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COMPARISON OF ORAL CLONIDINE VERSUS GABAPENTIN ON HEMODYNAMIC RESPONSES AFTER LARYNGOSCOPY AND INTUBATION

Anaesthesiology

KEYWORDS:

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ABSTRACT

BACKGROUND: Hemodynamic pressor response to direct laryngoscopy and intubation is a hazardous complication of general anesthesia which can be blunted by deepening the anesthesia, pre-treatment with vasodilators, adrenoceptors blockers,calcium channel blockers and opiods with variable results. So,the aim of study was to evaluate and compare both the oral drugs i.e clonidine & gabapentin and objective being to assess the haemodynamic responses of laryngoscopy and intubation. **METHOD:** 106 patients were included 53 in each group scheduled for elective surgery under general anaesthesia. Prospective , randomized and double blind study done after ethical committee & patient consent. Group A received oral clonidine 200mcg and Group B received oral gabapentin 900mg , 90 minutes prior to surgery with sips of water. Primary end point being heart rate ,secondary were sedation and BP changes. The data collected was analysed using statistical tests. **Conclusion:** Both clonidine and gabapentin showed significant sedation more so with clonidine. 2. HR response to laryngoscopy and intubation was fairly attenuated by clonidine however there was no attenuation with gabapentin. 3. SBP, DBP and MAP rise was completely obtunded by clonidine as compared to gabapentin. 4. Side effects were seen with both the drugs which didn't warrant any treatment.

INTRODUCTION

Laryngoscopy and endotracheal intubation are potent stimuli that can induce increased sympathetic activity leading to tachycardia, hypertension and dysrrhythmias.When laryngoscopy and intubation is carried out, there is mechanical irritation of stretch receptors situated in the respiratory tract leading to reflex hemodynamic responses through a sympathetic reflex causing a stimulatory adrenosympathetic response resulting in increased blood pressure, heart rate and plasma catecolamines.[1,2,9]These transient changes can result in potentially deleterious effects such as myocardial ischaemia, left ventricular failure and cerebral haemorrhage.[4,7]Various techniques and drugs have been tried to attenuate this circulatory response which include laryngoscopy and intubation in deeper plane of anaesthesia with inhalation agents like halothane[3], topical anaesthesia of upper respiratory tract prior to laryngoscopy with lidocaine in the form of spray[5], mouth wash[6], intratracheal and translaryngeal nerve blocks[4],Vasodilators, Calcium channel blockers[12], beta blockers[8,11],opioids ,modifications of instruments (use of different types of laryngoscope blades)[14] and the use of supraglottic intubating devices(e.g. laryngeal mask airway)[13] all have been tried to alter these haemodynamic responses. However no apparent consensus has been reached on which method is ideal to abolish or attenuate these reflex haemodynamic changes.

Raval DL et al (2002), studied oral clonidine premedication for attenuation of haemodynamic response to laryngoscopy and intubation on 100 patients of ASA grade I-II, age group 18 to 65 years to compare the effectiveness of oral clonidine 4 μgKg^{-1}

with oral diazepam 0.2$mgkg^{-1}$ and placebo(oral antacid) with sip of water 90 minutes prior to induction of anaesthesia. Clonidine produced marked sedation and better anxiolysis as compared to diazepam. Clonidine provided extra advantage over diazepam and placebo by blunting haemodynamic responses during laryngoscopy and endotracheal intubation and also by its antisialogogue effects. [15]

Memis D et al (2006), examined the effect of a single dose of gabapentin 400 or 800 mg given 1 hour before surgery, on reducing cardiovascular response on 90 patients undergoing various elective surgical procedures were divided into three groups (400mg in group I, 800mg in group II and placebo in group III).Patients receiving 800mg of gabapentin had significantly decreased mean arterial pressure and heart rate during the first 10 minutes after endotracheal intubation when compared with either 400mg or placebo[20].

From the review of above studies it seems that both clonidine and gabapentin are effective in attenuating the hemodynamic responses associated with laryngoscopy and endotracheal intubation, thus we had planned to evaluate and compare both the drugs in obtunding this response in normotensive patients undergoing elective surgery.

