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A RANDOMISED COMPARITIVE STUDY OF EFFECTS OF ORAL GABAPENTIN AND ORAL CLONIDINE ON PRE - OPERATIVE ANXIOLYSIS AND ATTENUATION OF STRESS RESPONSE TO ENDOTRACHEAL INTUBATION

Anaesthesiology

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ABSTRACT

BACKGROUND AND AIMS : A prospective,Randomized,comparative study was done to compare the effects of Clonidine (300µg) and Gabapentin (800mg) given orally as premedication in causing anxiolysis and attenuating the stress response to intubation in patients of ASA I/II category undergoing elective surgery.

MATERIALS AND METHODS : About 60 Adult patients (18-60 yrs) of physical status ASA I & II scheduled to undergo elective surgical procedures were divided into two groups of 30 each allotted randomly and labelled Group A and Group B.The Group A received 300µg clonidine and Group B received 800mg Gabapentin orally 90-120min before induction of Anaesthesia.The Heart rate, Systolic blood pressure,Diastolic blood pressure and Mean arterial pressure were recorded for baseline(before induction) and at 0,1,3,5,10 min of intubation.The VAS scores were noted before shifting to Operation theatre and before induction of anaesthesia.

RESULTS : The Groups were matched for Age,Sex,Weight and for time of induction of anaesthesia and intubation.VAS score before induction was better for clonidine group than for Gabapentin group.The attenuation of stress response to Endotracheal intubation was better with clonidine group than with gabapentin group ($P<0.05$).

CONCLUSION : Oral clonidine (300µg) provided better anxiolysis and attenuation of stress response to endotracheal intubation than oral Gabapentin (800mg) when used for premedication.

KEYWORDS

Clonidine,Gabapentin,Anxiety,Laryngoscopy,Stress response

INTRODUCTION

Most of the patients awaiting elective surgery experience pre-surgery anxiety.[1] Anxiety is an unpleasant emotion & may cause patients to avoid planned operation. Laryngoscopy & intubation are associated with cardiovascular changes such as hypertension, tachycardia, dysrhythmia, increased catecholamines & even ischaemia of myocardium[2].These responses are well tolerated in healthy patients, but may be dangerous in those with coronary artery insufficiency, vascular anomalies or intracranial disease.[3] Several techniques have been proposed to prevent or attenuate these hemodynamic responses such as deepening the plane of anaesthesia,[2] pretreatment with nitroglycerine,[4] β blockers,[5] calcium channel blockers,[6] opioids[7] etc.

The use of benzodiazepines in small doses for premedication is a well-established practice. As expected, the amnesic and anxiolytic properties of these drugs are also useful within the outpatient setting. Diazepam was previously the regularly used oral benzodiazepine but midazolam has become the drug of choice because of having a brief elimination half-life. Alprazolam has also been reported to be effective oral premedicants for outpatient surgery.

Gabapentin is a GABA analogue which was introduced as an anti-epileptic and later proved to be effective in neuropathic pain.[8] More recently, it has been studied to treat acute post operative pain. While conducting these studies, it was observed that it attenuates pre-operative anxiety & stress response to intubation. But there are only few randomized controlled trials to prove the equivalent. Mechanism of action of Gabapentin is poorly understood. Though it's a structural analogue of GABA, it doesn't act through GABA receptors.[10] It has been proposed that the auxiliary $\alpha_2\delta$ subunit of voltage-dependent calcium channels may be a molecular target for gabapentin, conceivably altering VGCC function. It is a drug well tolerated, with a favourable side effect profile. Side effects include dizziness(10.9%), somnolence(15.2%), nausea(3.2%), ataxia(2.6%), tremor, asthenia(6%),weight gain (2.6%),amblyopia(2.1%).

Clonidine is a selective central α2 agonist & is a potent antihypertensive drug.[9]Clonidine premedication is known to produce sedation & blunt the stress response to intubation. Premedication with α2 -adrenergic agonist drugs can reduce anaesthetic and analgesic dosage requirements and produce sedation and anxiolysis while also decreasing the heart rate and arterial pressure during anaesthesia. Oral clonidine, the prototypical α2 -agonist, has been successfully used for ambulatory premedication. Clonidine stimulates pre-synaptic alpha- 2 receptors & inhibits norepinephrine release from both central and peripheral adrenergic terminals .A dose of 300-µg clonidine orally or larger reduces sympathetic activity and blunts reflex tachycardia and hypertensive responses . The risk of undesirable side effects is extremely important in evaluating the overall safety of pre-anaesthetic medication. The potentially beneficial effect of α_2-agonists may be negated by bradycardia[11] and hypotension[12]. Adverse effects are relatively common & disturbing but it is devoid of respiratory depression. Adverse effects like Sedation, dizziness, headache, Anorexia, constipation, dryness of mouth,Bradycardia, orthostatic hypotension, pruritis, Withdrawal hypertension etc can be seen.

