A COMPARATIVE STUDY OF TWO DIFFERENT DOSES OF INTRAVENOUS CLONIDINE FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND INTUBATION

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ABSTRACT

Background: Laryngoscopy and intubation are almost always associated with an increased sympathetic activity. To attenuate the pressor response, various drugs have been tried. This study aimed at finding out the different doses of clonidine in attenuating the hemodynamic response to laryngoscopy and intubation in patients posted for any elective surgery under general anaesthesia.

Material and methods: This was a prospective, comparative, observational study, which involved two groups of patients. Each group had 30 patients, Group A (n=30) received injection Clonidine 1µg/kg diluted to 10 ml of normal saline and group B (n=30) received injection Clonidine 2µg/kg diluted to 10 ml normal saline intravenously. Patients were observed for 10 minutes. Baseline data of heart rate, mean arterial blood pressure, rate pressure product, respiratory rate, and sedation score were noted. All the parameters were recorded at different intervals up to 10 minutes after intubation. Results were compiled and statistically analysed.

Result: In group B, following laryngoscopy and intubation, there is more decrease in HR, MAP, RPP at 2 minutes and 3 minutes after intubation from baseline values compared to group A, which was statistically significant ($p<0.01$). So, there is more attenuation of

hemodynamic response in group B as compare to group A.
Conclusion: Clonidine 2 µg/kg was found to be marginally superior to Clonidine 1 µg/kg for attenuation of sympathetic response without any adverse effects.
Keywords: Laryngoscopy, intubation, clonidine, hemodynamic response

INTRODUCTION:

Endotracheal intubation is indeed one of the most remarkable contributions of anaesthesiologist to patient care. Laryngoscopy is a basic and essential step during tracheal intubation under general anaesthesia but both laryngoscopy and intubation are associated with haemodynamic changes which are transient and variable.[1]

The hemodynamic response to laryngoscopy and intubation is regulated by the hypothalamo-pituitary-adrenocortical and sympathetic adreno-medullary response.[2] As a result of which there is secretion of cortisol, nor epinephrine and epinephrine. The consequence of this neuro-endocrine system may vary from milder problems such as tachycardia, hypertension and occasional dysrhythmias to life threatening problems such as angina, myocardial infarction, stroke.

The circulatory responses have been reported immediately following laryngoscopy and intubation with a mean increase in systolic arterial pressure of 40 mm hg even in normotensive individuals.[3] It starts with 5 seconds, reaches peak in 1-2 minutes and returns to baseline within 5 minutes.[4] Various anaesthesia techniques and drugs are used to blunt this hemodynamic response to laryngoscopy and endotracheal intubation. The technique or drugs of choice depends on the urgency and duration of surgery, choice of anaesthesia technique, medical condition of the patient, individual preference and availability of equipment.[5] Several drugs have been used to attenuate haemodynamic changes such as lignocaine (intravenous and topical)[6], calcium channel blockers like nicardipine, verapamil, nifedipine, beta blockers like esmolol, labetalol, metoprolol, atenolol, opiates like morphine, fentanyl[7], alfentanil, sufentanil, nalbuphine, nitroglycerine[8], gabapentin but administration of each drug is associated with related side effects. Alpha-2 adrenoceptor agonists[9,10] have been used as premedication because of their beneficial properties in anaesthesia.

Clonidine which is mainly used as an antihypertensive agent also possesses beneficial effects on haemodynamics during stressful conditions like laryngoscopy and endotracheal intubation. Clonidine reduces anaesthetic requirements, attenuates adrenergic, hormonal and haemodynamic stress responses to surgery, reduces anxiety and also causes

sedation[11].

So, we decided to compare the different doses of intravenous clonidine in attenuating the hemodynamic response to laryngoscopy and intubation in patients posted for elective surgery under general anaesthesia.

METHODS:

A comparative, observational and prospective study was conducted in 60 patients of either sex, aged between 18 to 50 years, of ASA grade I and II, scheduled for elective surgery under general anaesthesia. Exclusion criteria were patients with a history of asthma/reactive airway disease, anticipated difficult airway, baseline heart rate <60bpm, history of cardiac disease and hypertension, patients on treatment with beta blockers or calcium channel blockers drugs, PR interval >0.24 seconds on ECG, 2nd and 3rd degree heart block, history of drug addiction/chronic narcotic use, known allergy to clonidine and pregnant and lactating females. Patients were divided into two groups.