MATERIALS AND METHODS

Methods

After obtaining Institutional Ethics Committee approval and written informed consent from all the patients, one hundred six ASA I and II consequent patients, aged 18-60 years, scheduled for elective abdominal surgery under general anaesthesia requiring tracheal intubation, were included in this study. The other inclusion criteria covered patients without receiving any drugs that could influence hemodynamic and autonomic function, patients with no difficult airways or obesity (body weight > 100 kg),no allergy or contraindications to anaesthetics or any drug used. Exclusion criteria include patients with hypovolemia,electrocardiographic abnormalities,congestive heart failure,diabetes mellitus, hypertension, coronary artery, respiratory, renal, cerebral diseases and pregnancy. If there was profuse change in the technique of anesthesia, the patients were excluded from the study. The study was carried out in SMS HOSPITAL AND MEDICAL COLLEGE,JAIPUR.The patients were randomly allocated to one of two groups before the induction of anaesthesia: patients who received Oral clonidine 0.2mcg(group A,N= 53) and those patients who received Oral gabapentin 900mg (group B,N=53)90 minutes prior to surgery. The study were prepared in a double blind fashion by a collaborator not involved in data recording and an appropriate code number was assigned. The same collaborator administered drugs while a blind observer collected data. If there was any side effect (such as bradycardia, hypotension, nausea and vomiting, respiratory depression, dizziness, somnolence, peripheral oedema and headache) it was recorded. In the operating room, an 18 G intravenous cannula was inserted in an appropriate antecubital vein and ringer's solution was started, at 10 ml/kg per hour. Monitoring included an automated BP cuff, electrocardiography, and pulse oximetry. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR) and rate pressure product (RPP) at pre-induction time were measured as baseline values.Preoxygenation followed by anaesthesia was induced after premedication with rantac,metoclopramide, glycopyrrolate,midazolam and tramadol . Thiopental 5 mg/kg, Succinylcholine 1.5mg/kg and atracurium 0.5 mg/kg as maintenance was given. Patients' lungs were manually ventilated with 100% oxygen before orotracheal intubation was performed.Direct

laryngoscopy was performed 3 minutes by using a Macintosh laryngoscope and tracheal intubation was accomplished within 15 seconds.Lungs were then mechanically ventilated with a tidal volume of 10 ml/kg and a respiratory rate of 12/min to maintain end tidal PaCO2 at around 38 mmHg.Anesthesia was maintained with propofol 150 µg/kg with a fresh gas flow of 4 L/min (50% N2O in O2).In each patient, the BP (SAP, DAP, MAP), and HR were measured at three time-points: baseline (3 min before induction), just before laryngoscopy, and post intubation (at 1, 3, 5min after starting laryngoscopy) by an independent investigator unaware of the group assignment.The incidence of hypertension, hypotension, tachycardia, and bradycardia was recorded during the study period and compared among the two groups. Following termination of surgery, the remaining neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

Following parameters were recorded during the study period :
1) Sedation Score[40] was noted on four point scale as under :
0. point — wide awake
1. point — sleeping comfortably but responding to verbal commands
2. point — deep sleep but arousable
3. point — deep sleep but not arousable

Sedation score was noted as just before the drug i.e. baseline (B1) and after the drug on operation table (B2).

2) Hemodynamic parameters -

a. Blood pressure (mmHg) : Systolic (SBP) , Diastolic (DBP) and mean arterial pressure (MAP) were recorded using NIBP monitor
-Base line (before the drug)(B_1)
-Before induction(after the drug) (B_2)
-Just before intubation (T_0)
-One, three and five minutes after intubation (T_1, T_3 & T_5)

b. Heart rate (beats per minute) : was also noted at the above mentioned times

c. ECG : ECG lead II was continuously monitored and any dysrrhythmias during this period were noted

d. SpO_2 :was also monitored throughout the study period and any episode of desaturation (Spo2<90%) was noted

No other stimulus such as patient's positioning or incision was permitted during the study period. Side effects pertaining to clonidine and gabapentin were noted preoperatively before induction of anaesthesia and postoperatively when patient was fully awake.

