



Efficacy of preoperative oral gabapentin for patients undergoing intracranial surgery: Effect on laryngoscopic stress response

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ABSTRACT

Background: A reflex sympathoadrenal response could be elicited by laryngoscopy and intubation in the form of tachycardia and hypertension. These responses could be attenuated to decrease cardiac work and oxygen demands. This study was conducted to assess the role of oral gabapentin in decreasing the stress response associated with intubation.

Objective: This study was conducted to assess the role of oral gabapentin in decreasing the stress response associated with intubation.

Patients and methods: A total of 70 cases who underwent intracranial surgery in Mansoura University Hospitals were included. They were divided into two groups; group C who received placebo, and group G who received gabapentin 1000 mg orally. Heart rate, blood pressure, and catecholamine levels were measured prior to intubation, then after 1, 5, 10, and 15 minutes.

Results there is no correction: When given 1 hr prior to surgery, gabapentin effectively attenuated blood pressure, heart rate, and catecholamine levels compared to the placebo after intubation, although no statistical differences were detected statistically before intubation.

Conclusion: Pre-treatment with 1000 mg oral gabapentin before induction of anesthesia is both safe and effective in reducing the stress response to laryngoscopy and intubation.

ARTICLE HISTORY

Received 19 February 2020

Revised Vxx xxx xxxx

Accepted 23 May 2020

KEYWORDS

Preoperative; gabapentin and laryngoscopic stress response

1. Introduction

Endotracheal intubation is considered an integral part of the anesthesiologist's contribution in patient care. However, it is a noxious stimulus that may initiate a transient sympathetic response in the form of increased heart rate, blood pressure, and arrhythmias. Moreover, this response may be marked in some cases [1].

Multiple measures have been used to decrease this stress response upon intubation including; lidocaine spray, deepening of anesthesia, intravenous lignocaine, opioids, sodium nitroprusside, nitroglycerine ointment, or oral clonidine [2].

Gabapentin belongs to the second generation of anticonvulsant agents that are also effective in the management of neuropathic pain. It acts by decreasing the synthesis of glutamate in the CNS. Also, it can bind to voltage-gated calcium channels (alpha 2 delta subunits). Nevertheless, it does not inhibit GABA uptake or degradation although it has a structural mimicry to it [3].

In the current literature, there is a growing evidence that pre-operative administration of analgesics has a greater impact on preoperative anxiety, stress response attenuation, and postoperative analgesia [4].

Recently, gabapentin was successfully used to attenuate the hemodynamic stress response to endotracheal intubation [5].

This study was conducted to evaluate the effect of preoperative intake of gabapentin on the stress response to laryngoscopy and intubation in intracranial surgeries.

2. Patients and methods

2.1. Study design

This is a prospective double-blinded, randomized, and controlled study that was conducted at the Mansoura University Anesthesia Department to evaluate the outcome of oral gabapentin intake on the laryngoscopic stress response.

2.2. Study cases

A total of 70 cases who underwent intracranial surgery were included in the study and they were divided randomly into two equal groups by sealed envelope method; Group C included 35 cases who received the placebo, while group G included the remaining 35 cases who received 1000 mg of oral gabapentin 1 hr prior to the operation.

2.3. Patient consent

A written informed consent was obtained from all cases before participating in our study after the explanation of the advantages and drawbacks of the tested drug. Moreover, the study was approved by the local ethical committee (IRB) with a reference number R.20.01.708 at 14/1/2020.

2.4. Inclusion criteria

- American Society of Anesthesiologists (ASA) physical status: I-III
- Age: 20–60 years.
- Gender: either sex.
- Patients with Glasgow coma scale score above 10/15.

2.5. Exclusion criteria

- Patient's refusal.
- Any known allergy or contraindication to drugs used.
- Pregnancy, lactating mother, and children.
- Subjects who were sleepy or hypotensive within 24 hours before surgery.
- Severe uncompensated diseases (cardiac, respiratory, hepatic, or renal disease).
- Morbidly obese patients.
- Significant gastrointestinal disorders (e.g. peptic ulcer disease or gastroesophageal reflux disease).

