Clinical Investigation

Attenuation of the haemodynamic responses to tracheal intubation with gabapentin, fentanyl and a combination of both: A randomised controlled trial

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ABSTRACT

Background and Aims: We conducted a prospective, randomised, double-blind, controlled clinical trial to examine (1) whether a single preoperative dose of 800 mg gabapentin would be as effective as 2 μg/kg of intravenous (IV) fentanyl in blunting the haemodynamic response to tracheal intubation and (2) whether a combination of both would be more effective in this regard. **Methods:** Seventy-five patients (American Society of Anaesthesiologists physical status I), aged 20–50 years were allocated into one of three groups: 2 μg/kg IV fentanyl, 800 mg oral gabapentin or a combination of both. Gabapentin was administered 2 h and fentanyl 5 min before induction of anaesthesia, which was achieved with 5 mg/kg thiopentone, and tracheal intubation facilitated with 0.1 mg/kg vecuronium. Laryngoscopy lasting a maximum of 30 s was attempted 3 min after administration of the induction agents. Serial values of mean arterial pressure (MAP) and heart rate (HR) were compared among the three groups and with the respective preinduction measurements. **Results**: Patients receiving gabapentin 800 mg alone showed remarkable increases in HR and MAP in response to tracheal intubation ($P < 0.05$). The increases were similar for the other two regimens. These haemodynamic changes were lesser in patients receiving fentanyl and the combination of gabapentin and fentanyl. **Conclusion:** Oral gabapentin does not produce significant reduction in laryngoscopy and tracheal intubation induced sympathetic responses as compared to IV fentanyl or the combination of gabapentin and fentanyl.

Key words: Gabapentin, haemodynamic response, intubation

INTRODUCTION

Laryngoscopy and intubation often provoke hypertension and tachycardia.[1,2] It is well-known that these haemodynamic changes are associated with the release of catecholamines.[3,4]

Gabapentin, a structural analogue of gamma-amino butyric acid, has been shown to have multi-modal effects which make it a potentially useful drug for premedication in adults, providing postoperative analgesia and preoperative anxiolysis while preventing chronic postsurgical pain, postoperative nausea and vomiting and delirium.[5] In addition, the drug has also been reported to successfully attenuate the cardiovascular responses to tracheal intubation. This beneficial effect of gabapentin is probably due to inhibition of membrane voltage gated calcium channels, an action similar to calcium channel blockers. Two recent randomised controlled trials have shown that oral gabapentin premedication attenuated the haemodynamic changes following tracheal intubation.[6,7]

The objective of the current study was to compare the effects of a single preoperative oral dose of 800 mg gabapentin with 2 μg/kg intravenous (IV) fentanyl on the haemodynamic responses to laryngoscopy and endotracheal intubation.

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The study also investigates the effects of administering both gabapentin and fentanyl compared to the administration of fentanyl alone in this regard.

METHODS

Approval of the Institute Ethics Sub Committee (human studies) of our university hospital was obtained, and also written informed consent from all the patients participating in the study. The study population comprised of 75 patients aged between 20 and 50 years, admitted for elective noncardiac surgery under general anaesthesia with endotracheal intubation. American Society of Anaesthesiologists (ASA) physical status I patients were included in the study. Patients with co-morbid illnesses such as hypertension, diabetes mellitus, ischemic heart disease etc., were excluded from the study. Also excluded from this study were patients on medications such as beta-blockers, calcium channel blockers, and vasodilators. Patients with predicted difficulty in intubation, those who required more than one attempt at laryngoscopy and those in whom the duration of laryngoscopy exceeded 30 s were excluded from the study. Patients having allergies to the drugs being administered during the course of the study, and those patients taking antacids and cimetidine were also excluded.

The study was designed as a double-blind randomised, parallel group clinical trial with an active control, wherein the allocation sequence was generated by a computer-generated random number table. Patients were divided into three study groups: Group G ($n = 25$): Gabapentin group, Group F ($n = 25$): Fentanyl group and Group B ($n = 25$): Both drugs administered.

