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HUMAN RESEARCH ANESTHESIA & CONCURRENT DISEASE

Premedication with gabapentin for laryngoscopy: a double-blind randomized control trial in hypertensive patients

Muhammad Imran Riasat, FCPS [1], Haris Tariq Chohan, FCPS [1], Arun Kumar, FCPS [1], Syed Farjad Sultan, FCARCSI, PhD [2], Hanya Javaid, MBBS [3], Safia Zafar Siddiqui FCPS, MSc (Pain Medicine) [4]

Authors' affiliations:

1- Senior Registrar, Department of Anesthesiology, SICU & Pain Management, Dr. Ruth K.M. Pfau Civil Hospital, Karachi, Pakistan.
2- Assistant Professor, Department of Anesthesiology, SICU & Pain Management, Dr. Ruth K.M. Pfau Civil Hospital, Karachi, Pakistan.
3- Anesthesia Resident, Department of Anesthesiology, SICU & Pain Management, Dr. Ruth K.M. Pfau Civil Hospital, Karachi, Pakistan.
4- Professor and Head, Department of Anesthesiology, SICU & Pain Management, Dr. Ruth K.M. Pfau Civil Hospital, Karachi, Pakistan.

Correspondence: Dr. Muhammad Imran Riasat, FCPS, Department of Anesthesiology, SICU and Pain Management, Dr. Ruth K.M Pfau Civil Hospital Karachi, Baba-e-Urdu Road, Karachi, Pakistan; Phone: +92-334-2947181; E-mail: dr.imranriasat@gmail.com

Abstract

Background & Objective: Laryngoscopy and intubation (L&I) are strong stimulus for cardiovascular system. Hypertensive patients have a greater incidence of coexisting coronary artery disease and cerebrovascular insufficiency. Several methods have been in practice to prevent or alter the hemodynamic response to L&I. Although the main use of gabapentin has been as an antiepileptic, but its effect on the hemodynamic reflexes is still under evaluation. We compared the effectiveness of a single dose of gabapentin 800 mg on the mean arterial pressure (MAP) in response to L&I in hypertensive patients undergoing day care surgery.

Methodology: This randomized, control trial was conducted in operating rooms, Dr Ruth K M Pfau Civil Hospital Karachi, from May 2017 to November 2017. A total of 150 patients undergoing elective surgery requiring general anesthesia with tracheal intubation were included in this study. Patients were randomly allocated equally into two group; Group G (gabapentin group) and Group P (placebo group). Patients in Group G received gabapentin 800 mg and Group P received placebo, 2 h prior to induction of anesthesia. MAP was measured at baseline (before induction), before intubation (after induction), at time 0 (immediately after intubation), and at 1 min, 3 min, 5 min, and 10 min after intubation. Effectiveness was defined as all the MAP reading to be within 30% of the baseline reading.

Results: There were 72(48%) males and 78(52%) females. Effectiveness was significantly higher in patients of Group G, as compared to placebo group (Group P) [94.7% vs. 65.3%; p = 0.0005].

Conclusion: Gabapentin effectively suppresses the increase in MAP in response to laryngoscopy and tracheal intubation as compared to the placebo.

Abbreviations: L&I: Laryngoscopy and intubation; MAP: Mean arterial pressure; ECG: Electrocardiography; ASA: American Society of Anesthesiologists; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Key words: Laryngoscopy; Intubation; Hypertension; Gabapentin; Stress response

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1. Introduction

Laryngoscopy for tracheal intubation (L&I) is a potent stimulus for sympathetic stimulation.[1] Hypertensive patients show accentuated pressor response to tracheal intubation and laryngoscopy that can result in life threatening hypertensive crisis.[2-5]

Multiple techniques such as increasing of the depth of anesthesia, avoiding cholinergic premedication, pre-treatment with vasodilators such as calcium channel blockers, nitroglycerin, opioids and beta-blockers have been used to prevent the pressor responses following laryngoscopy and intubation.[6]

