Saikat Majumdar, Anjan Das[1], Haripada Das, Sambhunath Bandyopadhyay[2], Bimal Kumar Hajra, Dipankar Mukherjee

Departments of Anaesthesiology, Nil Ratan Sarkar Medical College, Kolkata, [1]Anaesthesiology, College of Medicine and Sagore Dutta Hospital, Kolkata, [2]Departments of Gynecology and Obstetrics, Institute of Post-Graduate Medical Education and Research, Kolkata, West Bengal, India

Address for correspondence:
Dr. Anjan Das,
174, Gorakshabashi Road, Royal Plaza Apartment (4th floor, Flat No-1),
Nagerbazar,
Kolkata - 700 028, West Bengal, India.
E-mail: anjan2k8@yahoo.com

Comparative evaluation of oral gabapentin versus clonidine as premedication on preoperative sedation and laryngoscopic stress response attenuation for the patients undergoing general anesthesia

Abstract

Background: Laryngoscopy and endotracheal intubation (L and I) is associated with rise in blood pressure (BP), heart rate (HR), leading to adverse cardiological outcome especially in susceptible individuals. To compare the BP, HR during L and I as well as to evaluate the preoperative sedation status between oral clonidine (Group C) and oral gabapentine (Group G) as premedication for the patients undergoing major surgery under general anesthesia (GA). **Materials and Methods:** From April 2008 to December 2009; in a prospective, double-blinded, and randomized controlled study; 100 adult patients of either sex, aged 20-45, of American Society of Anesthesiologists status I and II scheduled to undergo major surgery of >1 hour duration, randomly allocated into groups C and G were pre treated with oral clonidine (200 μg) and gabapentin (800 mg) respectively 2 h prior to induction. Preoperative sedation was assessed 2 h after premedication administration. Hemodynamic parameters were noted just before induction, during L and I 1,3,5,7, and 10 min after intubation. The results obtained were then analyzed with statistical unpaired "t" test and Chi-square test and compared. **Results and Analysis:** Preoperative sedation between two groups were similar but group C attenuated HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) more significantly before induction, during L and I, 1, 3, and 5 min, following L and I, while comparing with group G. Again gabapentin-reduced HR, BP, (SBP, DBP, MBP) significantly more at 7 and 10 min after L and I on comparison clonidine. **Conclusion:** Oral clonidine is equally effective in producing preoperative sedation in comparison to oral gabapentin, while on the contrary oral clonidine is more efficacious in reducing laryngoscopic stress response than oral gabapentin.

Key words: Clonidine, gabapentin, general anaesthesia, laryngoscopy and endotracheal intubation, sedation

INTRODUCTION

The aim of anaesthesiologist is not only to ensure a smooth induction and intubation but also to ensure an uneventful postoperative period. The challenge in anesthesia is to maintain a balance between the stress of the laryngoscopy,

tracheal intubation, and surgical procedure with the cardiorespiratory depressant effects of deeper levels of anesthesia. The anesthesiologist uses both the skill in clinical examination and a host of technical monitors to provide ongoing feedback on the patient's physiological status and anesthetic requirements.

Laryngoscopy and tracheal intubation (L and I) is a strong stimulus for cardiovascular system under light anesthesia.[1] The magnitude of response is great with increasing force and duration of laryngoscopy.[2] The elevation in arterial pressure typically starts within 5 s of laryngoscopy, peaks in 1-2 min and returns to control level within 5 min.[1] Such hemodynamic changes can result in myocardial ischemia, especially in patients with cardiovascular disease.[2]

To attenuate the hemodynamic response, many techniques have been tried but none is ideal. It can be prevented by increasing the depth of anaesthesia but concentration changes of anesthetic agents in blood and effector sites occur slowly in relation to the onset and offset of airway stimuli and hemodynamic response. Volatile anesthetic agents with N_2O may be beneficial. Large doses of fentanyl, (5-10 μg/kg) may attenuate the hemodynamic response but cause prolonged respiratory depression. Aerosol or other application of topical anesthetics may be beneficial.[3] Combination of topical anesthetics and parenteral opioids may be useful.[4] Labetalol and esmolol may be used in combination with narcotics.