The random allocation sequence generation and group allocation was done by an anaesthesiologist who was not aware of the study protocol and was not participating in the study. Participants were enrolled for the study by one investigator. The patient and the observer were not aware of the drugs given. The drugs were prepared and administered by the theatre anaesthesiologist, who was not part of the data collection or analysis. The placebo used for blinding gabapentin capsules was generated by opening up and evacuating the gabapentin capsule contents and sealing it back with sugar inside. Group G received oral gabapentin 800 mg 2 h prior to intubation and normal saline IV 5 min prior to anticipated intubation. Similarly, Group F received oral placebo 2 h prior to intubation and fentanyl 2 μg/kg IV 5 min prior to anticipated intubation, while Group B received oral gabapentin 800 mg 2 h prior to intubation and fentanyl 2 μg/kg IV 5 min prior to anticipated intubation.

All patients were assessed in the ward in the evening prior to the study of fitness and informed written consent was taken after explaining the procedure to them. All patients were premedicated with diazepam 0.2 mg/kg on the previous night and on the morning of surgery. Omeprazole 20 mg and metoclopramide 10 mg were administered orally on the morning of surgery.

In the operation theatre, a peripheral IV cannula was placed, and the monitors were connected to the patient. Noninvasive blood pressure, heart rate (HR), continuous electrocardiogram and pulse oximetry (SpO_2) were monitored.

Following attachment of monitors, the patient was preoxygenated for 3 min after which, baseline mean arterial pressure (MAP) and HR were recorded. Incidence of dysrhythmias was noted. Following preoxygenation, anaesthesia was induced with thiopentone 5 mg/kg IV, followed by vecuronium bromide 0.1 mg/kg IV Anaesthesia was maintained with 1% isoflurane and 50% nitrous oxide in oxygen. After an interval of 3 min, when neuromuscular block was achieved, laryngoscopy and intubation were performed by an experienced anaesthesiologist using an appropriate sized Macintosh blade and endotracheal tube.

The total duration of laryngoscopy, from picking up the laryngoscope till withdrawal of blade from the mouth, was recorded by a stopwatch. The primary outcome measures were the haemodynamic variables, HR and MAP measured 1 min postintubation. All haemodynamic measurements were carried out at 1 min, 2 min, 3 min, 4 min, 5 min and 10 min after intubation. In the event that the systolic blood pressure (SBP) fell below 90 mm Hg, or 30% from baseline, 3 mg of mephentermine was administeredIV as a rescue measure. Incidence of dysrhythmias was noted. Bradycardia (HR below 60 beats/min), was treated with 0.3 mg atropine IV. The secondary outcome measures were postoperative adverse effects like dizziness, somnolence, nausea and vomiting (measured using a four point scale), for which the patients were observed and actively interrogated every 6 h for the next 24 h in the postoperative ward.

The calculation of sample size was based on a preliminary study of 15 patients. We assumed that a 15% difference in HR and MAP would be clinically meaningful with an estimated standard deviation (SD) of 15 for HR and 18 for MAP to ensure power of 0.8 with alpha error assumed to be 0.05.This yielded a sample size of 23 patients in each group. We assumed that there might be a dropout rate of 10%; therefore, 25 patients were included in each arm of the study.

Mean arterial pressure and HR were expressed as mean ± SD. Statistical significance was taken at 95%. Comparisons within a group were done using two-way repeated measures analysis of variance (RM-ANOVA). Comparisons between groups were done using a one-way analysis of variance (ANOVA). Statistical Package for Social Sciences Statistics version 17.0 software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.) and GraphPad Instat (GraphPad Software Inc, La Jolla, California, USA) were used to conduct analyses.

RESULTS

Seventy-five patients were enrolled in the study and divided into three groups of 25 patients each. The flow of participants enrolled in this study is shown in Figure 1. The mean age, mean body weight and sex distribution of patients were comparable across groups [Table 1]. The baseline haemodynamic parameters and the postinduction parameters are also shown in Table 1. Both the baseline and postinduction parameters were comparable between the three groups. Similarly, there were no significant differences between the three groups with respect to the duration of laryngoscopy.

While the baseline and postinduction HRs were comparable between the three groups, the postintubation HRs were significantly elevated in the gabapentin group in comparison to the other two groups, up to 10 min [Figure 2]. There was no significant difference between the fentanyl group and the 'both drugs' group with respect to postintubation HR.