2.6. Patient preparation

A: The day before surgery:

- Patients were kept fasting for 8 hours.
- In the preoperative visit: all patients were evaluated for (full medical and clinical examination including the manifestation of increased intracranial tension, Glasgow coma scale, ECG, and routine pre-operative laboratory investigations).

B: The day of surgery:

On arrival to the preanesthetic room, all patients were placed in supine position then a wide bore (18 G) intravenous cannula was inserted into a suitable peripheral vein then 5 ml/kg of normal saline was infused.

Baseline data were recorded as HR and NIBP. Additionally, a blood sample was taken for the measurement of adrenaline and noradrenaline levels by using Human Epinephrine and Norepinephrine ELISA Kit from Bioassay Technology Laboratory from SHANGHAI CRYSTAL DAY BIOTECH CO., LTD. All these parameters were measured and recorded before induction of general anesthesia (basal), at induction,

and then 1 minute, 5 minutes, 10 minutes, and 15 minutes after intubation, respectively.

After pre-oxygenation, anesthesia was induced with injection of Fentanyl 1 µg/kg, propofol 1.5–2.5 mg/kg and atracurium 0.5 mg/kg to facilitate intubation. Patient was intubated with appropriately sized tube. Laryngoscopy and intubation time were kept minimum (15 sec). If more than 3 attempts of laryngoscopy were done, the patient was excluded from our study.

Anesthesia was maintained by oxygen 30% in air mixture, isoflurane (MAC = 1.2), and atracurium at incremental doses 0.1 mg/kg every 20 minutes. Volume controlled mode of mechanical ventilation was attained. Minute volume was modified to keep end-tidal CO₂ about 35 mm Hg. High flow >0.5-minute volume was used for 20 minutes after induction and before extubation while low flow was used all through the procedure.

Warm saline 0.9% was infused to keep CVP about 5 mm Hg. Blood was transfused in a trial to keep HB ≥10 gm/dl or HCT about 30% mannitol (20%) 1 gm/kg during craniotomy via central line.

At the end of surgery, residual neuromuscular blockade was reversed using the injection of neostigmine 0.05 mg/kg and atropine 0.02 mg/kg, and the patient was extubated and then transferred to the surgical intensive care.

2.7. Sample size calculation

The power of this clinical trial was prospectively calculated using the G Power analysis program version 3. Using priory power analysis with accuracy mode calculations with catecholamine level as the primary variant and assuming type-I error protection of 0.05 and an effect size convention of 0.8, a total sample size of 70 patients produced a power of 0.90.

2.8. Data analysis

IBM's SPSS statistics (Statistical Package for the Social Sciences) for windows (version 25, 2017) was used for statistical analysis of the collected data. Shapiro–Wilk test was used to check the normality of the data distribution. All tests were conducted with 95% confidence interval. P (probability) value <0.05 was considered statistically significant. Charts were generated using SPSS' chart builder and Microsoft Excel for windows 2019. Quantitative variables were expressed as mean and standard deviation while categorical variables were expressed as frequency and percentage. Independent sample T and Mann Whitney tests were used for inter-group (between subjects) comparison of parametric and non-parametric continuous data with no follow-up readings, respectively. For pair-wise comparison of data (within subjects), the follow-up values were compared to their corresponding basal value

using paired samples T-test or Wilcoxon matched-pairs signed ranks test. Fisher exact and Chi-square tests were used for inter-group comparison of nominal data using the crosstabs function.

3. Results

The mean age of the included cases was 39.69 and 43.40 years for the control and gabapentin groups, respectively. In the control group, 20 males and 15 females were included, whereas the gabapentin group included 15 males and 20 females. Diabetes was present in six cases (17%) in the control group, while it was present in five cases (14%) in the gabapentin group. In addition, hypertension was present in 13 cases (37%) and 10 cases (39%) in both groups, respectively. None of the previously discussed variable was significantly different between the two study groups ($p > 0.05$). The laryngoscopy duration did not differ significantly between the two groups ($p = 0.75$). These data are illustrated in Table 1.