Gabapentin, 1–(aminomethyl) cyclohexane acetic acid, is a structural analogue of the neurotransmitter, γ–amino butyric acid (GABA) was introduced in 1993 as an adjuvant antiepileptic drug for the treatment of refractory partial seizure.[5] It was shown to be effective in treating postherpetic neuralgia,[6] other neuropathic pain,[7] postpoliomyelitis neuropathy[8] reflex sympathetic dystrophy.[9] Diabetic neuropathy[10] and it has antinociceptive, antihyperalgesic, and antiallodynic properties.[11] More recently, it has been used to attenuate the stress response to direct L and I. The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. The drug inhibits membrane bound voltage gated calcium channels, thus acting in a manner similar to calcium channel blockers.[12,13] Memis *et al.*,[12] concluded that gabapentin 800 mg before induction of anaesthesia is a simple and practical method for attenuating pressor response to L and I.

Clonidine, the α_2 agonist has shown properties that are potentially beneficial for premedication to reduce sympathetic activity, to diminish incidence of shivering and oxygen consumption during recovery from anaesthesia, to decrease anesthetic and analgesic requirement and to minimize post operative pain, nausea, and vomiting.[14] Carabine *et al.*,[15] concluded that 200 μg oral clonidine-reduced anxiety and laryngoscopy associated hemodynamic surge well in eighty female patients.

In view of these observations, the present study was designed to evaluate the efficacy of oral gabapentin (800 mg) versus oral clonidine (200 μg) premedication for sedation status, blunting the heart rate variability as well as pressor response to direct L and I.

MATERIALS AND METHODS

After obtaining Institutional Ethical committee permission, written consent was obtained from all the patients. Total 100 adult patients were randomly allocated to two equal groups (*n* = 50 in each group) using computer-generated random number list. Group C of patients received single dose oral 200 μg clonidine and group G patients received single dose oral 800 mg gabapentin 2 h before induction of general anesthesia. As clonidine is available in tablet form and gabapentin is available in capsule form we had to take help of DBcaps® Capsules to ensure blinding. DBcaps® are two-piece gelatin or HPMC capsules with a tamper evident design to specifically address the clinical trial challenges of testing without bias. Drugs were swallowed with sips of water in presence of resident doctor not taking part in study. Thus, double blinding was ensured.

Exclusion criteria
Patient refusal, any known allergy or contraindication to clonidine or gabapentin, pregnancy, lactating mothers and children, subjects who were sleepy or hypotensive within 24 h before surgery, hepatic, renal or cardiopulmonary abnormality, alcoholism, diabetes, significant gastrointestinal disorders (e.g. peptic ulcer disease or gastroesophageal reflux disease) were excluded.

In preoperative assessment, patients were enquired about history of (h/o) fluid electrolyte disbalance, fainting attack, any antiarrhythmic treatment received, h/o previous exposure to anesthesia, h/o seizure, chronic pain syndrome, psychiatric disorder, patient receiving β blocker. The patients were enquired about any history of drug allergy, previous operations, or prolonged drug treatment. General examination, systemic examinations, and assessment of the airway were done. Preoperative fasting of minimum 8 h was ensured before operation in all cases. All patients received premedication of tablet diazepam 10 mg orally the night before surgery as per preanesthetic check up direction to allay anxiety, apprehension, and for sound sleep. The patients also received tablet ranitidine 150 mg

in the previous night and in the morning of operation with sips of water.

After 8 h fasting, on the day of surgery the patients were brought to the observation room, baseline parameters such as heart rate (HR), systolic blood pressure (SBP), distolic blood pressure (DBP), mean arterial blood pressure (MBP), and oxygen saturation (SpO_2) were measured. Premedication was administered. After 2 h of premedication patient was shifted to the operation table and multichannel monitor was attached. HR, SBP, DBP, MBP, respiratory rate, electrocardiography, temperature were recorded before insertion of a 18G intravenous (IV) cannula.

I.V. infusion was started with ringer lactate. After 5 min preoxygenation with 100% O_2, premedication was given with inj. glycopyrrolate 4 μg/kg, Inj. fentanyl citrate 2 μg/kg. Induction was done with Inj. thiopentone sodium 5 mg/kg and intubation was done with Inj. succinylcholine 1.5 mg/kg and cuffed endotracheal tube of appropriate size. Anesthesia was maintained with 70% N_2O in O_2, isoflurane up to 1–2 MAC, inj. atracurium besylate (0.5 mg/kg) bolus and then as and when (0.2 mg/kg) indicated. After completion of surgery neuromuscular block was reversed with inj. glycopyrrolate 0.01 mg/kg and Inj. neostigmine 0.05 mg/kg and extubated when adequate spontaneous ventilation was established. All patients were shifted to postanesthesia care unit.