Hence present study was designed to study & compare the effects of oral Gabapentin (800mg)& oral Clonidine (300µg) on pre-operative anxiolysis & attenuation of stress response to intubation

MATERIALS AND METHODS

Hospital ethics committee clearance was obtained for this study. Patients taken into study were posted for general anaesthesia from Departments of General Surgery, Orthopaedics, Gynaecology and ENT. 60 Adult patients between 18-60 yrs ,of physical status ASA I & II and between weight of 45-65kg who had given written consent scheduled to undergo elective surgical procedures under General Anaesthesia from May 2011 to May 2012 were included.A prospective randomized comparative study was planned. Patients of ASA status III or greater,Age >60 yrs or <18 yrs,pregnant,lactating and menstruating females, with Drug/Alcohol abuse,with chronic pain,with psychiatric illness, anticipated difficult intubation, Hypertensive,patients concomitantly on Gabapentin or Clonidine or drugs with effect on nervous system except those determined by study protocol, Patients with h/o cardiac disease,Patients with severe renal or hepatic disease were excluded.

The pharmacist separated the tablets of Clonidine(300 micrograms) mentioned Group A & tablets of Gabapentin(800mg) mentioned Group B into 2 equal groups of 30 each and put them in thick opaque envelopes.

The patients were randomized by a computer generated table into 2 equal groups A & B so that Group “A” patient received all the tablets from one envelope labelled group “A”.Group “B” patient received all the tablets from one envelope labelled group “B'.

All patients were assessed the day before surgery. Visual analogue anxiety score (0= no anxiety, 100= worst imaginable anxiety) was explained to them.

The drug from the closed envelope was drawn and given to the patient by ward nurse with sips of water 90-120 min before induction. The identity of the tablet was not revealed to the patient. No other premedication was given other than the study drugs.

Upon arrival in the operating room, intravenous access was secured. 18 G catheter was inserted in a peripheral vein and a Ringer lactate solution was started. Monitoring of non invasive blood pressure (NIBP), heart rate, electrocardiogram and arterial oxygen saturation was carried out. A uniform anaesthetic technique was used in both the groups. After 3 min of preoxygenation, anaesthesia was induced with i.v thiopentone 5mg/kg; i.v scoline 1.5mg/kg to facilitate endotracheal intubation. Direct laryngoscopy & intubation was performed by an experienced anaesthetist (Consultant). The duration of laryngoscopy and intubation was limited to minimum possible time & was less than 15 seconds for all patients**.** Monitoring of vitals was done by another person. Systolic, diastolic arterial blood pressure (SBP and DBP) and HR were recorded before and after administration of the i.v. anaesthetic, immediately after intubation and cuff inflation and 1, 3, 5 and 10 min after. Our study ended at this point & surgery was commenced. Maintenance of anaesthesia was carried out using 67% N20 in 33% 02 and halothane 0.5% using controlled ventilation. Intra operative analgesia was provided with 2 µ/kg Fentanyl. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01mg/kg intravenously.

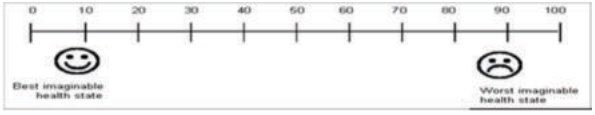

Fig 1: VAS

Base line VAS anxiety scores, heart rate & BP of the patient before giving the drug were measured and VAS anxiety scores, heart rate, systolic BP & diastolic BP just before taking the patient into OT, before induction on OT table, after administration of i.v scoline. during laryngoscopy and intubation(0 min) and at 1,3,5,10 min after intubation

Statistical Analysis

Results were represented as Mean±SD and percentage changes.A Paired t test was used for intragroup comparisons of changes from baseline to different study periods (for each group separately).Chi-square test was used for categorial data (Age, gender, weight, ASA grade).A p-value of 0.05 or less was considered for statistical significance

RESULTS :