There was a significant variation in the heart rate throughout follow-up period ($F = 201.5$, df 2.62, $P = <0.001$). There was a significant variation due to the treatment regimen between groups ($F = 42.15$, df 2.62, $P = <0.001$). In average, the overall readings of Gabapentin group were significantly lower than those of Control group by an average of 8.75 throughout the study (95% CI: 3.92, 13.58, $p = <0.001$).

There was a significant variation in the SBP throughout follow-up period ($F = 574.6$, df 2.59, $P = <0.001$). There was a significant variation due to the treatment regimen between groups ($F = 40.82$, df 2.59, $P = <0.001$). In average, the overall readings of Gabapentin group were significantly lower than those of Control group by an average of 17.36 throughout the study (95% CI: 9.89, 24.82, $p = <0.001$).

There was a significant variation in the DPB throughout follow-up period ($F = 43.64$, df 5, $P = <0.001$). There was a significant variation due to the treatment regimen between groups ($F = 5.5$, df 5, $P = <0.001$). In average, the overall readings of

Gabapentin group were significantly lower than those of Control group by an average of 10.95 throughout the study (95% CI: 6.16, 15.75, $p = <0.001$). These data are shown in Table 2 and Figures 1 and 2.

By comparing basal and follow-up values of the vital signs in both groups, we noticed reduced elevation in the three parameters (HR, SBP, DBP) in the Gabapentin group after the intubation compared to the control group. It is worth mentioning that the follow-up reading in the Gabapentin group dropped below the basal level at some instances, unlike the control group which remained above the baseline at all times.

There was a significant variation in the adrenaline throughout follow-up period ($F = 140.7$, df 1.64, $P = <0.001$). There was a significant variation due to the treatment regimen between groups ($F = 44.9$, df 1.64, $P = <0.001$). In average, the overall readings of Gabapentin group were significantly lower than those of Control group by an average of 5.67 throughout the study (95% CI: 0.91, 10.43, $p = 0.020$).

There was a significant variation in the noradrenaline throughout follow-up period ($F = 391$, df 1.29, $P = <0.001$). There was a significant variation due to the treatment regimen between groups ($F = 197.8$, df 1.29, $P = <0.001$). In average, the overall readings of Gabapentin group were significantly lower than those of Control group by an average of 31.84 throughout the study (95% CI: 27.97, 35.71, $p = <0.001$). These data are illustrated in Table 3 and Figures 3 and 4.

Within-subject comparison revealed a significant statistical difference between basal value and subsequent readings at all time points for the adrenaline in both groups and for noradrenaline in the control group; however, the gabapentin group reading of the noradrenaline starting from 2 minutes after induction did not show significant statistical variation.

4. Discussion

Gabapentin, which is a structural analogue for GABA (Gamma aminobutyric acid), is widely used in the treatment of seizures, neuropathic pain, and hot flushes. A recent evidence has suggested that it is useful in decreasing the stress response associated with laryngoscopy and intubation [6].

Several workers have found that 300–1200 mg oral gabapentin given 1 hr before surgical stimulus significantly reduces the incidence of pain and post-operative opioid consumption without significant side effects [7].

This study was conducted at Mansoura University Hospitals aiming to assess the effectiveness of gabapentin in the attenuation of hemodynamic stress response to laryngoscopy and intubation.

Table 1. Demographic data, medical history, RAAS, and intubation time in both groups.