The postintubation MAP was significantly higher in the gabapentin group in comparison to the other groups, up to the 4th min [Figure 3]. There was no significant difference between the fentanyl group and the "both drugs" group with respect to postintubation MAP.

Repeated Measures Analysis of Variance demonstrated a significant increase in HR and mean arterial blood

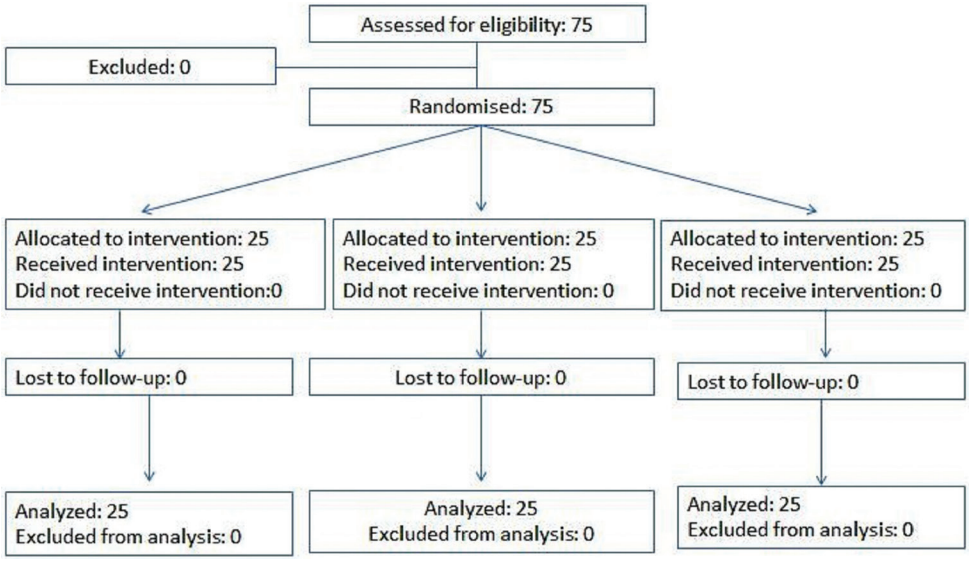

Figure 1: Diagram showing participant flow for the study

Table 1: Patient characteristics, baseline, and postinduction haemodynamic measurements and duration of laryngoscopy

Group	Sex (male: female)	Age (year)	Weight (kg)	Baseline HR (beats/min)	Baseline MAP (mmHg)	Postinduction HR (beats/min)	Postinduction MAP (mmHg)	Duration of laryngoscopy (s)
Gabapentin	11:14	41.8 (6.8)	61.9 (7.1)	80.1 (7.7)	85.4 (9.1)	75.3 (7.9)	73.1 (8.7)	22.9 (2.7)
Fentanyl	9:16	39.3 (8.6)	65 (7.6)	78.8 (8.8)	90.3 (7.5)	77.4 (8.2)	77.4 (8.2)	22.4 (2.9)
Both	12:13	36.7 (10.4)	61.5 (8.6)	80.1 (8.2)	88.7 (7.2)	75.6 (7.5)	75.6 (7.5)	21.9 (2.7)

Data are presented as mean (SD). At any variable, *P*>0.05. SD: Standard deviation; MAP: Mean arterial blood pressure; HR: Heart rate

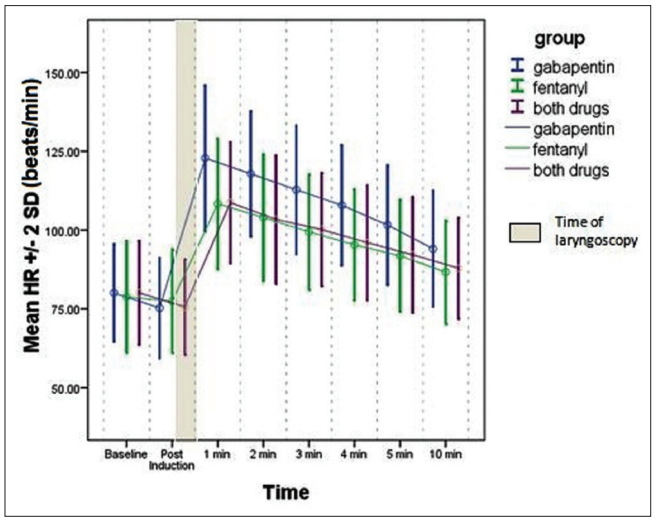

Figure 2: Error bar diagram showing change in heart rate from baseline among the three groups