Gabapentin is a structural analogue of the neurotransmitter, γ–aminobutyric acid (GABA) that was introduced as an antiepileptic drug.[7] It has proven its role in managing pain (neuropathic and acute postoperative) and has reduced the postoperative requirement of opioid.[8]

According to the current guide lines, hypertension should not lead to deferring or cancellation of surgery unless it is hypertensive crisis.[9,10] Although, Gabapentin is effective in attenuating in hemodynamic response to L&I in individuals without any significant coexisting diseases,[11] little is known about hypertensives. So, our rationale was to see the effect of gabapentin in controlled hypertensive patients who were undergoing elective day-care procedures and have missed their morning antihypertensive medication dose.

Objective: To compare the effectiveness of a single dose gabapentin 800 mg on the mean arterial pressure (MAP) in response to L&I in hypertensive patients undergoing day care surgery.

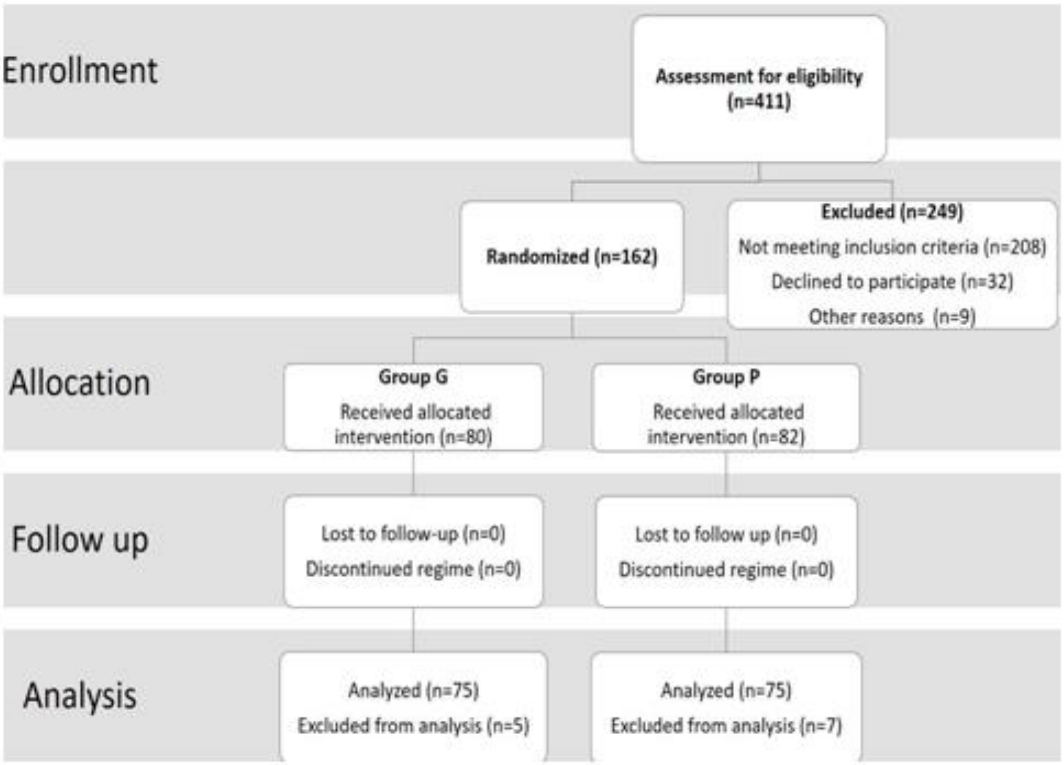

Figure 1: CONSORT Flow Chart

2. Research Methodology

This study was conducted at the Department of Anesthesiology, Dr. Ruth K. M. Pfau Civil Hospital Karachi, from May 2017 to November 2017. After obtaining approval from hospital ethical board and written informed consent, 150 known hypertensive patients were included. Hypertensives (35–60 y of age) who had missed their morning antihypertensive medication and were undergoing day-care surgery requiring general anesthesia with L&I were randomized to either gabapentin or control group. Patients with anticipated difficult intubation (grade 3 and 4 according to mallampati), having high risk of aspiration (known cases of hiatus hernia, and acid reflux disease), obesity (BMI > 30 kg/m2), any previous history of ischemic heart disease, arrhythmias, cerebrovascular disease and those who had taken their morning antihypertensive medications were excluded.