	Control group (n = 35)	Gabapentin group (n = 35)	95% CI	p
Age (years old)	39.69 ± 9.65	43.40 ± 9.76	– 8.34, 0.91	0.11
Weight (kg)	85.51 ± 6.48	82.97 ± 9.21	–1.25, 6.34	0.19
Height (meter)	175.03 ± 6.80	172.31 ± 7.57	–0.72, 6.15	0.12
BMI	27.99 ± 2.58	28.00 ± 3.19	–1.40, 1.36	0.98
Gender				
Male	57% (20)	43% (15)	–0.29, 0.18	0.81
Female	43% (15)	57% (20)		
DM	17% (6)	14% (5)	–0.2, 0.14	1
HTN	37% (13)	29% (10)	–0.31, 0.13	0.61
Laryngoscopy duration (seconds)	14.51 ± 4.38	14.2 ± 3.73	– 1.63, 2.25	0.75

Data are expressed as mean and standard deviation or as percentage and frequency. 95 CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05 .

Table 2. Basal and follow-up hemodynamics of both groups.

		Control group (n = 35)	Gabapentin group (n = 35)	95% CI	p
Heart rate (beat/min)	Basal	77.17 ± 11.63	73.37 ± 7.44	-0.86, 8.46	0.108
	Induction	76.34 ± 11.02	72.46 ± 8.52	-0.81, 8.58	0.103
	1 min PI	90.11 ± 11.85*	77.97 ± 9.36*	7.05, 17.24	0.001
	5 mins PI	88.20 ± 11.90*	76.34 ± 9.50*	6.72, 16.99	0.001
	10 mins PI	84.60 ± 12.37*	73.43 ± 9.09	5.99, 16.35	0.001
	15 mins PI	78.97 ± 12.31	69.31 ± 7.88*	4.73, 14.59	0.001
SBP (mm Hg)	Basal	139.57 ± 15.40	133.71 ± 16.01	-1.64, 13.35	0.124
	Induction	118.71 ± 14.87*	108.14 ± 15.63*	3.30, 17.85	0.005
	1 min PI	163.86 ± 17.78*	141.14 ± 14.71*	14.93, 30.50	0.001
	5 mins PI	158.00 ± 17.87*	136.14 ± 15.20	13.94, 29.77	0.001
	10 mins PI	147.43 ± 17.76*	125.14 ± 16.25*	14.17, 30.40	0.001
	15 mins PI	141.57 ± 16.71	120.71 ± 16.28*	12.99, 28.72	0.001
DBP (mm Hg)	Basal	82.29 ± 13.95	78.00 ± 12.67	-2.07, 10.64	0.183
	Induction	74.86 ± 13.03*	69.43 ± 13.22*	-0.83, 11.69	0.088
	1 min PI	98.57 ± 14.38*	83.43 ± 11.62	8.91, 21.38	0.001
	5 mins PI	95.71 ± 15.06*	83.14 ± 12.37	6.00, 19.14	0.001
	10 mins PI	86.00 ± 11.99	74.00 ± 11.81	6.32, 17.68	0.001
	15 mins PI	87.57 ± 13.14	71.29 ± 11.33*	10.43, 22.14	0.001

Data are expressed as mean and standard deviation. PI: post-intubation. 95 CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05. * indicates significant statistical difference from the respective basal value.

