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GABAPENTIN;

EFFECTIVENESS OF ORAL GABAPENTIN ON PRESSOR RESPONSE IN PATIENTS UNDERGOING ELECTIVE MAXILLOFACIAL SURGERIES AND NASOTRACHEAL INTUBATION

Brig (Retd) Muhammad Boota[1], Sohail Nasir[2], Imran Hyder[3]

1. FCPS
Associate Professor
Department of Anesthesiology
Foundation University Medical College Islamabad.
2. MBBS, FCPS
Registrar
Department of Anesthesia
Fauji Foundation Hospital Rawalpindi.
3. MBBS
Registrar
Department of Anesthesia
Fauji Foundation Hospital Rawalpindi.

Correspondence Address:
Dr. Sohail Nasir
Department of Anesthesia
Fauji Foundation Hospital Rawalpindi.
dr_sohailnasir@yahoo.com

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ABSTRACT… Introduction: There have been several methods used to prevent or attenuate the adverse hemodynamic changes following endotracheal intubation, but not many studies have been done for the same purpose in patients undergoing nasotracheal intubation. Deepening of anaesthesia, omitting cholinergic premedication, pre-treatment with vasodilators such as nitroglycerine, beta blockers, calcium channel blockers and opioids are few of the different techniques used when trachea is intubated orally or nasally, to blunt significant swings in hemodynamic parameters. We assessed the effectiveness of oral gabapentin to determine changes in hemodynamic response in normotensive patients following nasotracheal intubation with or without laryngoscopy for elective maxillofacial surgeries. **Study Design:** Randomized double blind, placebo-controlled clinical trial. **Setting:** Department of Anesthesia & Intensive Care, Fauji Foundation Hospital Rawalpindi. **Period**: 18 months after approval from the ethical committee. **Material & Methods:** Total 130 patients were included in the study. These patients were randomly divided into 2 groups. In Group-A patients were given 800 mg gabapentin and in Group-B patients were given placebo. Heart rate and mean arterial pressures were recorded just before intubation as base line values, and then average readings were taken at 1 minute, 3 minutes, 5 minutes and 10 minutes after intubation. Bradycardia and hypotension were adequately treated with intravenous atropine and vasopressors. Data entry and analysis was done by using SPSS 17. **Results:** Total 130 patients who underwent elective surgeries were included in the study and divided into 2 groups each group containing 65 patients each. At 1st minute MAP in Group-A (oral gabapentin) and in Group-B (Placebo) was 86.89±4.36 and 98.70±4.39. At 3rd minute MAP in Group-A, in Group-B was 83.40±4.05 and 92.93±4.79. At 5th minute MAP was 82.50±5.00 and 88.03±4.22 and lastly at 10th minute MAP was 79.81±5.37 in Group-A and 83.18±4.77 in Group-B respectively. P-value at 1st, 3rd, 5th and at 10th minutes showed that statistically MAP was different in both treatment groups at the above mentioned time intervals. 1st minute: p-value=0.042, 3rd minute: p-value=0.000, 5th minute: p-value=0.000 and at 10th minute: p-value=0.000. At 1st minute heart rate in Group-A and Group-B was 87.89±1.39 and 93.47±6.88 respectively. At 3rd minute heart rate in Group-A and Group-B was 83.47±5.47 and 89.70±6.76. At 5th minute heart rate was 82.10±5.01 and 84.60±5.91 and lastly at 10th minute heart rate was 78.09±6.79 in Group-A and 77.27±5.34 in Group-B respectively. P -value at 1st, 3rd and 5th minutes showed that statistically heart rate was different in both treatment groups at the above mentioned time intervals. But at 10th minute heart rate was statistically same in both treatment groups. 1st minute: p-value=0.144, 3rd minute: p-value=0.000, 5th minute: p-value=0.011 and at 10th minute: p-value=0.448. **Conclusion:** According to the results of this study it was observed that oral gabapentin is effective in modifying hemodynamic response to nasotracheal intubation in normotensive patients undergoing elective maxillofacial surgeries. MAP (10th Minute: Group-A vs. Group-B: 0.000) & Heart Rate (10th Minute: Group-A vs. Group-B:0.448)

Key words: Gabapentin, Hemodynamic Response, Laryngoscopy, Nasotracheal Intubation.