Electrocardiogram (ECG) (lead-II) and heart rate, SpO_2, SBP, DBP, MBP, $EtCO_2$, temperature were recorded during L and I, 1 min, 3 min, 5 min, 7 min, and 10 min after L and I and throughout procedure.

Visual analogue scale for postoperative pain score [(0-10 cm), 0 = no pain, 10 cm = worst pain imaginable]. Multichannel monitor (Kopran KCM-12) for monitoring HR, SpO_2, $EtCO_2$. SBP, DBP, MBP, and ECG.

Statistical analysis
Sample size was estimated using heart rate variation among two groups as the main primary variable. The average heart rate in each group was 70 beats/min (bpm) and to detect a difference of 10% (i.e. 7 bpm), at the $P < 0.05$ level, with a probability of detecting a difference this large, if it exists, of 80% (1−β =0.80). On the basis of previous study assuming within group standard deviation of 12 bpm and we needed to study at least 47 patients per group to be able to reject the null hypothesis that the population means of the groups are equal with probability (power) 0.80. So, we have taken 50 patients in each group. Raw data were entered into a MS Excel spreadsheet and analyzed using standard statistical

software SPSS® statistical package version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the Pearson's Chi-square test. Normally distributed continuous variables were analyzed using the independent sample t test and $P < 0.05$ was considered statistically significant.

RESULTS

There were no statistically significant differences between the two groups in terms of demographic characteristics of the patients namely age, sex and body weight, American Society of Anesthesiologists (ASA) status, duration of anaesthesia and surgery [as shown in Table 1]. Preoperative sedation and sedation after 2 h of premedication was assessed and scored as in Table 2. Patients who were noncommunicative when asked for due to deep sedation were to be excluded from this study. Table 3 shows preoperative preoperative sedation was quite comparable among two groups ($P > 0.05$). Group C controlled SBP during laryngoscopy and intubation, 1, 3 min following L and I in a statistically significant manner ($P < 0.05$) while compared with group G. Similarly DBP was significantly ($P < 0.05$) raised in group G than group C at

Table 1: Comparison of demographic data between the two study groups

Parameter	Group C (*n*=50)	Group G (*n*=50)	*P* value
Age (years)	29.14±3	28.74±2.64	0.59
Body weight (kg)	51.06±9.62	48.30±7.70	0.12
Sex (male/female)	42 (84%): 8 (16%)	38 (76%): 12 (24%)	0.81
ASA physical status (I/II)	33/17	31/19	0.78
Surgery time (min)	78±19	80±17	0.28
Anesthesia time (min)	109±21	111±18	0.26

(Unpaired *t* test), ASA=American society of anesthesiologists

Table 2: Scoring system for preoperative sedation and 2 h after premedication

Awake and initiating conversation himself	0
Awake but noncommunicative (spontaneously, but responded when asked for)	1
Drowsy quiet and nonncommunicative (spontaneously, but responded when asked for)	2

Patients who were noncommunicative when asked for due to deep sedation were to be excluded from this study

Table 3: Comparison of mean preoperative sedation score

Group	Sedation score-0	Sedation score-1	Sedation score-2
G	35	15	0
C	36	14	0
P value	0.90		

the time of L and T, 1, 3 min following L and T. Similar trend was noted in case of MAP at the same time interval. HR was significantly ($P < 0.05$) higher in Gabapentin (G) group than group C at the time of L and I and 1, 3 min after L and I.

DISCUSSION

Endotracheal intubation has become the mainstay of modern anesthesia as it secures the airway, prevents aspiration of gastric contents, delivered predictable Fio_2 and eliminates CO_2 from the body. It has been observed that L and I lead to reflex cardiovascular response, producing tachycardia and systemic arterial hypertension. These circulatory changes may produce detrimental effect in patients with cardiovascular and cerebrovascular disease and various operations. In order to reduce the incidence and severity of these deleterious effects on hemodynamics, numerous techniques have been used with varying degrees of success. These techniques include deepening[16] of the plane of anaesthesia (King *et al.*; 1951). A variety of drugs[17] have been used to control this hemodynamic response (Kovac; 1996).

The present study was carried out with oral premedication with clonidine (200 μg) and gabapentin (800 mg) 2 h before surgery to compare the attenuated hemodynamic response, following L and I and sedation status.