Table 1: Comparison of Demographic data between two group

Parameters	Group A (n=30)	Group B(n=30)	p value
Gender(Male:Female)	14:16	13:17	0.60
Age(yrs) (Mean±SD)	34.73±13.77	31.53±10.26	0.31 (NS)
Weight(Kg) (Mean±SD)	55.57±5.3	55.6±5.32	0.98(NS)
ASA (1:2)	25:5	17:13	0.14(NS)

There was no significant difference between the groups with respect to Sex,Age,Weight of patient and ASA status as their p-value is >0.05 and hence insignificant(NS)

Table 2:Changes in mean VAS anxiety scores & Intragroup comparison of VAS anxiety scores :

	Gr. A n=30 Clonidine				Gr. B n=30 Gabapentin			
	Mean ± SD	Diff from BL	% diff	P value	Mean ± SD	Diff from BL	% diff	P value
Before giving drug (baseline)	74.3± 16.9	-	-	-	71.5± 13.9	-	-	-
Before shift to OT	31.66± 11.54	42.64	57%	**<0.00**	61.66 ±9.22	9.84	14%	**<0.00**
Before Induction	33.16± 11.4	41.14	55%	**<0.00**	60± 8.3	11.5	16%	**<0.00**

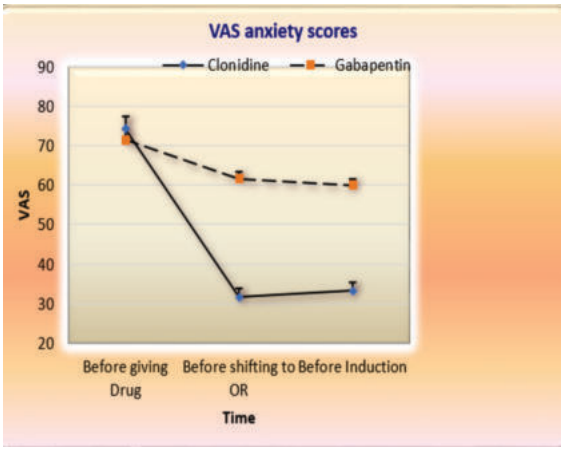

Figure 2: Changes in VAS anxiety scores in both groups

In table 3, we can see that the baseline VAS anxiety scores were 74.3±16.9 & 71.5±13.9 in group A & B respectively. The change in the values from baseline was significant in both the groups as p value is <0.01. There was 57% decrease in VAS score in clonidine group as compared to 14% in gabapentin groups.

Table 3 : Changes in mean heart rate in the groups (beats per min) & Intragroup comparison of changes in mean heart rate

	Gr. A n=30				Gr. B n=30			
	Mean ±SD	Diff from BL	% diff	P	Mean ±SD	Diff from BL	% diff	P Value
Baseline (BL)	83.83 ±12.2	-	-	-	78.5± 11.85			**<0.01**
Pre-induction	82.9± 15.2	0.93	1%↓	0.12	88.9± 15.1	10.4	13%↑	**<0.01**
Post scoline	87.23 ±13.4	3.4	4%↑	**0.2**	93.4± 14.15	14.9	19%↑	**<0.01**
0 min	97.3± 12.34	13.47	16%↑	**<0.01**	112.9± 12.46	34.4	44%↑	**<0.01**
1 min	93.26 ±10.8	9.43	11%↑	**<0.01**	104.4 ±14.6	20.57	26%↑	**<0.01**
3 min	89.1± 10.77	5.27	6%↑	**<0.01**	100.3 ±13.7	21.8	28%↑	**<0.01**
5 min	85.46 ±10.2	1.63	2%↑	**0.26**	94.43 ±15.4	15.93	20%↑	**<0.01**
10 min	83.33 ±8.3	0.5	0.5%↓	**0.57**	89.63 ±14.5	11.13	14%↑	**<0.01**

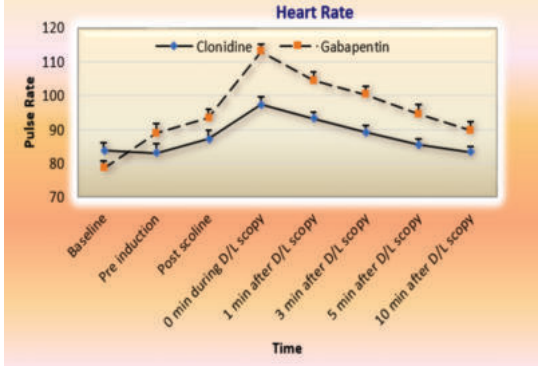

Figure 3: Changes in heart rate in both groups

In the clonidine group (Gr A) , the baseline mean heart rate was 83.83/min (table 3). During intubation their was transient rise of HR and was statistically significant (p<0.01). By 5 min the HR almost returned to baseline. The difference in HR at 5 min compared to baseline is not statistically significant .