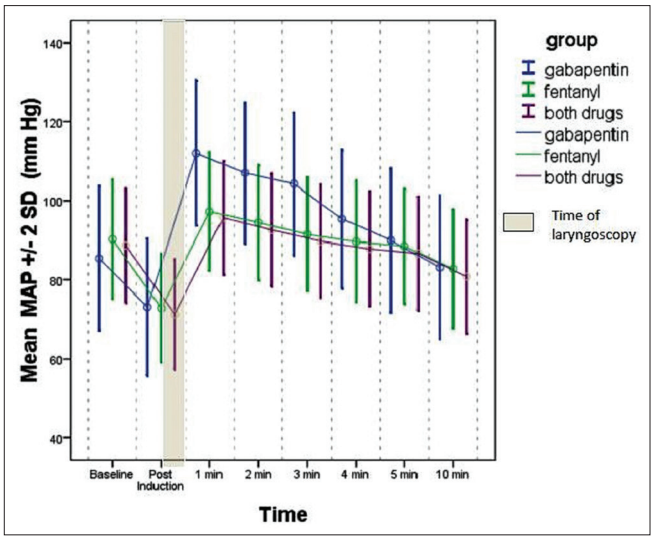

Figure 3: Error bar diagram showing change in mean arterial pressure from baseline among the three groups

pressure from the baseline, in all three groups, till 10 min postintubation. However, the magnitude of such changes was greater in the gabapentin group compared to the fentanyl and "both drugs" group [Table 2].

No patient in the present study developed severe hypotension or required mephentermine. No incidences of bradycardia, tachycardia, arrhythmia, ST segment alterations, or other electrocardiographic changes were observed during the study. There were no differences between the two groups in clinical outcomes, in terms of intra- or post-operative morbidity or mortality, possibly because only healthy ASA I patients without cardiovascular and cerebrovascular disease were included in this study. The most frequently reported side effects of gabapentin are somnolence, dizziness, ataxia, fatigue, nystagmus, headache, tremor, diplopia, and nausea. These are also side effects of commonly used premedication drugs. However, no side effects were observed in our patients.

Table 2: Maximum percentage increase in HR and MAP from baseline among groups

Group	Maximum increase in HR (%)	Maximum increase in MAP (%)
Gabapentin	63.7 (11.9)*†	54 (7.3)*†
Fentanyl	40.5 (11.1)	34 (3.1)
Both drugs	44.3 (12.2)	34.5 (3.5)

Data are presented as mean (SD). *P<0.05 versus fentanyl group, †P<0.05 versus both drugs. SD: Standard deviation; HR: Heart rate; MAP: Mean arterial blood pressure

DISCUSSION

In the current study, the fentanyl group served as an active control. For practical reasons, a placebo control group was not assigned in our study, the chief intention being to compare the effects of gabapentin with fentanyl. It is possible that gabapentin may act in a manner similar to calcium channel blockers in controlling the haemodynamic response associated with laryngoscopy and intubation.[8] A recent study has shown that the effects of gabapentin on haemodynamic variables during laryngoscopy and intubation may be dose-related up to a dose of 1000 mg.[9] We studied three groups of 25 patients each, with each group receiving either oral gabapentin 800 mg 2 h prior to laryngoscopy, IV fentanyl 2 μg/kg 5 min before laryngoscopy, or a combination of the two. We observed that patients who received gabapentin had increases in HR and blood pressure following intubation that were significantly higher than the other two groups. In addition, the haemodynamic changes in the fentanyl group were not significantly different from the group that received a combination of fentanyl and gabapentin, thus refuting our hypothesis of a significant synergistic effect between gabapentin and fentanyl. Studies have shown a synergistic effect of morphine and gabapentin in allaying postoperative pain, in both animal experiments and humans.[10] Hence, we had hypothesised that such synergism between gabapentin and opioids might extend to other aspects of perioperative care such as stress response attenuation. However, our results seem to suggest otherwise.