Clonidine, an imidazoline derivative, is a selective α_{2A} adrenergic receptor agonist. It is a potent antihypertensive drug. It produces a fall in heart rate and blood pressure associated with decreased cardiac output but unchanged peripheral resistance. Activation of central nervous system α_{2A} receptors, resulting in a decreased central outflow of impulses in the sympathetic nervous system and recently proved to have some beneficial premedicating effects like sedation,[18] reduction of dose of induction agent,[19,20] attenuation of laryngoscopic stress response.[18,21]

Gabapentin, 1-(aminomethyl) cyclohexane acetic acid, is a structural analogue of the neurotransmitter γ–aminobutyric acid. The mechanism of gabapentin in controlling this haemodynamic response remains unknown. Since, gabapentin inhibits membrane voltage gated calcium channels (VGCCs), it is possible that it may have a similar action to calcium channel blockers. There is, as yet, no data, on the possible role of gabapentin in the attenuation of other aspects of the stress response to surgery.[4] Some studies demonstrated that the descending noradrenergic system, spinal α_2 adrenergic receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to α_{2A} interaction of VGCCs.[22,23]

The demographic profile (age, sex, body weight, ASA status) between two groups which was statistically insignificant ($P > 0.05$) of our patients was quite similar with other research investigations and provided us the uniform platform to evenly compare the results obtained. A study conducted by Marashi *et al.*,[24] in a total of 75 patients yielded similar results. The mean duration of anesthesia and surgery were almost comparable in both the groups with no significant statistical difference [Table 1].

In our study group G had a significant rise of systolic blood pressure [Figure 1] during, 1 min and 3 min following L and I, thereafter it decreases below base line during 7 min and 10 min after L and I. In group C, there was mild increase in systolic blood pressure during, and 1 min after L and I but those are statistically insignificant. There was significant difference between the two groups ($P < 0.05$) throughout the observation period following L and I and group C more effectively controlled the surge associated with L and I than group G.

Regarding DBP, group G showed significant increase in DBP during 1 min and 3 min following L and I [Figure 2] thereafter it decreases at 5, 7, and 10 min after L and I. In group C there was mild increase in DBP during 7 min after L and I which is statistically insignificant ($P = 0.07$). While comparing between two groups a statistically highly significant difference found between the groups ($P < 0.0001$) and group C maintains hemodynamics more steadily than group G.

In comparison of MAP, group G showed a significant increase in MAP during, 1 and 3 min, following L and I [Figure 3]. Thereafter, decreases toward base line following 5, 7, and 10 min after L and I. In group C mild increase during L and I, and 1 min after L and I then decrease at 3 and 5 min but again increase at 7 and
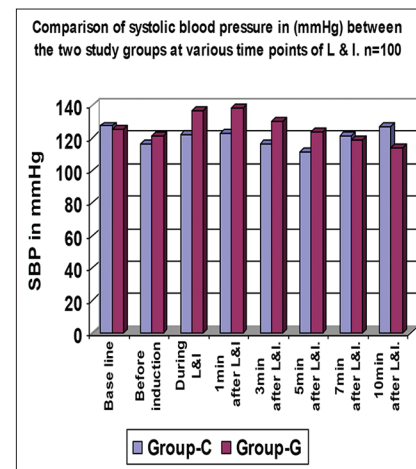

Figure 1: Comparison of systolic blood pressure between two groups

10 min after L and I. There was statistically significant difference found between the two groups throughout the observational period ($P < 0.05$) and group C maintained hemodynamics better than group G.

In our study base line heart rate [Figure 4] was comparable between the groups ($P > 0.05$). In group G, there was statistically significant ($P = <0.0001$) rise of heart rate during, 1 and 3 min following (L and I) when compared with group C. Thereafter, decrease below the base line at 7 min ($P > 0.05$) and 10 min after L and I. In group C, there was no significant rise of heart rate throughout the observation period.

Marashi *et al.*, in 2009[24] conducted a double blind, placebo-controlled, randomized study for elective orthopaedic surgery. The author used 900 mg gabapentin and 200 µg clonidine, 2 h before surgery and concluded that both gabapentin and clonidine have effective role in blunting the hyperdynamic responses following L and I more so with gabapentin. In our study, blunting the hemodynamic reflex response following L and I, clonidine has better response than gabapentin.

