Attenuation of Hemodynamic Responses to Intubation by Gabapentin in Coronary Artery Bypass Surgery: a Randomized Clinical Trial

Seyed Mojtaba Marashi, Seyed Mostafa Saeedinia, Mostafa Sadeghi,

Ali Movafegh, and Shaqayeq Marashi

Department of Anesthesiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract- A varieties of medications have been suggested to prevent hemodynamic instabilities following laryngoscopy and endotracheal intubation. This study was conducted to determine the beneficial effects of gabapentin on preventing hemodynamic instabilities associated with intubation in patients who were a candidate for coronary artery bypass surgery (CABG). This double blinded randomized, parallel group clinical trial was carried out on 58 normotensive patients scheduled for elective CABG under general anesthesia with endotracheal intubation in Shariati Hospital. Patients were randomly allocated to two groups of 29 patients that received 1200 mg of gabapentin in two dosages (600 mg, 8 hours before anesthesia induction and 600 mg, 2 hours before anesthesia induction) as gabapentin group or received talc powder as placebo (placebo group). Heart rate, mean arterial pressure, systolic and diastolic blood pressure were measured immediately before intubation, during intubation, immediately after intubation, 1 and 2 minutes after tracheal intubation. Inter-group comparisons significantly showed higher systolic and diastolic blood pressure, mean arterial pressure and heart rate immediately before intubation, during intubation, immediately after intubation, 1 and 2 minutes after tracheal intubation in the placebo group in comparison to gabapentin group. The median of anxiety verbal analog scale (VAS) at the pre-induction room in gabapentin and placebo groups were 2 and 4, respectively that was significantly lower in the former group (*P*. value =0.04); however, regarding median of pain score no difference was observed between them (*P*. value =0.07). Gabapentin (1200mg) given preoperatively can effectively attenuate the hemodynamic response to laryngoscopy, intubation and also reduce preoperative related anxiety in patients who were a candidate for CABG.
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Introduction

The inappropriate response of systolic blood pressure or cardiac arrhythmia to laryngoscopy and endotracheal intubation can increase preoperative and postoperative morbidity and mortality, particularly in patients with cardiovascular diseases or undergoing coronary artery interventions (1,2). A variety of medications has been suggested to control these hemodynamic responses and prevent hemodynamic instabilities. One of the recently recommended drugs for this purpose is gabapentin which its effectiveness and well tolerability are proved in some randomized controlled trials (3). Gabapentin is a structural analog of the neurotransmitter g-aminobutyric acid (GABA) that it's beneficial effects on treating chronic pain conditions including neuropathic pain, regional pain syndrome, inflammatory pain, malignant pain and different types of headaches have been well demonstrated (4-9). Furthermore, the potential role of this drug in postoperative analgesia, preoperative anxiolysis, prevention of postoperative nausea and vomiting and postoperative delirium has been evaluated; however, its effective role in attenuation of the hemodynamic response to direct laryngoscopy and intubation, especially in those who were a candidate for surgery is already conflicting. It seems that the probable effect of gabapentin to regulate the hemodynamic response to intubation might be similar to the action of calcium channel blockers (10). It should be noted that gabapentin effect on prevention of surgery related

Corresponding Author: Sh. Marashi
Department of Anesthesiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 84901, Fax: +98 21 88633039, E-mail address: shm1377@yahoo.com

hemodynamic instability not only might be dose dependent (11), but also can be resulted in wide spectrum of unfavorable side effect profile such as somnolence, dizziness, asthenia, headache, nausea, ataxia weight gain and amblyopia with the prevalence rate ranged 2% to 15% (9,12). Overall, it is hypothesized that preoperative gabapentin can blunt hypertension and tachycardia of intubation. There are few published studies on the possible role of gabapentin in preventing vital hemodynamic instability as well as attenuation of different aspects of stress response to cardiac surgery. This study was conducted to determine the effect of gabapentin on preventing hemodynamic instabilities associated with laryngoscopy and intubation in patients undergoing coronary artery bypass surgery (CABG).

Materials and Methods

This double-blind randomized, parallel group clinical trial was carried out on 58 patients scheduled for elective CABG under general anesthesia. Patients were blinded to the groups they were included. Patients with known sensitivity to gabapentin, positive history of seizure, positive history of gabapentin consumption, psychiatric disorders, drug abuse, known liver, and renal disease, chronic pain syndrome chronic analgesic intake or intake of it during the last 24 hours, Mallampati >= 3, rate other than sinus and heart rate < 60 or > 100 were excluded from the study.