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INTRODUCTION

Maxillo-facial surgeries present unique challenges in the operating rooms to anesthesiologists for establishing definitive airways. A specific type of conduits, designated nasotracheal tubes are used in most of the elective maxilla-facial surgeries

involving head, neck and face apart from invasive airway equipment including tracheostomies. Nasotracheal Intubation, like endotracheal intubation is commonly performed by direct laryngoscopy, fibreoptic bronchoscopy, or blindly for maintenance of airway and protection against aspiration of gastric contents during general anesthesia.[1] Laryngoscopy and nasotracheal intubation may induce a transient but marked sympathetic response characterized by increase in heart rate, blood pressure & arrhythmias and is widely recognized as pressor response. These changes are well tolerated by patients labelled ASA I and II, but in patients suffering from cardiovascular and cerebrovascular diseases, such clinically significant variations may result in fatal life threatening complications like myocardial ischemia & infarction, left ventricular failure, pulmonary edema and cerebrovascular haemorrhage.[2-3] Several pharmacological agents have been used to suppress these hemodynamic responses such as deepening of anesthesia with inhalational agents, I/V lidocaine short acting opioids like fentanyl & remifentanil, esmolol and clonidine. One such agent studied in various medical centers in the West is Gabapentin.

Gabapentin is anticonvulsant agent. It is being used to treat partial seizure but is also effective in controlling neuropathic and acute post-operative pain.[4-9] Gabapentin also decreases hemodynamic response to laryngoscopy and intubation by binding to α-2/δ subunit of presynaptic voltage gated Ca^{++} channels responsible for the inhibition of Ca^{++} influx and decreasing synthesis of neurotransmitter glutamate.[9,10] Previous studies have shown that with 800mg gabapentin, mean arterial blood pressure was 79±12 and heart rate was 92±15 which were significantly lower at 10 minutes after intubation as compared to placebo. While in placebo group MAP and HR at 10 minutes after intubation were 88±13, 101±18 respectively.[11] It has been hypothesized that oral gabapentin (800 mg) is better as compared to placebo in terms of mean hemodynamic response to nasotracheal intubation in normotensive patients undergoing elective surgeries.

OBJECTIVE

To assess the effectiveness of oral gabapentin in modifying hemodynamic response to nasotracheal intubation in normotensive patients undergoing elective surgery.

MATERIAL AND METHODS

Patient Selection and Randomization

This was a randomized double blind, placebo-controlled clinical trial performed in Department of Anesthesiology, Intensive Care and Pain Medicine, Fauji Foundation Hospital, Rawalpindi for the duration of 18 months after approval from ethical committee. With the help of WHO sample size calculator, keeping level of significance at 5%, the power of test at 80% the sample size (n) turned out to be 65 patients in each group. Consecutive sampling technique was used.

Inclusion Criteria

Patients included in this study were aged between 18 to 50 years, having ASA grades 1 and 2, Mallampati class 1& 2, posted for elective surgeries including open reductions and internal fixations, dental excisions, glossectomies, tumors and salivary glands excisions, flap-reconstruction etc. Patients with nasal suspected pathologies e.g, polyps, hypertrophied turbinates and history of previous trauma were managed in consultation with ENT for identification and preparation of appropriate nostril/passage for nasotracheal intubation.

Exclusion Criteria

Patients with Le-Forte II & III fractures, temporo-mandibular joint trauma leading to CSF rhinorrhea, history of hypertension, diabetes, liver disease and renal failure, patients on antihypertensive, sedatives, hypnotics and antidepressant drugs and those with histories of allergy to anesthetic and study drug were excluded. Obese, pregnant and lactating females were also not included in the study samples.

Protocol

After approval from hospital ethical committee and taking written consent patients were randomly divided into two groups. Group "A" and Group "B"

by Lottery method with 65 patients in each group. The study drug was prepared by a consultant anesthetic not related to study. Radiopaque sealed envelopes containing drug was marked with appropriate code no. and randomly assigned to patients based on lottery method. These envelopes either containing 800mg gabapentin or placebo were only known to person who prepared drugs and was given to patients 2hrs before surgery with sips of water. In operative room, crystalloid infusion was started through an intravenous cannula. All standard monitors were attached to patient (pulse oximeter, ECG, Noninvasive blood pressure). For premedication 0.07mg/kg of midazolam and injection nalbuphine 0.1 mg/kg was given 5 minute before intubation. After adequate pre-oxygenation for 3 min induction was done with intravenous injection propofol 2mg/kg and injection atracurium 0.5mg/kg. Patient was ventilated with face mask and bag for 3 minutes. Selected nostril was sprayed with vasoconstrictor agent and NTT of appropriate size (7.0-6.5 mm for males and 6.5-6.0 mm for females) lubricated with lidocaine gel and intubation was done after direct laryngoscopy by consultant anesthetist. An independent observer was responsible for recording hemodynamics just before intubation and after intubation. HR and MAP were recorded just before intubation as base line value then average readings were taken at 1 minute, 3 minutes, 5 minutes, 10 minutes after intubation. MAP less than 60mmHg and SAP less than 90mmHg was treated with intravenous phenylephrine 50 micrograms. Heart rate less than 50 beats /min was treated with intravenous injection atropine 0.5mg.