Raval and Mehta *et al.*, (2002)[25] studied the effect of oral clonidine premedication for attenuation of haemodynamic responses to L and I. They studied 100 ASA groups–I, II patients aged between 18 and 65 years to compare the effectiveness of oral clonidine as a premedicant and for attenuation of hemodynamic responses to L and I with oral diazepam and placebo. The patients were divided into three groups, group C [$n = 40$] received tablet clonidine 4 µg/kg (max. 0.2 mg), group D [$n = 40$] received tablet diazepam 0.2 mg/kg and group-P [$n = 20$] received tablet placebo (antacid) with sip of water, about 90 min before induction of anesthesia. Clonidine produced marked sedation and better anxiolysis as compared with placebo but less sedation and same level of anxiolysis as compared to diazepam. There were no changes in respiratory rate in either group. Clonidine provided extra advantage over diazepam and placebo by blunting haemodynamic responses during L and I. This study results corroborated with our study though we have given 800 mg gabapentin and 200 µg clonidine 2 h before surgery.

Kumari and Pathania (2009)[26] conducted a randomized double blind placebo controlled study of oral gabapentin (900 mg) given 2 h before induction and concluded that attenuation of blood pressure response to L and I was effectively seen only after 10 min of intubation. In our study, we have seen gabapentin-induced hemodynamic response was attenuated after 7 min following L and I. So, this study results nearer to with our study though we have given lesser doses (800 mg gabapentin).
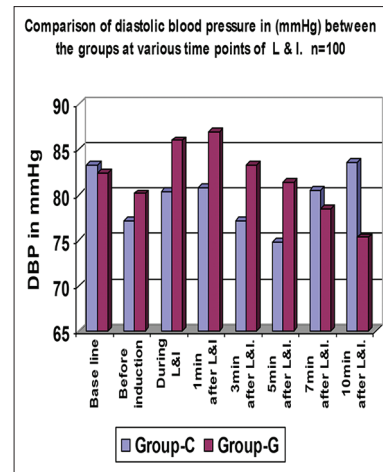

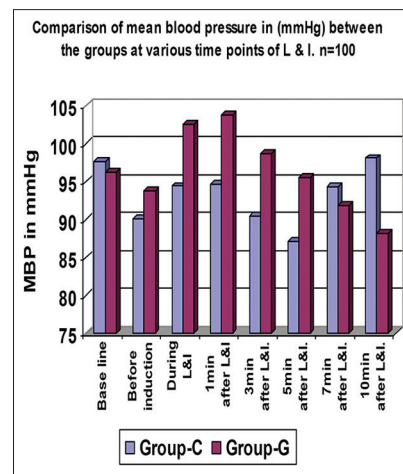**Figure 2:** Comparison of diastolic blood pressure between two groups

Figure 3: Comparison of mean arterial pressure between two groups
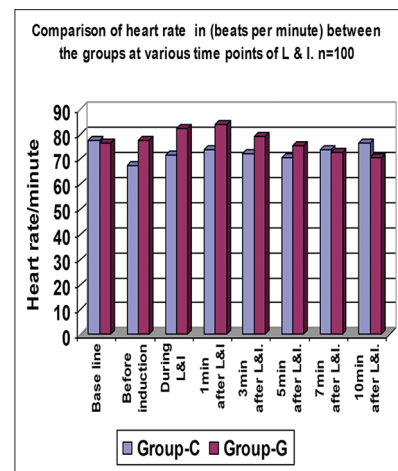

Figure 4: Comparison of Heart Rate (HR) between two groups

Preoperative sedation was assessed and scored as in Table 2. Patients who were noncommunicative when asked for due to deep sedation were to be excluded from this study. In this study, the preoperative sedation between two groups clonidine

and gabapentin ($P > 0.05$) [Table 3] were comparable and both the drugs had produced similar sedation.

Gabapentin produced this sedative action by virtue of its GABA potentiating action.[11,12] The sedative effects of clonidine appeared to be mediated by central α_{2A} receptor stimulation.[14,15]

CONCLUSION

Oral clonidine (200 μg) is the better attenuator among the two drugs studied over here to attenuate the cardiovascular responses to L and I. Oral gabapentine (800 mg) is equally effective in producing sedation when compared with gabapentin in a setting of major abdominal surgery cases. Further studies are required to find out the optimal dose of the drugs which will effectively prevent the pressure response to L and I.