The study protocol was approved by ethical committee of Tehran University of medical sciences, and informed consent was obtained from all patients. In the preoperative visit, demographic characteristics of patients were recorded, and patients were trained to use verbal analog scale (VAS) of pain and anxiety (0 indicates no pain and anxiety and 10 means the worse imaginable pain or anxiety). Patients were randomly assigned to two groups of 29 patients who received 1200 mg of gabapentin (Sobhan Co., Tehran, Iran) in two dosages (600 mg, 8 hours before anesthesia induction and 600 mg, 2 hours before induction) as the gabapentin group or received placebo as placebo group using a computer-generated randomization list. The drugs were orally administered as two capsules (each one contains 300 mg gabapentin or talc powder). Placebo and gabapentin capsules were identical in appearance. The night before surgery all patients received 20 mg Omeprazole and 10 mg Oxazepam orally. At surgery room and after the setting of EKG monitoring and pulse oximetry, an intravenous line was secured with 14 gauges I.V cannula and ringer lactate infusion (8-10 CC /kg) was started. All patients were uniformly premedicated with intravenous Diazepam 0.15 mg/kg and Fentanyl 7mcg/kg. Before induction of general anesthesia, the arterial line from radial artery was maintained under local anesthesia with 1 ml of Lidocaine 2% for invasive blood pressure monitoring then the level of anxiety and pain of radial artery cannulation were assessed in patients. After preoxygenation with 100% O2, anesthesia was induced with sodium thiopental (2 mg/kg) and atracurium (0.5 mg/kg). After three minutes, patients were intubated with appropriate size endotracheal tube. All intubations were performed by an expert anesthesiologist. An anesthesiology resident who was blinded to the study recorded baseline vital parameters of patients including Heart Rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) immediately before intubation, during intubation, 1 and 2 minutes after tracheal intubation. MAP was calculated by this formula: (SBP + 2 DBP) / 3. Data were presented as mean $\pm$ standard deviation (SD). For statistical analysis of demographic data and for comparison of groups repeated measures analysis of variance ANOVA, Fisher's exact test and independent t-test analyzes were performed. Statistical significance was determined as a P-value of ≤ 0.05. All statistical analysis was performed using SPSS (version 20.0, SPSS Inc, Chicago, Illinois).

Results

The two study groups of gabapentin and placebo were comparable in mean age and weight. The duration of intubation was also similar in both groups (Table 1).

Table 1. Patients characteristics

	Placebo group	Gabapentin group	*P*-value
Age(years)	57±8.3	58.6±9.02	0.4
Weight(kg)	73.9±11.3	72.9±12.6	0.6
Intubation duration(sec)	10.8±3.1	10.37±32	0.57

The baseline hemodynamic variables including SBP, DBP, MAP, and HR were all similar in two groups (*P*

value >0.05). Table 2 describes the hemodynamic parameters of two groups at different time points. Inter-group comparisons showed significantly higher SBP, DBP, MAP and HR immediately before intubation, during intubation, immediately after intubation and 1 and 2 minutes after tracheal intubation in placebo group than in gabapentin group; however, there were similar

trend in these hemodynamic parameters compared with the baseline values in both groups so that that SBP and MAP were both elevated in the time interval between intubation beginning and 1minute after intubation, while these two parameters were gradually decreased in both groups after that.

Table 2. Comparing clinical signs between the Gabapentin and placebo groups at the different time points of intubation

Parameter		Baseline	Before intubation	During intubation	1 minute after intubation	2 minutes after intubation
Systolic blood pressure (mmHg)	**Gabapentin group**	145.1 ± 15.5	90.8 ± 18.5	103.1 ± 29.1	114.6 ± 28.1	105.1 ± 24.4
	Placebo group	146.2 ± 24.1	103.1 ± 29.1	120.7 ± 24.5	145.7 ± 28.4	137.3 ± 29.1
	P-value	0.837	0.049	0.016	< 0.001	< 0.001
Diastolic blood pressure (mmHg)	**Gabapentin group**	84.1 ± 10.6	57.2 ± 12.5	65.2 ± 19.1	72.4 ± 20.2	66.2 ± 16.1
	Placebo group	86.7 ± 19.0	65.5 ± 13.6	77.5 ± 20.6	89.8 ± 16.5	87.7 ± 26.9
	P-value	0.523	0.019	0.022	< 0.001	< 0.001
Mean arterial pressure (mmHg)	**Gabapentin group**	101.1 ± 10.8	68.4 ± 14.1	77.8 ± 21.0	86.4 ± 22.4	79.1 ± 18.4
	Placebo group	106.5 ± 19.8	78.1 ± 15.0	91.9 ± 21.3	108.5 ± 19.3	104.1 ± 26.3
	P-value	0.203	0.014	0.014	< 0.001	< 0.001
Heart rate (beat/min)	**Gabapentin group**	70.3 ± 16.3	66.9 ± 10.7	65.2 ± 19.1	73.2 ± 14.3	69.8 ± 12.5
	Placebo group	75.5 ± 12.1	74.1 ± 11.0	77.5 ± 20.6	83.7 ± 11.2	80.2 ± 11.2
	P-value	0.173	0.014	0.022	0.003	0.002