At the end of the study decoding was done and data was compiled. Independent "t"-test paired and unpaired were applied for quantitative data; for non-quantitative data and association between groups with respect to various characteristics chi-square test was applied. . A 'p' value of <0.05 considered significant, <0.001 highly significant and >0.05 was taken insignificant. Following observations were made during the present study :

Discussion:

Demographic profile of patients

The demographic profile of patients in two groups is shown in the **TABLE-1:**

Parameters	Group A (n=53)	Group B (n = 53)	p value
Age in years (Mean + SD)	33.44+ 8.80	32.14 + 8.58	0.456 (p>0.05)
Weight in Kgs (Mean + SD)	55.82 + 8.82	54.86 + 8.24	0.575 (p>0.05)
Sex (male/female) (n)	19/34	18/35	0.84 (p>0.05)

n= No. of patients. SD = Standard Deviation

Patients in both groups were comparable with respect to mean age, weight and sex wise distribution, (p>0.05).

Duration of laryngoscopy and endotracheal intubation table 2:

Parameters	Group A (n=53)	Group B (n=53)	p value
Duration of Laryngoscopy & Endotracheal Intubation (Mean+SD)	11.18+1.063	11.38+1.210	0.3821 (p>0.05)

Patients in both groups were comparable with respect to duration of laryngoscopy and endotracheal intubation, (p>0.05).

Distribution of sedation score within the two groups table 3 and fig 1

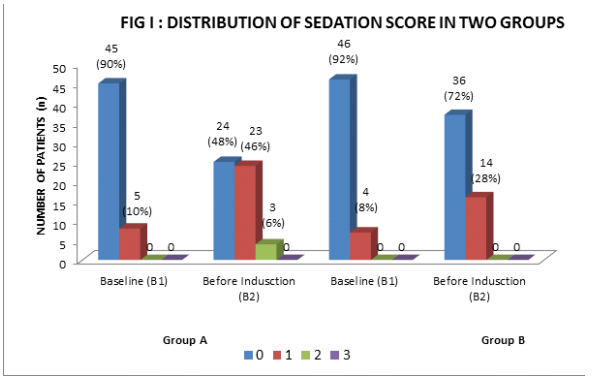


Table 3

Group	Sedation Score				p value
	0	1	2	3	
Group A (n=53)	25	24	4	0	0 (p<0.001)
Group B (n=53)	38	15	0	0	

After giving the drug there were significantly higher number of patients in clonidine group (A) with higher sedation score as compared to gabapentin group (B), (p<0.001).

Baseline haemodynamics parameters in two groups (beats/min) were compared in TABLE 4 and Fig 2(MEAN+SD) (RANGE)

TABLE 4

Haemodynamics	Group A (n=53)	Group B (n=53)	p value
HR (beats/min) Range	79.64+6.30 (64-94)	82.00+8.08 (68-98)	0.106 (p>0.05)
SBP (mmHg) Range	126.44+9.09 (106-146)	123.08+8.96 (104-150)	0.658 (p>0.05)
DBP (mmHg) Range	79.52+6.86 (68-94)	77.58+5.86 (68-90)	0.131 (p>0.05)
MAP (mmHg) Range	95.16+7.00 (83-111)	92.74+6.19 (80-107)	0.070 (p>0.05)

Postoperative side effects (percentage)

Side Effects	Dry Mouth	Hypotension	Bradycardia	Headache	Drowsiness	Dizziness
Group A (n=53)	34 (64.15%)	5 (9.43 %)	2 (3.77 %)	0	0	0
Group B (n=53)	0	0	0	2 (3.77%)	6 (11.3 %)	2 (3.77 %)

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Postoperatively in group A 34(64.15%) patients continued with complaint of dryness of mouth, while bradycardia was seen in 2 (3.77 %) patients and 5(9.43%) patients developed hypotension. While in group B no patient had dry mouth and bradycardia. In group B 2 (3.77 %) patients complaint of headache, while drowsiness was seen in 6 (11.3 %) patients and dizziness in 2 (3.77 %) patient

ECG / Spo_2

There were no changes in Spo_2 and ECG in either groups which warranted attention

Discussion:.