Eligible patients were randomized into one of the two groups through randomization.com. Group G included patients who received oral gabapentin 800 mg and Group P received a placebo (empty capsule). Both the drugs were in form of capsules and were labelled study drug and were given a serial number in pharmacy of our hospital and then were sent to preoperative assessment area. The anesthesiologists of the pre-operative clinic were instructed to give the study drug with a sip of water 2 h prior to surgery. Standard monitoring with pulse oximeter, non-invasive blood pressure (NIBP), electrocardiography (ECG), end-tidal concentration of carbon dioxide was done intra-operatively for every patient by a consultant anesthesiologist (having 5 or more years of experience).

Propofol 1 mg/kg and nalbuphine 0.1 mg/kg were used for induction followed by atracurium 0.5 mg/kg, then anesthesia was maintained with 40% oxygen with 1.2 volume% isoflurane. Nerve stimulator was used and endotracheal tube was placed when the train of four counts reached zero. If more than two attempts were made for laryngoscopy or the intubation tool more than 2 min the data was noted and the patient was excluded from the study.

Heart rate (HR), blood pressure (BP) and electrocardiograph were recorded as baseline (before induction), before intubation (after induction), at time 0 (immediately after intubation), and at 1 min, 3 min, 5 min, and 10 min after intubation MAP was noted. As the exact thresholds of BP are undefined[12] and change of MAP of more than 30% was associated with a poor outcome[13] so, effectiveness was labelled when all the reading were within 30% of baseline.

Hypotension [mean arterial pressure less than 65 mmHg or more than 30% decrease from baseline lasting for less than one minute] (which might occur as a side effect of IV induction agent, inhalation agent or our study drug) was managed with intravenous fluid or boluses of 50 µg of phenylephrine; atropine was used to manage bradycardia (HR < 40/min).

Tachycardia (HR >120 beats/min or > 30% increase from baseline lasting for >1 min) or hypertension (DBP > 110 mmHg or SBP >180 mmHg or > 30% increase from baseline lasting for more than 1 min). Isoflurane concentration was increased if the drug was ineffective and further management was as per the anesthesiologist's clinical practice. This information, along with age, sex, ASA status, height and weight, was noted.

Statistical analysis: Statistical Package for Social Science (v.20, SPSS Inc., Chicago, IL, USA) was used to analyze data. Frequencies and percentages were computed for categorical variables like ASA status, sex, effectiveness. Mean and standard deviation was computed for quantitative variables like age, duration of hypertension, duration of treatment of hypertension, BMI, SBP, DBP and MAP. The groups were compared in terms of efficacy, applying chi square test.

Stratification of age, BMI, ASA status, sex and duration of treatment of hypertension was done to control these effect modifiers on outcome variables. P ≤ 0.05 was considered as significant.

3. Results

A total of 162 patients were recruited for our study, while 150 patients completed it and were analyzed for effectiveness (as shown in Figure 1). The average age of the patients was 44.32 ± 7.57 y and 43.40 ± 6.83 y in group P and Group G respectively. There were 72(48%) males and 78(52%) females.

Effectiveness of gabapentin 800 mg was significantly high as compared to placebo [94.7% vs. 65.3%; p = 0.0005] as shown in Table 1.