DATA ANALYSIS

All data was entered in SPSS-20. mean ± standard deviation was calculated for quantitative variable likes HR and MAP. Hemodynamic response for qualitative variable like gender frequency and percentage was also calculated. Line charts were also made for comparisons of HR and MAP in both study groups. Student "t" test was used to compare the two groups in term of means. p-value of less than 0.05 % was considered statistically significant.

OPERATIONAL DEFINITIONS

HEMODYNAMIC RESPONSE

1. **Heart Rate**
   Heart Rate in beats/min was measured by Pulse oximertery. Heart Rate was recorded just before intubation as base line value then mean value was taken at 1 minute, 3 minutes, 5 minutes, 10 minutes after intubation.
2. **Systolic Arterial Pressure**
   SAP was measured by noninvasive blood pressure (NIBP).
3. **Diastolic Arterial Pressure**
   DAP was measured by NIBP.
4. **Mean Arterial Pressure**
   MAP calculated with following formula

$$MAP = DAP + (SAP - DAP) / 3$$

MAP was recorded just before the intubation as base line value then mean values were taken at 1 minute, 3 minutes, 5 minutes, 10 minutes after intubation.

RESULTS

Total 130 patients who underwent elective surgeries were included in the study and divided into 2 groups each group containing 65 patients each. Mean age of all 130 patients were 34.00±6.01 years. In Group-A and in Group-B mean age of patients was 34.96±5.78 and 33.03±6.12 years respectively. In Group-A 28(43.1%) patients were male and 37(56.9%) patients were females. While in Group-B 24(36.9%) patients were male and 41(63.1%) patients were females. In Group-A and in Group-B mean weight of patients was 61.40±5.21 and 62.00±5.28 kg respectively. Mean arterial pressure before intubation in Group-A and in Group-B was 75.56±4.03 and 74.01±4.55. At 1st minute MAP in Group-A and in Group-B was 86.89±4.36 and 98.70±4.39. At 3rd minute MAP in Group-A and in Group-B was 83.40±4.05 and 92.93±4.79. At 5th minute MAP was 82.50±5.00 and 88.03±4.22 and lastly at 10th minute MAP was 79.81±5.37 in Group-A and 83.18±4.77 in Group-B respectively. p-value at 1st, 3rd, 5th and at 10th minutes showed that statistically MAP was different in both treatment groups at the above mentioned time intervals. 1st minute: p-value=0.042, 3rd minute:

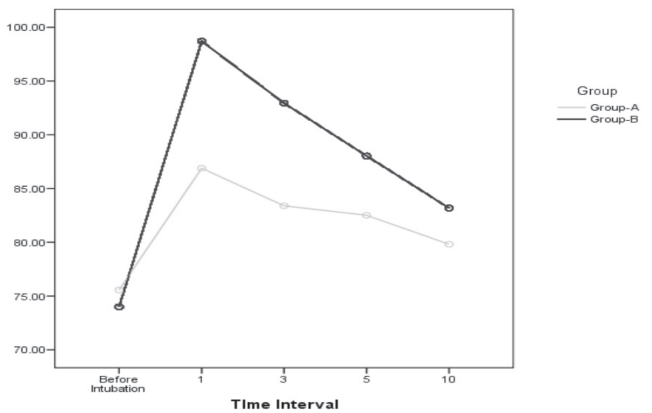
p-value=0.000, 5th minute: p-value=0.000 and at 10th minute: p-value=0.000 (Table-I&II). Heart rate before intubation in Group-A and in Group-B was 75.12±6.94 and 73.33±6.88. At 1st minute heart rate in Group-A and in Group-B was 87.89±1.39 and 93.47±6.88. At 3rd minute heart rate in Group-A and in Group-B was 83.47±5.47 and 89.70±6.76. At 5th minute heart rate was 82.10±5.01 and 84.60±5.91 and lastly at 10th minute heart rate was 78.09±6.79 in Group-A and 77.27±5.34 in Group-B respectively. p-value at 1st, 3rd and 5th at minutes showed that statistically heart rate was different in both treatment groups at the above mentioned time intervals. But at 10th minute heart rate was statistically same in both treatment groups. 1st minute: p-value=0.144, 3rd minute: p-value=0.000, 5th minute: p-value=0.011 and at 10th minute: p-value=0.448.

