Comparative Evaluation Of Gabapentin, Clonidine And Combination Of Both The Drugs To Attenuate The Pressor Response To Direct Laryngoscopy And Intubation.

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Citation

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Abstract

Background: The aim of our study was to compare the relative effectiveness of gabapentin and clonidine in attenuation of pressor response to direct laryngoscopy and intubation, and to evaluate the synergistic effect of combination of both drugs.Materials and methods: 120 patients of either sex of age between 20-60 years of American Society of Anaesthesiologist (ASA) grade I and II admitted 24 hours before elective surgery requiring general anaesthesia (GA) were included in the study. Patients were randomly allocated into four groups of 30 patients each: patients received oral 800 mg of gabapentin (group A), 300 µg of clonidine (group B), 400 mg of gabapentin and 150µg of clonidine (group C) and placebo (group D); 60 minutes (min.) prior to induction of anaesthesia. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were measured before induction, intubation and at 0,1,3,5 and 10 minutes after intubation.Results: Analysis revealed that there was significant rise in HR at 0 minute in all the groups ($p<0.05$) except in group B. It remained to significant levels in group C and D up to 10 minutes ($p<0.001$ and $p<0.01$) but in group A it returned to insignificant level at 3 minutes. There was statistically highly significant rise in SBP, DBP and MAP ($p<0.001$,$p<0.001$ and $p<0.01$) in all the groups except in group A. In group A statistically significant ($p<0.001$) fall in SBP, DBP and MAP continued up to 10 minutes.Conclusion: Given 60 minutes before induction of GA, oral gabapentin and clonidine in the dose of 800mg and 300µg attenuate the pressor response but gabapentin blunts the increase in arterial blood pressure better than clonidine. The combination of these two drugs in the studied dosage was not effective in attenuating the pressor response to laryngoscopy and intubation.

INTRODUCTION

Laryngoscopy and intubation performed as a part of GA is a noxious stimulus and is capable of producing marked circulatory effects known as presssor response characterized by tachycardia, hypertension and altered rhythm[1],[2]. Various drugs and techniques have been proposed to prevent or attenuate this response such as deepening of anaesthesia[3],omitting cholinergic premedication[4], use of vasodilators such as nitroglycerine[5],beta blockers[6],calcium channel blockers[7] and opioids[8] but no single technique has achieved universal acceptance.

Gabapentin, a structural analogue of -animobutyric acid, is used as an anticonvulsant drug. The inhibition of Ca2+ flux in muscle cells with a consequent inhibition of smooth muscle contraction might explain the effectiveness of gabapentin in attenuation of the pressor response to laryngoscopy. Thus it act in a manner similar to Ca2+ channel blocker[9].

Clonidine is a $_2$-adrenoceptor agonist with sedative and analgesic effects, also has beneficial effect of blunting hyperdynamic responses due to laryngoscopy and tracheal intubation as it decreases the release of stress hormones [10]. Present study was undertaken to study the effects of clonidine 300µg, gabapentin 800mg and their combination in half doses on attenuation of pressor response to laryngoscopy and intubation.

MATERIALS AND METHODS

After obtaining informed consent and approval from the hospital ethics committee, the randomized controlled trial was conducted on 120 patients of either sex of age between 20-60 years of ASA Grade I and II admitted at least 24 hours before for elective surgery requiring GA. After taking a detailed history, thorough general physical and systemic

examination, all pertinent investigations were carried out to exclude any systemic disease. Exclusion criteria for this study were-Anticipated difficult intubation, consumption of antihypertensive drugs, sedatives, hypnotics and antidepressant drugs except those included in the study.

Patients were prepared with 6 hours preoperative fasting. Omeprazole 40mg was given night before surgery to all the patients.

Patients were randomly allocated to one of the following four groups of 30 each according to the drug given as pretreatment 60 min. prior to induction of anaesthesia:-

Group A - received 800mg of gabapentin orally.

Group B - received 300 µg of clonidine orally.

Group C - received 400mg of gabapentin and 150µg of clonidine orally.

Group D - Patients in this group were not given any pretreatment and served as the control group for the study.