Table 1: Comparative effectiveness between two groups

Effectiveness	Group P N = 75	Group G N = 75	Total	p-value
Yes *[MAP within 30 % from baseline]*	49 (65.3%)	71 (94.7%)	120 (80%)	0.0005
No [change of *MAP >30 % from baseline]*	26 (34.7%)	4 (5.3%)	30 (20%)	
Chi-square= 20.167				

Age was stratified in three groups and observed the effect of age on efficacy; however, effectiveness of Group G was significantly high in ≤ 40 and 41 to 50 y of age except above 50 y of age. It was statistically more significant in females (p = 0.0005). Similarly, effectiveness was also high in groups G after stratification of BMI and duration of hypertension of treatment. (Table 2)

Table 2: Effectiveness according to different variables

Variables	Total patients (n)	Total Effective (E)	Group P E/n (%)	Group G E/n (%)	p-value
Age (Y)					
≤ 40	65	50	18/30 (60%)	32/35 (91.4%)	0.003
41-50	52	44	19/27 (70.4%)	25/25 (100%)	0.003
> 50	33	26	12/18 (66.7%)	14/15 (93.3%)	0.095
Gender					
Male	72	60	21/29 (72.4%)	39/43 (90.7%)	0.041
Female	78	60	28/46 (60.9%)	32/32 (100%)	0.0005
BMI (kg/m^2)					
≤ 25	96	83	33/43 (76.7%)	50/53 (94.3%)	0.012
25.1-29.9	40	27	12/24 (50%)	15/16 (93.8%)	0.004
30-35	14	10	4/8 (50%)	6/6 (100%	0.085
Duration of treatment of hypertension (Y)					
< 10	54	46	22/29 (75.9%)	24/25 (96%)	0.038
> 10	96	74	27/46 (58.7%)	47/50 (94%)	0.0005

4. Discussion

Laryngoscopy and tracheal intubation result in marked stress response that manifests itself in the form of changes in HR, BP and arrthymias.[14] These temporary responses have no dire consequence in healthy individuals but may be dangerous and life threatening to the ones with pre-existing hypertension or other past medical conditions, such as myocardial infarction or cerebrovascular disease. It is, therefore, of prime importance to prevent the likely hemodynamic changes following tracheal intubation in hypertensive patients.[15]

Attenuation of hemodynamic stress response to L&I in normotensive patients has been documented in various studies in the literature. A study by Serhat Koc et al. compared 400 mg and 800 mg of gabapentin, and they reported that the lower dose was ineffective in preventing pressor response after tracheal intubation.[16]

There is scarcity of data regarding the evaluation of the effect of gabapentin pre-treatment on L&I in patients with hypertension. One such study conducted by Bala et al. by using 800 mg gabapentin on controlled hypertensives showed similar results as our study,[17] despite the fact that we only included those who had missed their antihypertensive medication because of the overnight fasting instructions. This finding may