The sympathoadrenal activation associated with laryngoscopy and tracheal intubation causes the rise in arterial blood pressure, tachycardia and dysrrhythmias so, smooth induction with minimal reflex haemodynamic response during laryngoscopy and endotracheal intubation remains an important anaesthetic goal.

Several strategies have been evolved to blunt this undesirable haemodynamic response but each method has its own advantages and disadvantages. Deep anaesthesia has the disadvantage in that it acts by causing myocardial depression[2]. Topical anaesthesia in various forms has been used, but these simple methods are time consuming, circumstantial and relatively ineffective when used alone in preventing haemodynamic response associated with laryngoscopy and intubation.[5,10]

Clonidine and gabapentin are drugs under intense investigation as an adjunct to anaesthesia in various forms[15,20,21]. Clonidine originally introduced as antihypertensive drug, analgesic, sedative and anxiolytic properties.It improves the quality of induction,maintenance and recovery from anaesthesia.By its central sympatholytic action, it tends to attenuate the haemodynamic response to any surgical nociceptive stimulus and improve overall perianesthetic cardiovascular stability[19]. When used alone it was useful in attenuation of haemodynamic response to laryngoscopy and endotracheal intubation[15].

Similarly, gabapentin originally introduced as antiepileptic,effective in neuropathic pain and most recently has been evaluated as analgesic, anti-hyperalgesic, or both perioperatively[16].

We did a prospective, randomized, double blind study in 106 adult patients of either sex belonging to ASA grade I or II divided in two groups of 53 each. We evaluated and compared oral clonidine and gabapentin in attenuating the haemodynamic response to laryngoscopy and endotracheal intubation.

A. In our study both groups were comparable regarding age, weight and sex distribution.

B. Premedication with opioids like morphine and large induction dose of thiopentone sodium, propofol which can largely increase the depth of anaesthesia thereby it may indirectly influence this haemodynamic response to laryngoscopy and intubation[5,21]. In our study, no opiods was given and fixed dose of thiopentone 5 $mgkg^{-1}$ was used for induction in both the groups to avoid this bias.

C. Size of endotracheal tubes and time taken for larygoscopy and as an Intubation was comparable in both the groups,($p>0.05$). In our study the mean duration of laryngoscopy and intubation did not exceed 11.35 secs.

D. Preoperative anxiolysis and sedation are main objective of premedication and both involve a number of possible mechanisms of action implicating central gamma amino butyric acids[16].Clonidine is a α2 adrenergic agonist with antinociceptive and sedative properties due to decreased tonic activity of locus coeruleus which modulates the stimuli arriving in the central nervous system and adrenergic receptor[19]. Role of gabapentin in attenuation of haemodynamic response,sedation and antianxiolytic has been highlighted by Memis et al and Fassoulaki et al[20,21].In our study both clonidine and gabapentin showed sedation in a significant proportion of subjects ($p<0.001$) respectively. Results of our study regarding sedation were comparable to Faheim et al.[22]

E. In our study, basline haemodynamic parameters heart rate(HR), systolic blood pressure(SBP), diastolic blood pressure(DBP) and mean arterial pressure(MAP) were comparable in both the groups ($p>0.05$). Raval et a1[15] stated that clonidine(200 μgm) decreases HR before and after induction, but after intubation, HR increased marginally which persisted for a very short period. In our study also the effect of clonidine (200 micro gram) on HR was similar to the study done by Raval et al. Memis et a120 observed complete attenuation of HR with gabapentin 800mg given 1 hr before surgery. In our study we also didn't observe any attenuation of HR response even with 900 mg gabapentin.

In our study HR response to laryngoscopy and intubation was not completely obtunded by either drug. HR rise was however less marked and short lived in clonidine group. Our results are in contrast to the studies of Faheim et al22 and Marashi et al23 who observed complete attenuation of HR response with both the drugs because of high dosage of drugs used as premediction and time interval between drug given and induction was more than our study.

