented by El Bakry *et al*.,[24] but the study was done on patients undergoing cataract surgery under peribulbar block.

The decrease in heart rate and arterial blood pressure may be as a result of a significant decrease in catecholamine release caused by gabapentin,[13,25] or inhibition of membrane voltage-dependent calcium channels,[5] thus acting as calcium channel blockers.[6,26]

The present study showed that the intracranial pressure decreased significantly in the gabapentin group compared to the control group. This may be as a result of the decreased end-tidal sevoflurane and increased urine output with gabapentin group compared to the control group. The dose of fentanyl decreased significantly in Group G in comparison to Group C and this correlates with the result of Türe *et al*.;[21] this correlates with the results of other studies.[21,27,28]

The end tidal sevo concentration and propofol dose decreased in group G compared with control group

Table 6: Intraoperative and postoperative data of patients (data are presented as mean±SD, number)

variable	Group G (*n*=78)	Group C (*n*=78)	*p*
Heart rate (bpm)			
<50	12	3	0.031
>100	4	18	0.002
MAP (mm Hg)			
<60	13	4	0.020
>100	6	16	0.036
Temperature (°C)	36.22± 0.36	36.31± 0.42	0.152
Procedure duration (minute)	243.65± 84.35	240.18± 82.74	0.795
Total fentanyl dose (mcg)	452.85± 58.10	480.51± 63.46	0.005
End-tidal sevoflurane (%)	1.68± 0.68	1.96± 0.72	0.013
Urine output (ml)	3275.35±258.40	2893.73±247.96	0.001
Recovery time (minute)	27.40± 5.63	38.25± 8.35	0.001
Extubation time (minute)	36.18± 7.49	49.42± 9.57	0.001
Nausea and vomiting			
Incidence	12	31	0.009
Metoclopramide	10	21	0.043
Ondansetron	2	10	0.034
Types of brain tumours			
Glioma	27	32	0.542
Meningioma	30	28	0.758
Astrocytoma	21	18	0.722
Glasgow coma scale			
T0	12.67± 1.82	12.90± 1.57	0.399
T7	13.47± 1.44	12.80± 1.20	0.002
Glasgow coma scale <8	2	8	0.049

MAP=Mean arterial blood pressure, T0=The reading before administration of the study medication, T7=The reading 2 hours after extubation.
Group G: Gabapentin group, Group C: Control group

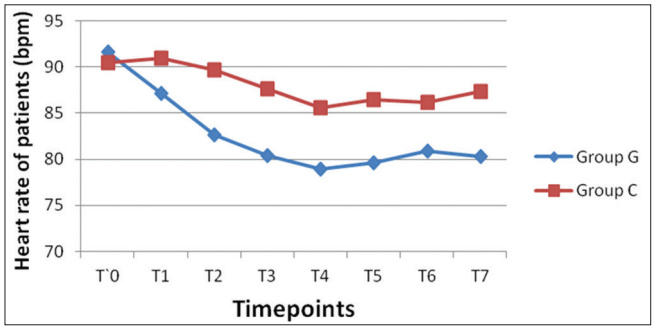

Figure 2: Heart rate changes T0=before administration of the study medication, T1=5 minutes after induction of anaesthesia, T2=30 minutes after induction, T3=one hour after induction, T4=at the of end surgery, T5=on admission to the ICU, T6=The reading before extubation and T7=2 hours after extubation

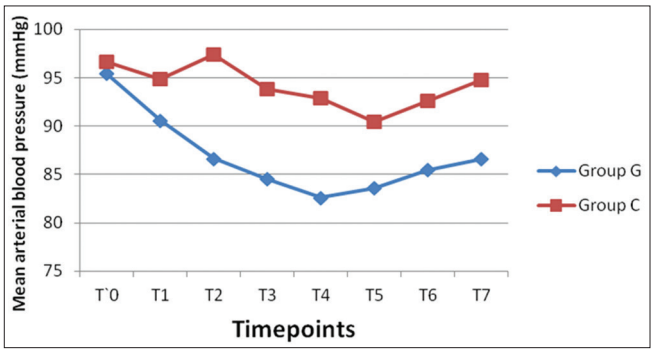

Figure 3: Mean arterial blood pressure changes T0=before administration of the study medication, T1=5 minutes after induction of anaesthesia, T2=30 minutes after induction, T3=one hour after induction, T4=at the of end surgery, T5=on admission to the ICU, T6=before extubation and T7=The reading 2 hours after extubation

,and the same has been observed in previous studies also.[20,21]

However, Prabhakar *et al.*[29] reported that there was no effect of gabapentin on the anaesthetic dose compared

to placebo, but this may be related to the used dose of gabapentin as they used 800 mg; and in the present study, it is 1200 mg.

The recovery and extubation times were shorter in the gabapentin group compared to Group C ($P < 0.05$) and this may be as a result of the lower doses of sevoflurane and fentanyl used with gabapentin.

The incidence of nausea and vomiting decreased significantly with gabapentin and the requirement for antiemetic drugs decreased compared to the control group. These findings are in agreement with other studies on this benefit of gabapentin.[30-32] The mechanism of gabapentin in the prevention of post-operative nausea and vomiting is unknown, but it may be related to the post-operative analgesic effect or the decreased perioperative narcotics.[33-36]

The urine output increased significantly in the gabapentin group compared to the control group and this may be a result of the decreased catecholamine with gabapentin,[13,23] thus inducing renal artery vasodilatation and increasing the urine output.

The Glasgow coma scale was better in Group G than the Group C, and this may be related to the decreased dose of sevoflurane or fentanyl with gabapentin group compared to the control group or as a result of the neuroprotective effects of gabapentin. Gabapentin has been observed to provide brain protection in many experimental studies.[37-44] In spite of the decreased end-tidal sevoflurane concentration with gabapentin, there was no awareness with gabapentin and this may be related to the hypnotic, sedative and amnestic effect of gabapentin.[45-48]

CONCLUSION

Pre-operative administration of gabapentin in patients undergoing craniotomy under general anaesthesia minimised the fluctuations in haemodynamics, reduced the requirements for sevoflurane and fentanyl, decreased intracranial pressure and improved the outcomes. There were few side effects associated with gabapentin such as hypotension. It also decreases the incidence of postoperative nausea and vomiting.

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Conflicts of interest

There are no conflicts of interest.

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