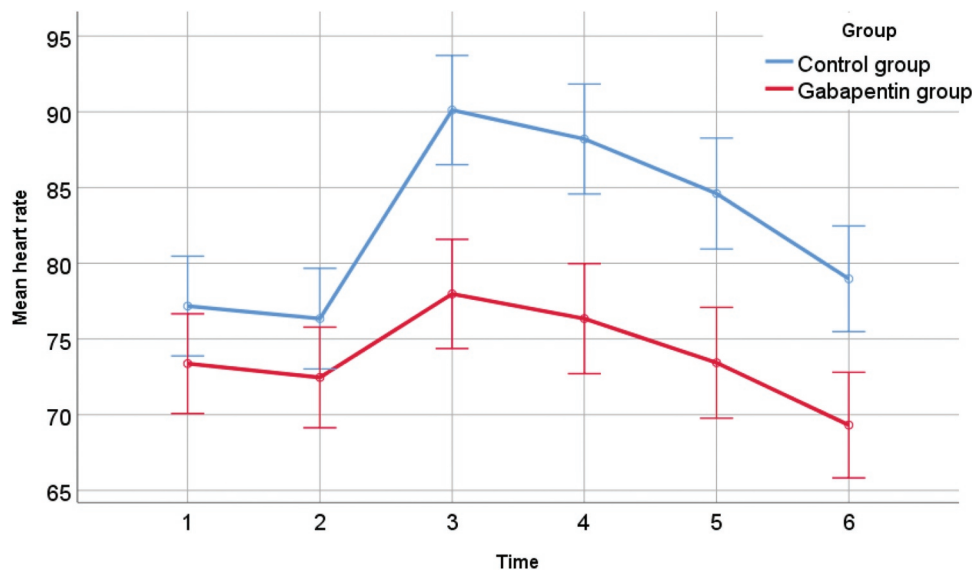


Figure 1. Heart rate between the study groups at different time points.

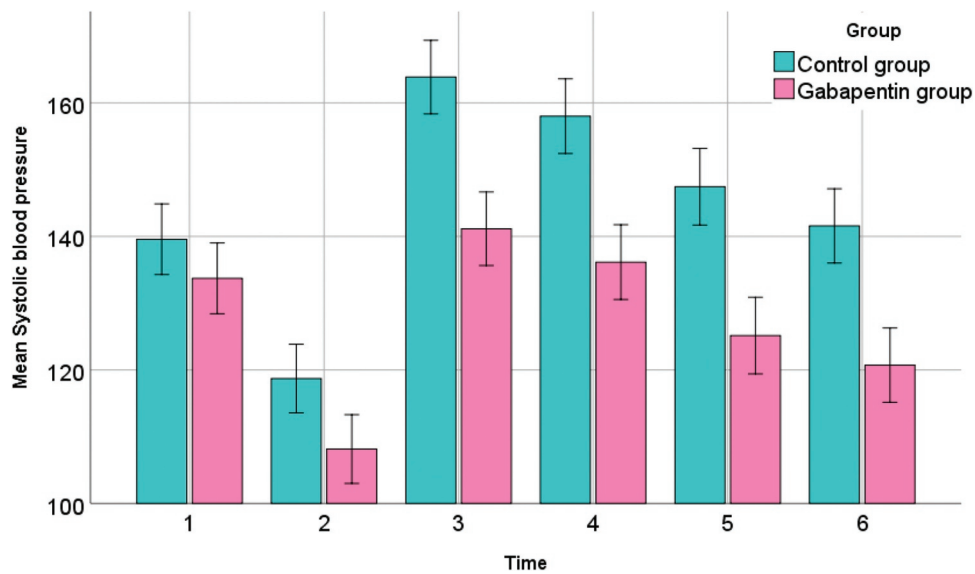


Figure 2. Systolic blood pressure between the study groups at different time points.

Table 3. Basal and follow-up adrenaline and noradrenaline of both groups.

		Control group (n = 35)	Gabapentin group (n = 35)	95% CI	p
Adrenaline (pg/ml)	Basal	44.91 ± 7.73	47.65 ± 8.89	-6.71, 1.24	0.174
	Induction	43.46 ± 7.86*	46.11 ± 9.04*	-6.69, 1.39	0.195
	1 min PI	64.82 ± 11.60*	57.22 ± 9.93*	2.45, 12.75	0.004
	5 mins PI	54.42 ± 12.22*	43.86 ± 11.00*	5.01, 16.10	0.001
	10 mins PI	53.10 ± 12.20*	42.79 ± 11.16*	4.73, 15.89	0.001
	15 mins PI	53.64 ± 12.87*	42.70 ± 11.80*	5.05, 16.83	0.001
Noradrenaline (pg/ml)	Basal	193.80 ± 9.43	194.84 ± 9.43	-5.54, 3.46	0.646
	Induction	186.96 ± 9.40*	188.59 ± 9.15*	-6.06, 2.79	0.463
	1 min PI	259.62 ± 11.53*	214.00 ± 10.13*	40.44, 50.79	0.001
	5 mins PI	246.78 ± 12.15*	197.24 ± 10.77	44.06, 55.01	0.001
	10 mins PI	241.53 ± 11.81*	191.80 ± 10.86	44.32, 55.14	0.001
	15 mins PI	237.46 ± 11.68*	188.61 ± 11.51	43.32, 54.38	0.001

Data are expressed as mean and standard deviation. PI: post-intubation. 95 CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05. * indicates significant statistical difference from the respective basal value.