BLOOD PRESSURE

Baseline SBP, DBP and MAP were similar in both the groups. After giving the drug and following induction significant fall in SBP, DBP and MAP was seen in both the groups, but this fall was significantly more in clonidine group(group-A), ($p<0.001$). Following intubation also SBP, DBP and MAP remained below the baseline in both the groups except at 1 min (T1) when rise was seen in gabapentin group (group-B) which was significant,($p<0.001$).

Our results are similar to the study of Raval et a115 who also observed persistent fall with 200μgm clonidine. However with gabapentin our results are in contrast to the study of Memis et al20 who documented complete attenuation of MAP with 1600 mg gabapentin because of difference in drug dosage. On comparative evaluation of two groups also our results are slightly in contradiction to the studies of Faheim et al22 and Marashi et al23 who documented that both gabapentin and clonidine are equally effective in attenuating blood pressure response to laryngoscopy and intubation and further stated that infact gabapentin was more superior because of high dosage of gabapentin used than our study

We observed no dysrrhythmias or episodes of desaturation ($SPo2<90\%$) in any of the patient in either groups.

Side effects

Both clonidine and gabapentin have certain adverse effects inherent to their structure. Most common side effects with clonidine are dry mouth and sedation, seen in almost 50% of patients and less common are sexual dysfunction and marked bradycardia19. Similarly unsteadiness, clumsiness and uncontrollable back and froth eye movements or eye rolling are commonest side effects seen with gabapentin but depression ,irritability and mood changes can also be there16. It is also pertinent to mention here that these side effects are transient and usually abolish on their own21

In the present study clonidine was associated with high incidence of dryness of mouth (64.15 %), although hypotension (9.43 %) and bradycardia (3.77 %) was also seen. While in gabapentin group there was no incidence of unsteadiness, clumsiness or eye rolling however few cases of drowsiness (11.3 %), headache (3.77 %), dizziness (3.77 %) were seen. Clinically it didn't warrant any treatment.

Thus in our study, oral clonidine 200microgm, 90 mins before anaesthesia, provided good attenuation of haemodynamic response to laryngoscopy and intubation as compared to oral gabapentin (900 mg). Gabapentin also obtunded the hypertensive response but, not

the tachycardiac response.

RESULTS AND CONCLUSIONS

Following results were drawn from this study:

1. Demographic profile of the patients i.e. age, weight and sex distribution was comparable in both the groups

2. Size of endotracheal tube and intubation time were also comparable in two groups

3 Baseline sedation score were also similar in two groups. Both clonidine and gabapentin produced sedation,but it was significantly more with clonidine i.e. group A ($p<0.001$).

4. Baseline HR was comparable in both the groups. HR decreased after giving clonidine (group A) while it was maintained with gabapentin (group B). Following induction there was further decrease in HR in two groups. However, HR remained below baseline in group A except at 1 min following intubation whereas rise in HR persisted in group B even at 5 min.

6. Baseline SBP, DBP and MAP were similar in both the groups. After giving the drug and following induction significant fall in SBP, DBP and MAP was seen in both the groups, but this fall was significantly more in clonidine group. SBP, DBP and MAP remained below the baseline in both the groups even after intubation, except at l min when rise was seen in the gabapentin group.

7. Most patients in the clonidine group complained of dryness of mouth (64.15 %), although hypotension (9.43 %) and bradycardia (3.77 %) was also seen. In gabapentin group drowsiness (11.3%), headache (3.77 %), dizziness (3.77 %) was seen.

8. There was no episode of dysrrhythmias or desaturation in any of the patients in either group.

We conclude that:

1. Both clonidine and gabapentin showed sedation in a significant proportion of subjects, more so with clonidine.

2. HR response to laryngoscopy and intubation was fairly attenuated by clonidine except for transient increase immediately after intubation. However there was no attenuation with gabapentin.

3. SBP, DBP and MAP rise following intubation was completely obtunded by clonidine as compared to gabapentin.

4. Side effects were seen with both the drugs which didn't warrant any treatment.

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