	Group	N	Mean	SD	p-value
MAP Before Intubation	Group-A	65	75.56	4.03	0.042
	Group-B	65	74.01	4.55	
MAP.1	Group-A	65	86.89	4.36	0.000
	Group-B	65	98.70	4.39	
MAP.3	Group-A	65	83.40	4.05	0.000
	Group-B	65	92.93	4.79	
MAP.5	Group-A	65	82.50	5.00	0.000
	Group-B	65	88.03	4.22	
MAP.10	Group-A	65	79.81	5.37	0.000
	Group-B	65	83.18	4.77	

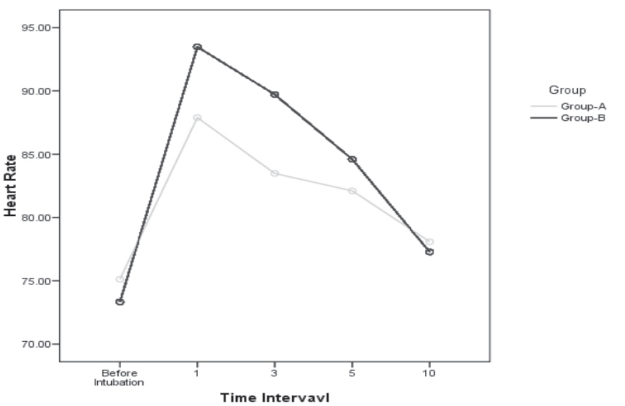
Table-I. Arterial pressures in treatment groups
Group-A= Oral Gabapentin Group-B= Placebo

	Group	N	Mean	SD	p-value
Heart Rate Before Intubation	Group-A	65	75.12	6.94	0.144
	Group-B	65	73.33	6.88	
Heart Rate-1	Group-A	65	87.89	1.39	0.000
	Group-B	65	93.47	6.88	
Heart Rate-3	Group-A	65	83.47	5.74	0.000
	Group-B	65	89.70	6.76	
Heart Rate-5	Group-A	65	82.10	5.01	0.011
	Group-B	65	84.60	5.91	
Heart Rate-10	Group-A	65	78.09	6.79	0.448
	Group-B	65	77.27	5.34	

Table-II. Heart rates in treatment groups
Group-A= Oral Gabapentin Group-B= Placebo



Group-A= Oral Gabapentin Group-B= Placebo
Figure-1. Mean arterial pressure in treatment groups



Group-A= Oral Gabapentin Group-B= Placebo
Figure-2: Heart rate in treatment groups

DISCUSSION

Successful airway management is one of the most critical areas in the present-day general anesthetics and as such maxillofacial and oral surgeries present a unique challenge to both surgeons and anesthesiologists because of the need to maximize operative field in an already limited space and shared airway. Vedapally KA and associates[12] showed that surgical field and ease of operability improved significantly by adopting algorithms for oral and maxillofacial surgeries for establishing airway in 634 patients undergoing a variety of procedures involving oral and maxillofacial region. However it were S. Singh and J. E Smith who studied pressor response to nasotracheal intubation at three different stages, in 75 patients of ASA I & II statuses. They concluded that "nasopharyngeal intubation causes a significant pressor response, stimulation of the larynx and trachea by the passage of the tracheal tube, but not direct laryngoscopy, causes a significant increase in this response".[13] F. S. Xue, X. Liao et al demonstrated in 2007 that there were no significant differences in circulatory responses to nasal or oral intubation in 62 healthy children undergoing general anesthesia as part of their management plan. Blood pressure and heart rates had shot up in response to both oral and nasal intubations.[14] To our knowledge, attenuation of this pressor response has not been studied in Pakistani populace using gabapentin.