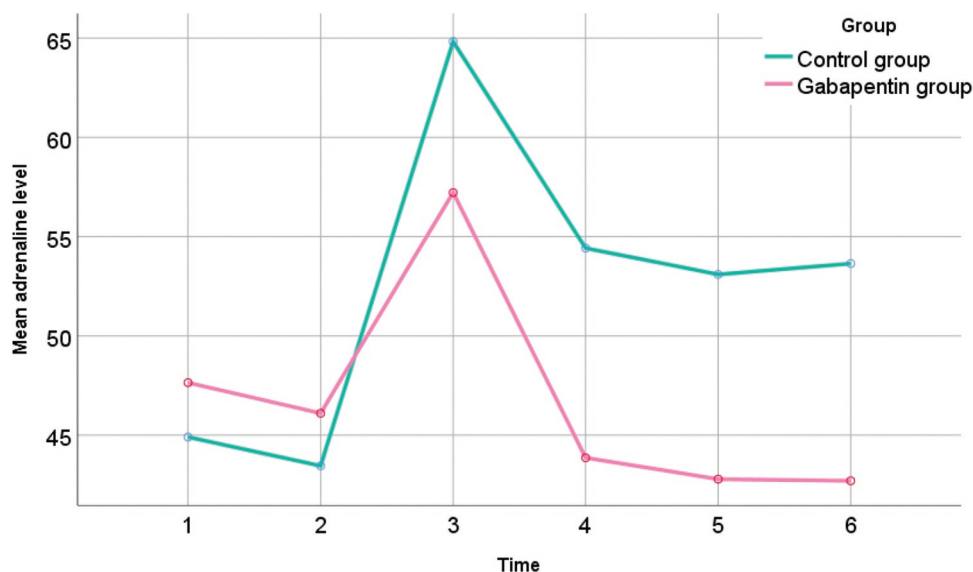


Figure 3. Adrenaline levels at different time intervals between the two groups.

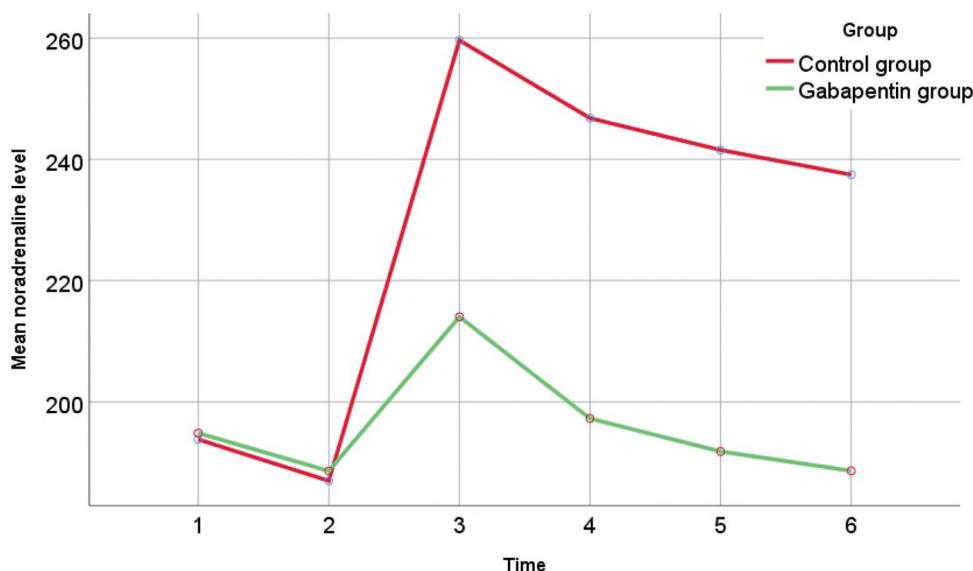


Figure 4. Noradrenaline levels at different time intervals between the two groups.