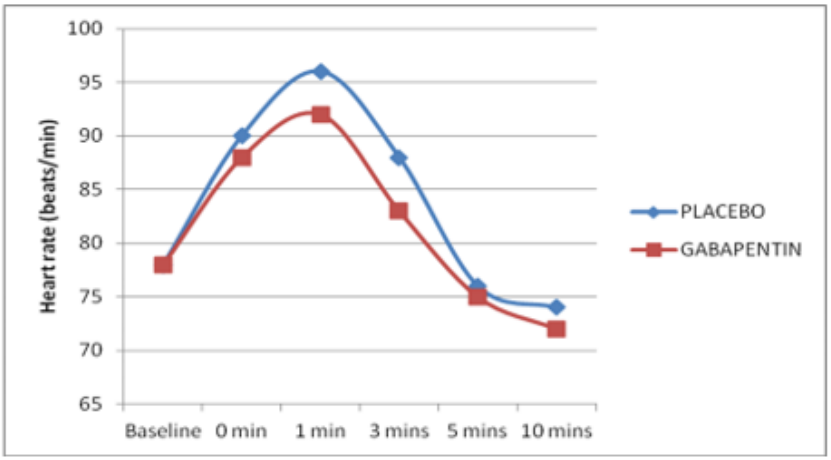

Figure 2: Comparative effect on heart rate in two groups

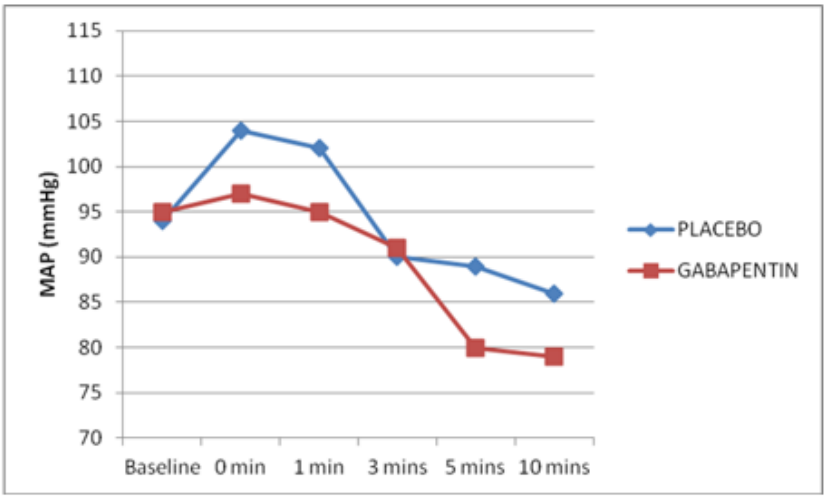

Figure 3: Comparative effect on MAP in two groups

prove beneficial in non-compliant hypertensive patients who might otherwise have their procedures postponed.

In contrast to our study, another study was conducted by Farzi et al.[18] in patients undergoing septorhinoplasty. They used 900 mg gabapentin and did not find a significant effect on the hemodynamic changes induced by laryngoscopy except for SBP. It could be because of the difference in time intervals taken to measure BP. We found the maximum attenuation just after intubation and at one minute after that, while their first measurement was taken at 3 min after induction. The other consideration could be the procedure of septorhinoplasty itself, as the procedure normally involves infiltration of local anesthetic and vasoconstricting agent which may have contributed to their findings.

When compared with other standard agents such as lidocaine or fentanyl, gabapentin was inferior for many hemodynamic outcomes.[19,20] But in our country, the high cost and the availability of fentanyl and clonidine is a serious problem. On the other hand, gabapentin is easily available and relatively cheap. Despite the fact that clonidine and beta blockers have manifested promising results in reducing perioperative cardiac effects,[21] a higher incidence of clinically significant hypotension and cardiac arrest were noted with clonidine, but no evidence of refractory hypotension or ischemic changes were noted with gabapentin.[22]

A meta-analysis conducted by Doleman B. et al. concluded the effectiveness of gabapentin in attenuating the pressor responses following intubation when compared with the control group.[23]

The strength of our study was double blinded randomization on specific sub-group of hypertensive patients.

5. Limitations

Our study had certain limitations. Firstly, the patients included in our study were on various antihypertensive drugs which included beta blockers that could also have affected the hemodynamics. Even though, there are studies which show no additional benefits from bispectral index (BIS) monitoring, [24] lack of depth of anesthesia monitoring could lead to increased awareness and pain, and effect the hemodynamic parameters.

The other limitations included overlooking the incidence of postoperative sedation, postoperative hypotension and pain scores.

Hemodynamic responses in hypertensive patients are not only seen in response to L&I, but other intraoperative factors could also give rise to these variations. Such as, intra-abdominal hypertension caused by gas insufflation in laparoscopic procedures. Future studies could be done keeping these factors in mind.

6. Conclusion

We conclude that 800 mg gabapentin is an effective drug in attenuating the cardiovascular pressor response to laryngoscopy and tracheal intubation in hypertensive patients.

7. Conflict of interests

No conflict declared by the authors. No funding or grant was involved in the conduct of this study.

8. Authors' contribution

MIR: Concept, design of study
HTC: Acquisition & analysis
AK: Interpretation & manuscript drafting
SFS: Overlooked all study work, and accuracy of study
HJ: Drafting and revising critical content
SZS: Overall supervision

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