There are marked differences in approach towards establishing airway using conventional endotracheal tubes and nasotracheal tubes. Of various parameters, time to intubation varies markedly between placing endotracheal tubes and nasotracheal tubes as shown by Yeom JH and Oh MK et al. Incidence of epistaxis, sore throat and dental injury may also vary between these two different routes used for establishing airway. In some cases use of laryngoscope or other such equipment utilized to visualize the airway may be precluded in patients planned for maxillo-facial surgeries. Single and multiple doses have comparable haemodynamic effects. Arterial pressure and heart rate responses have been shown to be greater when the duration of laryngoscopy exceeds 30 seconds.[15]

Peipho, Tierbach and Werner published a case report of a patient whose failed nasotracheal intubation led them to formulate an algorithm for unanticipated difficult airway following uncontrolled epistaxis. Based on Cormac-Lehane grades (CL) of glottis views, they suggested that for CL-1 & 2, nasotracheal intubation should be attempted after excluding any obvious difficulties or pathologies.[16] This algorithm affords the anesthesiologist for managing unanticipated difficult airway with planned nasotracheal intubation, the choice of intubating trachea with alternatives like flexible fibreoptic bronchoscope and rapid sequence intubation. It helps to save precious time and avoid large variations in hemodynamic indices in addition to prevent unwanted complications like epistaxis and oropharyngeal trauma. We have adopted the algorithm suggested by Peipho et al for the smooth conduct of anesthesia, as it suits our resource-constrained setup.

Ahmad Nusrath, Tong JL and Smith JE used 3 different types of nasotracheal tubes, to assess the frequency of epistaxis in patients undergoing oral and maxillofacial surgeries.[17] Their findings showed that the reinforced nasotracheal tubes lead to lesser incidence of epistaxis, because they traversed a safer passage inferior to the inferior turbinate. However preformed nasotracheal tubes took less favourable routes between middle and inferior turbinates despite deliberate attempts to avoid middle conchae and area near cribriform plate, resulting in more incidence of unwanted nasal bleed. It may be stressed here that choice of adequate nasotracheal tubes types and the predetermined sizes of tubes for males and females help alleviate the factors that may lead to more attempts, prolonged intubation times and consequently prove safer for the patients in terms of minimal adverse hemodynamics.

Shipra Aggarwal and associates studied the effect of gabapentin in patients for variability in heart rate, systolic blood pressures, diastolic blood pressures, and mean arterial pressures.[18] They used 600mg and 900mg of gabapentin in 2 divided doses during the perioperative periods. Their results showed that using gabapentin was

not effective in blunting tachycardia in response to laryngoscopy and endotracheal intubation however clinically significant fall in mean arterial pressure was observed in the groups of patients taking 600mg and 900mg gabapentin ($p < 0.05$). Similar results were demonstrated by Fassoulaki et al using much higher doses of gabapentin. They used 1600 mg in four divided doses one day prior to surgery and results showed dampening of rise in blood pressure but not on tachycardia.[19]

Tahira Iftikhar et al studied the effect of gabapentin 800 mg given orally one hour before surgery on hemodynamic responses to laryngoscopy and tracheal intubation in the local population. In the study by Iftikhar they reported a significant difference for heart rate in Gabapentin and placebo group.[20] There is yet an undocumented but strong observation that population in our part of the world is very sensitive to the sedative effects of gabapentin. It is worthwhile noting that studies by Shirpa, Fassoulaki and Tahera exclude nasotracheal intubation in patients undergoing oral and maxillofacial surgeries and it appears that pre-operative gabapentin blunts the heamodynamic response to nasotracheal intubation as well as in endotracheal intubation.

Other authors have studied effects of gabapentin on pressor responses in the patients undergoing surgeries in combination with a number of other agents. Gabapentin in combination with dexamethasone has been shown to suppress the swings in both blood pressure and heart rate.[21] Gabapentin with esmolol and clonidine in separate researches have also been proven to be beneficial for the patients in terms of preventing both the tachycardia and clinically significant increases in mean arterial pressure.[22]

CONCLUSION

Premedication with oral 800mg gabapentin gives better and effective results in terms of mean hemodynamic response to nasotracheal intubation in normotensive patients undergoing elective surgeries.

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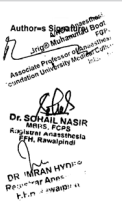
A fool says what he knows,
and a wise man knows what he says.

– Yiddish Proverb –

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Brig (Retd) Muhammad Boota	Supervision of Practical conduct and primary author.	
2	Sohail Nasir	Principal investigator, literature search & corresponding author.	
3	Imran Hyder	Statistical analysis & manuscript editing.	