ANAESTHESIA TECHNIQUE

In the operating room an i.v. cannula of 18G was inserted in a peripheral vein and a crystalloid infusion started. Inj. metoclopramide 10mg was given to all the patients 10 min. before induction of anaesthesia. Continuous ECG, peripheral oxygen saturation and non-invasive blood pressure monitors were attached to the patient.

After 3 min. of preoxygenation, anaesthesia was induced with propofol 2.5mg/kg and rocuronium 0.9mg/kg to facilitate tracheal intubation. The patients were ventilated for 3 min. with face mask with 100% O_2 before laryngoscopy was attempted. All intubations were performed by experienced anaesthesiologist. The duration of laryngoscopy and intubation was limited to 30 seconds in all the patients. All the patients were maintained with 33%oxygen, 66% nitrous oxide, 0.5-1% isoflurane/halothane and rocuronium 0.15mg/kg as intermittent boluses. Intra operative analgesia was provided with inj. tramadol 1 mg/kg. At the end of the surgery neuromuscular blockade was reversed with inj. neostigmine 0.05mg/kg and inj. glycopyrolate 0.008mg/kg before extubation.

Following parameters were recorded before and after administration of i.v. anaesthetic; immediately after intubation and cuff inflation (0 min.); and at 1, 3, 5, and 10 min.: SBP, DBP, MAP and HR.

The data obtained was analyzed and presented as mean and standard deviations. The baseline characteristics were evaluated to ascertain comparability among the groups. To detect 20% difference in hemodynamic parameters across 4 groups considering the as 95% (0.05) and power of the study being 80%, approximately 25 patients shall be needed in each group to demonstrate the mentioned difference. The statistical significant difference among the groups was assessed by the use of repeated measures ANOVA. Appropriate posthoc tests were used to evaluate statistical significant difference among different groups. A p value of <0.05 was considered as statistically significant.

RESULTS

Figure 1

Table 1 Comparison of age and weight in the four groups

Group	Age(in years)	Weight(in kg)
Group A	36.63± 11.17	54.62 ±5.15
Group B	39.03 ±10.82	58.13 ±5.43
Group C	38.70 ±6.48	57.13 ±5.02
Group D	36.03 ±7.23	55.93± 4.95
	p-value-0.774	p-value-0.445

On comparing the four groups using ANOVA, the difference among the groups was statistically insignificant (p-value<0.05).

Figure 2

TABLE 2: Heart rate changes in the groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C		Group D	
	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value
Before induction	84.23±6.34		85.47±8.63		85.20±8.38		87.03±9.89	
Before intubation	77.63±7.43	0.001	78.03±8.23	0.002	78.40±9.19	0.005	79.53±8.57	0.002
After laryngoscopy and intubation								
0 min.	90.27±7.15	0.002	88.80±6.33	0.099	103.80±9.70	0.000	104.87±11.17	0.000
1min.	88.10±6.94	0.032	87.60±5.97	0.275	100.77±9.45	0.000	102.27±10.27	0.000
3min.	85.40±6.68	0.490	79.17±5.71	0.275	94.60±7.87	0.000	96.60±10.17	0.001
5 min.	81.13±6.23	0.066	72.83±4.47	0.002	89.30±7.53	0.045	92.90±9.70	0.027
10 min.	78.53±4.23	0.000	72.83±6.31	0.000	84.97±6.47	0.906	84.20±8.96	0.254

The mean difference is significant at p-value < 0.05 and highly significant at p-value < 0.001.

Figure 3

TABLE 3: Systolic blood pressure changes in the four groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C		Group D	
	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value
Before induction	127.17±8.15		129.27±8.08		127.80±10.66		128.43±11.10	
Before intubation	115.20±9.35	0.000	116.43±8.11	0.000	118.50±11.82	0.000	118.50±10.91	0.000
After laryngoscopy and intubation								
0 min.	125.01±7.95	0.307	144.67±9.70	0.000	156.03±12.86	0.000	160.26±11.42	0.000
1min.	115.67±6.32	0.000	139.90±8.46	0.000	151.20±12.08	0.000	155.67±11.90	0.000
3min.	110.53±6.49	0.000	133.03±6.90	0.061	144.47±10.75	0.000	148.40±11.06	0.000
5 min.	107.30±6.35	0.000	132.33±5.06	0.081	139.90±11.58	0.000	139.00±12.44	0.000
10 min.	104.90±5.58	0.000	128.43±6.01	0.651	135.10±9.99	0.004	136.93±10.64	0.001

The mean difference is significant at p-value < 0.05 and highly significant at p-value < 0.001.