The median of anxiety VAS score in gabapentin and placebo groups were 2 and 4, respectively which was significantly lower in the former group (P=0.04); however, regarding median of pain score (3 in both groups) no difference was observed between them (P=0.07).

Discussion

We found that the trend, if the changes in hemodynamic variables were comparable in the groups, received gabapentin or placebo, but the measures of these indicators were significantly lower in former group at all time points. Also the median anxiety score at the time of entry to recovery room was significantly lower in those whom gabapentin was administered compared with placebo group. On the other hand, gabapentin 1200 mg given before operation could significantly attenuate hemodynamic response to laryngoscopy and intubation and also reduce preoperative related anxiety in patients who were a candidate for CABG. Review of recent literature had similar results. In a similar study by Bafna and colleagues, attenuation of the hemodynamic response to intubation and the level of this response was directly associated with the dose of administered

gabapentin (11). This beneficial effect was also revealed by Kaya *et al.*, They showed that the use of oral gabapentin 800 mg two hours before surgery effectively attenuate the increase in MAP secondary to endotracheal intubation (13). In another study by Memis *et al.*, 800 mg gabapentin one hour before surgery blunted the rise in arterial blood pressure and heart rate in first 10 minutes after endotracheal intubation (14). In the study of Amani *et al.*, Gabapentin (1200 mg) prevented the increase in heart rate and mean arterial pressure secondary to laryngoscopy and intubation, but gabapentin (800 mg) was not effective in controlling hemodynamic response during intubation (15).

Tracheal intubation can usually activate sympathetic pathway which manifests as an elevation in pulse rate and blood pressure and also cardiac arrhythmias. Although these changes can be well tolerated by healthy subjects, it may potentially result in hemodynamic instability and even life-threatening events in patients with heart diseases (16-17). Because a notable number of these patients will be scheduled for CABG, anesthesiologists should be in search of safest and the most efficient medication for preventing cardiovascular responses to the intubation procedure. In this context, some single and combined medications have been

examined for this purpose; however, none of them were considered as the first choice. For instance, the quest for an effective blockade of hemodynamic response had put forward the administration of topical and systemic lidocaine, vasodilators, adrenergic blocking agents, angiotensin converting enzyme inhibitors, inhaled anesthetic agents and opiate but because of major side effects of these agents, their use has been limited (18,19).

The present study in parallel with other similar studies has obtained some powerful evidence indicating that the use of oral gabapentin, even hours before tracheal intubation can be efficacious for attenuation of the hemodynamic response to laryngoscopy and intubation. The mechanism of hemodynamic response attenuation following preoperative gabapentin administration is already unknown. One of the proposed mechanisms is inhibition of membrane voltage-gated calcium channels that is similarly identified following use of calcium channels blockers. In fact the non-strychnine site of NMDA receptor and two subunits of voltage -sensitive calcium channels have been indicated as the binding sites of gabapentin, thus can mediate hemodynamic indices stability by gabapentin (20,21). In another study, decreasing the synthesis of some neurotransmitters such as glutamate has been suggested as the mechanism of hemodynamic stability following gabapentin administration (22). Besides, it has been shown that the change in arterial pressure usually occurs the following laryngoscopy while the maximum increase in heart rate can occur during endotracheal intubation (23). On the other hand, gabapentin mechanism of action in attenuating heart rate and blood pressure response to tracheal intubation might be different (24), and more studies in this field are needed.

In the current study, the administration of oral gabapentin resulted in a reduction of preoperative anxiety. In a similar study by Me'nigaux et al., patients with 1200 mg gabapentin significantly had lower preoperative VAS anxiety scores in comparison to placebo; however, its beneficial effect in anxiety prevention was lower than oxazepam (15mg) (25). It should be mentioned that we did not measure stress mediators such as endogenous plasma catecholamines or cortisone to confirm our results that should be considered in future studies.

In conclusion, preoperative administration of gabapentin 1200 mg can effectively attenuate hemodynamic response to laryngoscopy and intubation besides reduction in preoperative anxiety in patients undergoing CABG.

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