The dose of gabapentin we opted for was chosen after careful consideration of the oral bioavailability of the drug as well as a few previous trials done on similar lines. Gabapentin bioavailability is not dose proportional; that is, as dose is increased,

bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Further, effective single doses of gabapentin seem to lie somewhere between 800 and 1000 mg. Thus, we chose the 800 mg oral dose which we thought would give us a bioavailability of 34% (2400 mg in three divided doses). The timing of administration of the drug was at 6 AM in the morning along with other premedication drugs anticipating induction as the first case on the operating list at 8 AM. The elimination half-life of gabapentin being 5–7 h, we reasoned that 2 h would be adequate time for attainment of peak effect of the single dose administered.

When assessing techniques to ameliorate the cardiovascular responses to intubation, different agents used for induction and maintenance of anaesthesia may influence the results. We induced anaesthesia with thiopentone as opposed to most of the previous authors who have used gabapentin with propofol.[11-13] Propofol is believed to block the catecholamine and haemodynamic responses to laryngeal manipulation more effectively than thiopentone.[14] Thus; we believe that the results of our study can only be extrapolated to clinical settings where thiopentone is used. In fact, in such studies, where thiopentone has been used as the induction agent, gabapentin has not been shown to be as effective as other agents such as clonidine.[15]

A major limitation of our study is that stress mediators were not measured. The issue of correlation between haemodynamics and plasma catecholamine changes following tracheal intubation can be rather controversial. Barak *et al*.[16] did not find a correlation between haemodynamic changes and catecholamine levels, in contrast to some authors who have observed a correlation between the haemodynamic responses associated with tracheal intubation and the changes in plasma catecholamine concentrations.[17] In addition, the catecholamine response to tracheal intubation is the greatest in central venous samples, compared with arterial or peripheral venous samples. However, central venous cannulation was deemed not ethical in ASA I patients undergoing minor surgery, and hence we refrained from the same.

Many techniques have been devised to reduce the extent of cardiovascular responses to intubation, including the use of opioids, lidocaine, adrenergic blocking agents, and vasodilating agents.[18] However, it has been suggested that the omission of opioids during induction of anaesthesia in ASA I patients, as in our gabapentin group, should not be of significant concern.[7] We recorded the duration of laryngoscopy and intubation for each patient, and these were comparable for all three groups. Patients requiring more than one attempt at laryngoscopy, or >30 s of laryngoscopy were to be excluded from analysis. Arterial pressure and HR responses have been shown to be greater when the duration of laryngoscopy exceeds 30 s. Laryngoscopy alone or followed by tracheal intubation increases arterial pressure and catecholamine levels while intubation significantly increases HR.

Ramsay has commented that the severity of side effects of gabapentin is usually of a minor degree.[19] We found that gabapentin is generally well tolerated with a favourable side effect profile. The side effects reported with gabapentin have mainly been with long-term use as in seizure treatment[20] or for chronic pain treatment.[21,22]

Our experience of using gabapentin against fentanyl to blunt the haemodynamic response to laryngoscopy and intubation seems to suggest that it is unlikely to add significant benefits to standard perioperative drug regimens that utilize thiopentone as the induction agent. While its performance against placebo, as suggested by previous studies, might encourage its use as a multi-modal perioperative drug, for sole purposes of blunting stress responses associated with anaesthesia and surgery, it might under-achieve. Of course, we admit that the drug needs to be assessed alongside various other anaesthetic agents, before a final comment on its utility for reducing cardiovascular perturbations associated with intubation can be made. Future studies are required to verify whether attenuation of haemodynamic changes with oral gabapentin is influenced by alternative anaesthetic regimens especially in patients with hypertension, for example, hypertension arising from chronic renal failure.

CONCLUSION

Oral gabapentin (800 mg) administered alone as premedication 2 h prior to laryngoscopy and intubation did not lead to a significant reduction in the haemodynamic responses, as compared to IV fentanyl administered 5 min before airway manipulation. Further, administering both drugs did not seem to have

any added advantage over administration of IV fentanyl alone. Attenuation of the pressor and tachycardic responses to tracheal intubation with an oral dose of gabapentin could, therefore, be unsatisfactory with the anaesthetic regimen that we have followed in this study.

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