In gabapentin group (Gr B), the baseline HR was 78.5/min(table 3). During intubation it was 112.9/min representing a rise of 44%. The

increase in HR from baseline was statistically significant (P<0.01).

Table 4 : Mean systolic BP in both groups & Intragroup comparison of changes in mean systolic BP

	Gr. A n=30				Gr. B n=30			
	Mean± SD	Diff from BL	% diff	P	Mean± SD	Diff from BL	% diff	P
Baseline (BL) (mm of Hg)	114.6± 12.8	_	_		114.2± 7.8	_	_	
Pre-in Duction (mm of Hg)	107.76 ±16.28	6.84	6%↓	<0.01	123.3± 11.23	9.1	8%↑	<0.01
Post scoline (mm of Hg)	108.93 ±16.7	5.67	5%↓	<0.01	125.4± 14.9	11.2	10%↑	<0.01
0 min (mm of Hg)	136.4± 19.58	21.8	19%↑	<0.01	159.3± 20.68	45.1	40%↑	<0.01
1 min (mm of Hg)	132.2± 20.5	17.6	15%↑	<0.01	152.1± 21.05	37.9	33%↑	<0.01
3 min (mm of Hg)	123.56 ±21.7	8.96	8 % ↑	0.07	136.5± 21.03	22.3	20%↑	<0.01
5 min (mm of Hg)	111.86. ±19.01	2.74	3%↓	0.31	125.6± 16.6	11.4	10%↑	<0.01
10min (mm of Hg)	107.7± 16.12	6.9	6%↓	<0.01	118.76 ±13.11	4.56	4%↑	<0.05

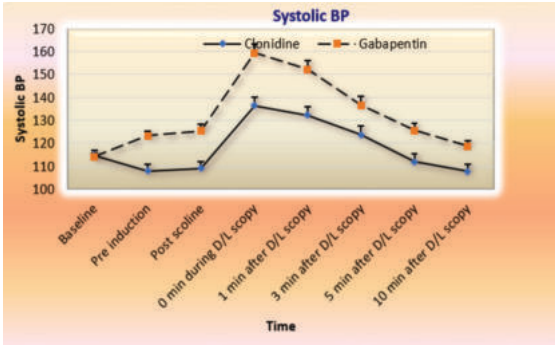

Figure 4: Changes in systolic BP in both groups

In clonidine group , the baseline mean SBP was 114.6 mmHg(table 4). The increase in SBP during intubation compared to baseline value was statistically significant (p<0.01). Subsequently the elevated SBP started settling down.

In gabapentin group, the baseline SBP was 114.2mmHg (table 4). During intubation there was statistically significant (p<0.01) increase in SBP from baseline.

Table 5: Mean diastolic BP in the groups & Intragroup comparison of changes in mean DBP

	Gr. A n=30				Gr. B n=30			
	Mean± SD	Diff from BL	% diff	P	Mean± SD	Diff from BL	% diff	P
Baseline (BL) (mm of Hg)	74.53± 7.7	_	_		75.3± 7.9	_	_	
Pre-induction (mm of Hg)	72.7±7 .7	1.83	3% ↓	<0.05	79.4± 8.7	4.1	5% ↑	<0.01
Post scoline (mm of Hg)	77.67± 8.8	3.14	4% ↑	**0.86**	88.8± 11.77	13.5	18% ↑	<0.01
0 min (mm of Hg)	92.6±1 3.1	18.07	24% ↑	<0.01	109.2± 14.7	33.9	45% ↑	<0.01
1 min (mm of Hg)	87.5±1 2.67	12.9 7	17% ↑	<0.01	101.9± 12.9	26.6	35% ↑	<0.01
3 min (mm of Hg)	81.7±1 3.3	7.17	10% ↑	**0.15**	92.43± 13.1	17.13	23% ↑	<0.01
5 min (mm of Hg)	77.06± 12.5	2.53	4% ↑	**0.91**	83.03± 11.4	7.73	10% ↑	<0.01
10 min (mm of Hg)	73.56± 9.9	0.97	1% ↓	**0.08**	80.4± 10	5.1	7% ↑	<0.01