A total of 70 cases were included, and they were divided into two groups; group C included the controls who received the placebo, while the remaining 35 cases received oral gabapentin 1 hr before surgery. There

were no significant differences regarding the demographics between our two study groups ($p > 0.05$).

Another Egyptian study handling the same perspective included 50 cases who were divided into

two equal groups. The authors did not report any significant differences between the two groups regarding demographics [6]. This comes in line with our study results.

The present study demonstrated that a single oral dose of gabapentin before surgery attenuated the hemodynamic stress response to intubation in adults. Moreover, it was successful in attenuation of both epinephrine and norepinephrine levels.

Our results agree with the results published by Memis and his colleagues who reported that the administration of an oral single dose of 400–800 mg gabapentin was significantly successful in reducing mean arterial blood pressure and heart rate during the first 10 minutes after intubation [8].

Doddaiah and his associates found that oral 800 mg of gabapentin attenuated both blood pressure and heart rate at 1 and 5 minutes after intubation [9].

Another study has reported that administration of 1600 mg of oral gabapentin (divided into 4 doses) successfully attenuated the pressor response. However, heart rate was not significantly reduced [10].

In another study, oral gabapentin 1000 mg 1 hr prior to surgery resulted in a significant decrease in mean arterial pressure and heart rate during the study period ($p < 0.05$). Moreover, the effect was found to be dose-dependent [3].

Kaya and coworkers had studied the effect of pre-operative gabapentin 800 mg, given 2 h before surgery on intraocular pressure (IOP) and hemodynamic changes in response to endotracheal intubation and concluded that pretreatment with gabapentin 800 mg effectively suppressed the increase in intraocular pressure and attenuated the increase in the MAP but not the HR associated with tracheal intubation [11].

Ayatollahi and his colleagues have reported that administration of 800 mg of oral gabapentin 1.5 hours prior to surgery was effective in the attenuation of both diastolic and mean arterial pressure. However, both systolic blood pressure and heart rate were not significantly affected [12].

Ifthekahar et al. noticed that the mean arterial pressure was the only variable significantly attenuated by oral 800 mg of gabapentin [13]. Both these workers concluded that gabapentin was ineffective in preventing tachycardia following laryngoscopy. This contradicts with our study findings, but it may be due to different dosages or different surgical operations.

The previously mentioned Egyptian study also reported that gabapentin had failed to decrease catecholamine levels in response to intubation [6]. The results of this study suggest that gabapentin may decrease blood pressure and heart rate without affecting catecholamine secretion. The important determinant of the level of arterial pressure to tracheal intubation may be reactivity to norepinephrine and not the plasma concentration [14].

However, gabapentin was significantly effective in attenuating catecholamine levels compared to our study controls.

A previous study has evaluated the role of gabapentin in decreasing catecholamine release from the chromaffin cells, which are the predominant source of these chemical compounds. Gabapentin did not alter the catecholamine content of the chromaffin cells but produced a statistically significant reduction in secretion evoked by cholinergic agonists or by direct membrane depolarization [15].

The mechanism by which gabapentin attenuates this stress response is still unknown. However, its binding to the calcium-gated channels in the dorsal root ganglia may have a role [2].

The main drawback regarding this study is that it included a relatively small sample size. Therefore, multiple studies including more cases should be conducted in the near future.

5. Conclusion

Pre-treatment with 1000 mg oral gabapentin before induction of anesthesia is both safe and effective in reducing the stress response to laryngoscopy and intubation.

Disclosure statement

No conflict of interest emerged during the implementation of this work. The paper had not been presented at any congress before.

Funding

The authors declare hereby that the study did not receive any form of financial support.

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