REFERENCES

1. Henderson J. Airway management in the adult. In: Ronald D Miller, editor. Miller's Anesthesia. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010. p. Chapter-50. 1573-609.
2. Rose DK, Cohen MM. The airway: Problem and predictions in 18,500 patients. Can J Anaesth 1994;41:372-83.
3. Takita K, Morimoto Y, Kemmotsu O. Tracheal lidocaine attenuates the cardiovascular response to endotracheal intubation. Can J Anaesth 2001;48:732-6.
4. Kong VK, Irwin MG. Gabapentin: A multimodal perioperative drug? Br J Anaesth 2007;99:775-86.
5. Turan A, Kaya G, Karamanlioglu B, Pamukcu Z, Apfel CC. Effects of oral gabapentin on postoperative analgesia. Br J Anaesth 2006;96:242-6.
6. Segal AZ, Rodorf G. Gabapentin as a novel treatment for postherpetic neuralgia. Neurology 1996;46:1175-6.
7. Rosmer H, Rubin L, Kestenbaum A. Gabapentin adjunctive therapy in neuropathic pain states. Clin J Pain 1996;12:56-8.
8. Zapp JJ. Postpoliomyelitis pain treated with gabapentin. Am Fam Physician 1996;53:2442, 2445.
9. Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with gabapentin. Arch Phys Med Rehabil 1997;78:98-105.
10. Backonja M, Baydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, *et al*. Gabapentin for the sympathetic treatment of painful neuropathy in patients with diabetes mellitus: A randomized control trial. JAMA 1998;280:1831-6.
11. Rose MA, Kam PC. Gabapentin: Pharmacology and its use in pain management. Anaesthesia 2002;57:451-62.
12. Memis D, Turan A, Karamamlioglu B, Seker S, Ture M. Gabapentin
13. Fassoulaki A, Melemeni A, Paraskeva A, Petropoulos G. Gabapentin attenuates the pressor responses to direct laryngoscopy and tracheal intubation. Br J Anaesth 2006;96:769-73.
14. Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: The effect of clonidine on preoperative hemodynamics and isoflurane requirements. Anesthesiology 1987;67:3-10.
15. Carabine UA, Wright PM, Moore J. Preanaesthetic medication with clonidine: A dose-response study. Br J Anaesth 1991;67:79-83.
16. King BD, Harrin LC Jr, Greifenstein FF, Elder JD Jr, Dripps RD. Reflex circulatory responses to direct laryngoscopy and endotracheal intubation performed during general anaesthesia. Anesthesiology 1951;12:556-66.
17. Kovac AL. Controlling the haemodynamic responses to laryngoscopy and endotracheal intubation. J Clin Anesth 1996;8:63-79.
18. Maze M, Tranquilli W. Alpha-2 Adrenoreceptor agonist: Defining the role in clinical anaesthesia. Anaesthesiology 1991;74:581-605.
19. Imai Y, Mammoto T, Murakami K, Kita T, Sakai T, Kagawa K, *et al.* The effects of preanesthetic oral clonidine on total requirement of propofol for general anesthesia. J Clin Anesth 1998;10:660-5.
20. Morris J, Acheson M, Reeves M, Myles PS. Effect of clonidine pre-medication on propofol requirements during lower extremity vascular surgery: A randomized controlled trial. Br J Anaesth 2005;95:183-8.
21. Lyons FM, Bew S, Sheeran P, Hall GM. Effects of clonidine on the pituitary hormonal response to pelvic surgery. Br J Anaesth 1997;78:134-7.
22. Suzuki R, Rahman W, Rygh LJ, Webber M, Hunt SP, Dickenson AH. Spinal-supraspinal serotonergic circuits regulating neuropathic pain and its treatment with gabapentin. Pain 2005;117:292-303.
23. Tanabe M, Takasu K, Kasuya N, Shimizu S, Honda M, Ono H. Role of descending noradrenergic system and spinal alpha2-adrenergic receptors in the effects of gabapentin on thermal and mechanical nociception after partial nerve injury in the mouse. Br J Pharmacol 2005;144:703-14.
24. Marashi SM, Ghafari MH, Saliminia A. Attenuation of hemodynamic responses following laryngoscopy and tracheal intubation--comparative assessment of clonidine and gabapentin premedication. Middle East J Anesthesiol 2009;20:233-7.
25. Raval DL, Mehta MK. Oral clonidine premedication for attenuation of haemodynamic responses to laryngoscopy and intubation. Indian J Anaesth 2002;46:124-9.
26. Kumari I, Pathania VS. A prospective randomized double blind placebo controlled trial of oral gabapentin in attenuation of haemodynamic responses during laryngoscopy and tracheal intubation. J Anaesth Clin Pharmacol 2009;25:439-43.