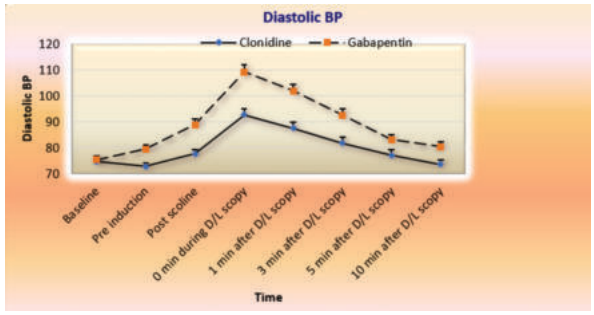

Figure 5: Changes in Diastolic BP in both groups

In clonidine group, the baseline DBP was 74.53mmHg (table 5). The increase in DBP during intubation compared to baseline value was statistically significant (p<0.01). Subsequently the elevated DBP started settling down. By 10 min DBP was 73.56mmHg which is less than the baseline value.

In Gabapentin group, the baseline SBP was 75.3mmHg (table 5). During intubation There was statistically significant (p<0.01) increase in SBP from baseline .

Table 6: Mean MAP in the groups & Intragroup comparison of changes in mean MAP

	Gr. A n=30				Gr. B n=30			
	Mean	Diff from BL	% diff	P	Mean	Diff from BL	% diff	P
Baseline (BL) (mm of Hg)	87.9	_	_		88.16			
Pre-induction (mm of Hg)	84.26	3.64	4% ↓	<0.05	94	5.84	7% ↑	<0.01
Post scoline (mm of Hg)	88.17	0.27 ↑	3%	<0.01	100.9	12.7 4	15% ↑	<0.01
0 min (mm of Hg)	107.2	19.3	22% ↑	<0.01	125.9	37.7 4	43% ↑	<0.01
1min (mm of Hg)	102.36	14.46	17% ↑	<0.01	118.6	30.4 4	35% ↑	<0.01
3 min (mm of Hg)	95.56	7.6	9% ↑	<0.08	107.0 7	18.9 1	22% ↑	<0.01
5 min (mm of Hg)	88.67	0.77	0.8% ↑	**0.73**	97.23	9.07	10% ↑	<0.01
10 min (mm of Hg)	84.97	2.93	3% ↓	<0.05	93.2	5.04	6% ↑	<0.01

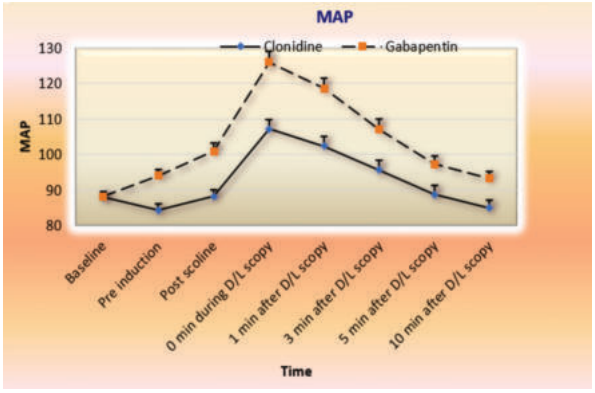

Figure 6: Changes in Mean arterial pressure (MAP) in both groups

In clonidine group the baseline MAP was 87.9mmHg (table 6).The increase in MAP during intubation compared to baseline value was statistically significant (p<0.01). Subsequently the elevated MAP started settling down. By 10 min mean MAP was 84.97mmHg which is less than the baseline value .

In gabapentin group the baseline MAP was 88.16mmHg (table 6). During intubation there was statistically significant (P<0.01) increase in MAP from baseline.

DISCUSSION

Anxiety before surgery is an important problem because it produces undesirable effects on anaesthesia & peri-operative outcome. It changes not only the doses of drugs which are needed for induction, maintenance of anaesthesia, recovery from anaesthesia, but also it affects psychological condition of patients.[13] Stress and anxiety stimulate hypothalamous-hypophysis-adrenal axis and increase glucocorticoid level. Stress releases hormones such as cortisol, cathecolamines and cytokinin. These hormones increase negative nitrogen balance and catabolism and ultimately delay wound repair and weaken immune system postoperatively.[13]

Vikas Saini et al[14] and Ahmed B A et al[15] have used oral clonidine for premedication in the dose of 5µg/kg & 150µg respectively 90-120min before intubation. They observed good anxiolysis with the said doses of oral clonidine. We used 300µg oral clonidine and found effective pre-operative anxiolysis. Several researchers have used different scales for measuring pre-operative anxiety i.e., STAI, VAS, 5 point scale .VAS scale was used by us because it is easy to assess and reliable.