Figure 4

TABLE 4 : Diastolic blood pressure changes in the four groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C		Group D	
	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value
Before induction	84.00±6.11		82.67±7.05		82.33±7.07		80.47±8.56	
Before intubation	74.77±7.00	0.000	74.23±6.19	0.000	76.40±7.09	0.004	74.30±7.17	0.005
After laryngoscopy and intubation								
0 min.	85.73±6.67	0.303	92.07±7.80	0.000	102.97±8.73	0.000	103.70±9.51	0.000
1min.	76.00±4.81	0.000	89.00±8.37	0.004	100.73±8.92	0.000	101.23±9.57	0.000
3min.	74.00±4.22	0.000	83.83±6.94	0.525	96.30±8.74	0.000	96.97±7.64	0.000
5 min.	70.37±4.43	0.000	82.70±8.09	0.988	86.50±9.00	0.055	88.33±8.40	0.001
10 min.	67.00±4.69	0.000	79.10±6.98	0.058	82.07±9.00	0.902	82.87±8.55	0.286

The mean difference is significant at p-value < 0.05 and highly significant at p-value < 0.001.

Figure 5

TABLE 5: Mean arterial pressure in the four groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C		Group D	
	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value	Mean±S.D	p-value
Before induction	97.87±5.33		98.30±6.53		96.77±8.03		97.34±9.43	
Before intubation	88.60±7.09	0.000	88.47±5.45	0.000	90.04±7.56	0.002	89.20±7.97	0.01
After laryngoscopy and intubation								
0 min.	96.67±6.68	0.448	109.19±7.22	0.000	120.87±9.87	0.000	122.73±9.29	0.000
1min.	88.77±4.72	0.000	105.60±6.38	0.000	117.93±8.87	0.000	118.83±9.09	0.000
3min.	86.17±4.24	0.000	100.03±5.19	0.265	112.93±7.84	0.000	114.17±7.16	0.000
5 min.	82.53±4.23	0.000	98.83±6.17	0.749	104.27±8.17	0.001	106.13±9.02	0.001
10 min.	79.53±4.50	0.000	94.90±5.43	0.036	96.93±8.54	0.941	98.37±8.54	0.661

The mean difference is significant at p-value < 0.05 and highly significant at p-value < 0.001.

Figure 6

TABLE 6: Intergroup comparison of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure.

Variables	Time (min)	A vs B (p-value)	A vs C (p-value)	A vs D (p-value)	B vs C (p-value)	B vs D (p-value)	C vs D (p-value)
Heart rate	0	1.00	0.000	0.000	0.000	0.000	1.00
	1	1.00	0.000	0.000	0.000	0.000	1.00
	3	0.015	0.000	0.000	0.000	0.000	1.000
	5	0.010	0.012	0.019	0.000	0.000	1.000
	10	0.026	0.001	0.001	0.000	0.000	1.000
Systolic blood pressure	0	0.000	0.000	0.000	0.000	0.000	0.757
	1	0.000	0.000	0.000	0.000	0.000	0.516
	3	0.000	0.000	0.000	0.000	0.000	0.570
	5	0.000	0.000	0.000	0.140	0.536	0.989
	10	0.000	0.000	0.000	0.015	0.013	0.339
Diastolic blood pressure	0	0.032	0.000	0.000	0.006	0.003	1.000
	1	0.000	0.000	0.000	0.000	0.000	1.00
	3	0.000	0.000	0.000	0.000	0.000	1.000
	5	0.000	0.000	0.000	0.032	0.005	1.000
	10	0.000	0.000	0.000	0.330	0.261	1.00
Mean blood pressure	0	0.000	0.000	0.000	0.000	0.000	1.000
	1	0.000	0.000	0.000	0.000	0.000	1.00
	3	0.000	0.000	0.000	0.000	0.000	1.000
	5	0.000	0.000	0.000	0.029	0.001	1.000
	10	0.000	0.000	0.000	0.367	0.071	1.000

The mean difference is significant at p-value < 0.05 and highly significant at p-value < 0.001.