Clonidine decreases peripheral norepinephrine release by stimulation of prejunctional inhibitory α_2 adrenoceptors and by inhibition of neural transmission in different brainstem areas. Hypnotic-sedative, analgesic and anxiolytic actions of clonidine may be modulated via the α_{2A} adrenoceptor subtype.[14]

Christophe M et al.[16] showed that premedication with 1200mg gabapentin 1-2 hours before surgery improved preoperative anxiolysis & postoperative recovery.

Our study doesn't confirm these findings i,e gabapentin 800mg does not produce effective pre-operative anxiolysis. Hance Clarke et al have also found that gabapentin 600mg administered 2 hours before surgery does not reduce pre-operative anxiety.[17]

Laryngoscopy & intubation can cause striking changes in hemodynamics probably as a result of intense sympathetic nervous system responses to stimulation.

Gabapentin & Clonidine have been employed orally in various doses for blunting the cardiovascular response to laryngoscopy and intubation. Oral Gabapentin is used in the range of 300mg-1600mg in both single[21] & multiple doses. Oral Clonidine is used in the range of 100µg-300µg.[22] We used '800mg' Gabapentin & '300µg' clonidine because this was the dose used by many authors who have studied these drugs.

Peak action of both the drugs was known to be 1-2 hours after oral administration[9]. So we gave the study drugs 90-120 min before induction of anaesthesia.

In the present study, the groups were comparable with respect to their demographic variables and their baseline values of HR, SBP and DBP. There was a significant increase in SBP, DBP and heart rate compared to baseline in both the groups during laryngoscopy & intubation. But there was less rise in clonidine group when compared to gabapentin group. Attenuation of rise in the heart rate by clonidine is evident and statistically significant when compared with gabapentin**.**Among the two drugs studied, only clonidine attenuated the rise in SBP following laryngoscopy. Gabapentin was not successful in attenuation of SBP.

Among the two study drugs, clonidine showed attenuation of DBP during laryngoscopy & intubation. Gabapentin was not successful in attenuating DBP.

Attenuation of mean arterial pressure is significant in clonidine group as compared to gabapentin group.

The efficiency of clonidine in attenuation of cardiovascular responses similar to our study has been verified by many other studies.

Batra YK, Indu B, Puri GD18 have studied the attenuation of pulse rate and blood pressure response to laryngoscopy and tracheal intubation by clonidine in forty healthy patients. Heart rate and blood pressure were significantly lower in the clonidine treated group immediately after intubation. Our study fully confirms the findings of the above authors i.e, clonidine 300µg decreases the stress response (HR, SBP & DBP) to laryngoscopy & intubation.

Indira Kumari & Vikrant Singh Pathania[19] have studied the changes in systolic, diastolic & mean blood pressure and heart rate following laryngoscopy & intubation after administering gabapentin 900mg 2 hours before induction. Significant rise in SBP, DBP & MAP was observed following laryngoscopy and tracheal intubation in placebo group as compared to gabapentin group. No significant change in heart rate was documented in both the groups.

Kiran[20] has studied the effects of gabapentin (800mg) in attenuation of haemodynamic responses to direct laryngoscopy and tracheal intubation in hundred patients undergoing elective surgery. SBP, DBP & MAP was significantly lower in the gabapentin as compared to the control group but tachycardiac response was not completely eliminated. Our study partly confirms the findings of above authors. Even we found no significant attenuation of HR & BP with laryngoscopy & intubation with single dose of gabapentin 800mg.

Kong V K F & Irwin M G[8] reviewed many controlled trials and found that the effects of gabapentin were dose-dependent and the changes in heart rate were inconsistent and concluded that further studies are needed to confirm the effects of gabapentin in attenuating stress response to laryngoscopy & intubation.

CONCLUSION

From the present study it can be concluded that Oral gabapentin (800mg), given 90-120min before induction is not effective in neither attenuating preoperative anxiety nor in attenuating stress response to laryngoscopy and intubation.Oral clonidine (300µg), given 90-120min before induction is effective in attenuating preoperative anxiety and in attenuating both HR & BP rise associated with laryngoscopy and intubation.

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