RESULT SUMMARY

Table 1 shows distribution of mean age and weight in each group with no significant differences between the four groups(respectively; p-value<0.05).

HR: There was statistically significant rise in heart rate after laryngoscopy and intubation at 0 min in all the groups (p<0.05) except in group B. Heart rate decreased to insignificant levels in group A (p-value>0.05) at 3 min., whereas it remained significant in group C and D upto 10 min.

SBP: It was observed that after laryngoscopy and intubation SBP shot up significantly (p-value<0.001) in all the groups except in group A. In group A there was a fall in SBP at 1min. after laryngoscopy and intubation which continued upto the 10 th min.

DBP: It was observed that after laryngoscopy and intubation diastolic blood pressure shot up significantly (p-value<0.001) in all the groups except in group A. In group A there was a fall in diastolic blood pressure at 1min. after laryngoscopy and intubation which continued upto the 10 th min.

MAP: There was statistically highly significant (p-value>0.01) rise in mean arterial pressure in all the groups except in group A. In group A statistically significant fall in mean arterial pressure was observed 1 min. after laryngoscopy and intubation (p-value<0.001) which continued upto 10min. after laryngoscopy and intubation.

DISCUSSION

All the four groups were comparable in weight and age(table 1).There was no statistically significant difference in HR, SBP,DBP and MAP amongst the four groups before intubation(table2,3,4,5). The statistically significant fall in HR and arterial blood pressure was noted in all the four groups which can be attributed to the use of propofol as induction agent (table2,3,4,5).

In group A, HR, SBP, DBP and MAP were significantly lower in comparision to group D at various time intervals of our study (table 6). Our observations are in accordance with the findings of Kiran and Verma[11]. Memis et al reported complete attenuation of reflex increase in heart rate and MAP after laryngoscopy and intubation with 800mg of gabapentin when given 1 hour before surgery[12]. However, another study reported that gabapentin attenuate increase in blood pressure but not the tachycardia response to laryngoscopy and intubation[13].

In group B, HR was significantly lower in comparison to group D as various time intervals. Though there was an increase in SBP, DBP and MAP, but it was of smaller magnitude and for lesser duration in group B when compared with group D (table 6).Our findings are in accordance with those of Batra et al[14], Orko et al[15] and Pouttu[16]. Wright et al observed attenuation of HR in response to intubation in clonidine pretreated group but the magnitude of increase in arterial pressure was not altered[17]. In contrast to these findings, Nishikawa et al reported an insignificant rise in SBP and MAP in response to tracheal intubation but the tachycardia response was not attenuated[18].

In group C the significant increase in HR, SBP, DBP and MAP observed just after intubation which persisted for 5min were comparable with those in group D.

While doing intergroup comparison, we found that there was no statistically significant difference between group A and B with regard to HR at 0 and 1 min. after laryngoscopy and intubation (p-value>0.05) (Table 6). But the mean HR was lesser in group B as compared to group A at 3, 5 and 10 min. after intubation which was statistically significant (p-value<0.05) (Table 6).The statistically significant higher arterial blood pressure was noted in group B as compared to group A at various time intervals of the study (p-value>0.001) (Table 6).The results of our study are in accordance with the findings of Marashi et al[19]. The reflex increase in HR and arterial blood pressure in group C was statistically significant as compared to groups A and B. Koc et al examined the role of gabapentin 800mg and dexamethasone 8mg and their combination in varicocele surgery[20]. They showed that combination of both the drugs provides significant decrease in MAP and heart rate values in first 10min. after induction of anaesthesia than the single drug gabapentin or dexamethasone. We did not find any advantage of using combination of gabapentin and clonidine in the half doses over the individual drugs. This may be because we have used their half doses. No cardiac rhythm disturbances were noted in any of the groups

Thus, we conclude that pretreatment with both gabapentin 800mg and clonidine 300µg is effective in attenuation of pressor response to laryngoscopy and intubation. However, the rise in blood pressure is better attenuated by gabapentin.

Though clonidine abolishes increase in heart rate after intubation more effectively but the difference was not statistically significant when compared to gabapentin upto 1min. The combination of these two drugs in the studied dosage was not effective in controlling the HR and blood pressure in response to direct laryngoscopy and intubation.

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