Group A: Patients receiving inj. Clonidine 1µg/kg diluted to 10ml with normal saline iv slowly. **Group B:** Patients receiving inj. Clonidine 2µg/kg diluted to 10ml with normal saline iv slowly.

All the patients were scheduled for routine pre anaesthetic check-up with necessary routine investigations. Physical examinations of all systems were carried out. Airway assessment was done using Mallampati classification. The nature of study and procedure was explained to the patients. Written and informed consent was obtained from all the patients. All the patients were kept nil by mouth at least for 6 hours before the surgery.

On arrival to operating room, all patients were monitored with electrocardiography, pulse oximetry and non-invasive blood pressure. After establishing intravenous access, an infusion of Ringer lactate was started. All the patients were premedicated with inj. Glycopyrrolate (0.004mg/kg) iv and inj. Ondansetron (0.08mg/kg) iv as premedication. The respective study drug was injected as mentioned above. Patients were observed for 10 minutes. Baseline data of heart rate, mean arterial blood pressure, rate pressure product, respiratory rate, arterial oxygen saturation and sedation score were noted. Rate Pressure Product is a product of Heart rate and Systolic Blood pressure, it is a cardiac index used to determine myocardial workload.

The degree of sedation was graded according to Campbell Sedation Score:

o Sedation score 1- Wide awake

o Sedation score 2- Awake and comfortable

- Sedation score 3- Drowsy and difficult to arouse

- Sedation score 4- Not arousable

Any other complaints like nausea, vomiting, headache, restlessness, pruritus, bradycardia (pulse rate <60 per minute), hypotension (decrease in SBP/MAP by >20% of baseline), ischemic changes and allergic reaction were noted. Bradycardia in any patient during the study period was treated with inj. Atropine 0.6 mg iv. Hypotension in any patient during the study period was corrected first with intravenous fluids and then inj. Mephentermine 6 mg iv was given to patients unresponsive to iv fluids.

All patients were preoxygenated with 100% oxygen. Patients were then induced with inj. Propofol 2-3mg/kg iv. After confirming the ability to mask ventilate, inj. Succinylcholine 2 mg/kg iv was given to facilitate laryngoscopy and intubation. Patients were intubated with appropriate size endotracheal tubes and were maintained with O_2 (50%), N_2O (50%) and Sevoflurane. Intraoperative relaxation was maintained with inj. Atracurium 0.5mg/kg iv loading dose and 0.1mg/kg iv as maintenance dose on return of respiration. All intubations were accomplished within 15 seconds of laryngoscopy in a single attempt. Any untoward events during induction were recorded. Vitals to be monitored were HR, MAP and RPP. Any surgical interventions like catheterization, nasogastric tube insertion and incision were allowed 10 mins after intubation to avoid disturbance in data recording. All the parameters were recorded at following stages up to 10 mins after intubation. Baseline values, 10 mins after studying drug, immediately after intubation (0 min), At 1 min, 2 mins, 3 mins, 5 mins, 7 mins, 10 mins after intubation. Inj. Fentanyl 1-2µg/kg iv given after 10 mins of intubation for intraoperative analgesia. Reversal of neuromuscular blockade was carried out with inj. Glycopyrrolate 0.008mg/kg iv and inj. Neostigmine (0.05mg/kg) iv. Patients were extubated once adequate, spontaneous, and regular breathing was established, as well as the return of adequate muscle tone, power and all protective reflexes, hemodynamic stability and were able to respond to verbal commands. Patients were shifted to post-anaesthesia care unit.

Statistical analysis was done using the statistical package for social sciences (SPSS) version 21.0. The data obtained was statistically analysed and expressed as mean ± standard deviation (SD) and percentage and was compared using unpaired student “t” test. P value <0.05 was considered significant (S). P value >0.05 was considered non-significant (NS). P value <0.001 was considered highly significant (HS).

RESULTS:

In this study all patients (of both groups) were between 18yrs to 50yrs of age with mean age of 37yrs in Clonidine 1µg/kg group and 38yrs in Clonidine 2µg/kg group. As per table-1, sex ratio of Group A is 15 males and 15 females and Group B is 14 males and 16 females.

TABLE-1: DEMOGRAPHIC DATA

PARAMETRS	GROUP - A	GROUP - B
No. of patients	30	30
Age (in years)	37.63 ± 8.511	38.24± 7.94
Male:Female Ratio	15:15	14:16
Weight (in kgs.)	57.73 ± 5.22	59.20 ± 5.39

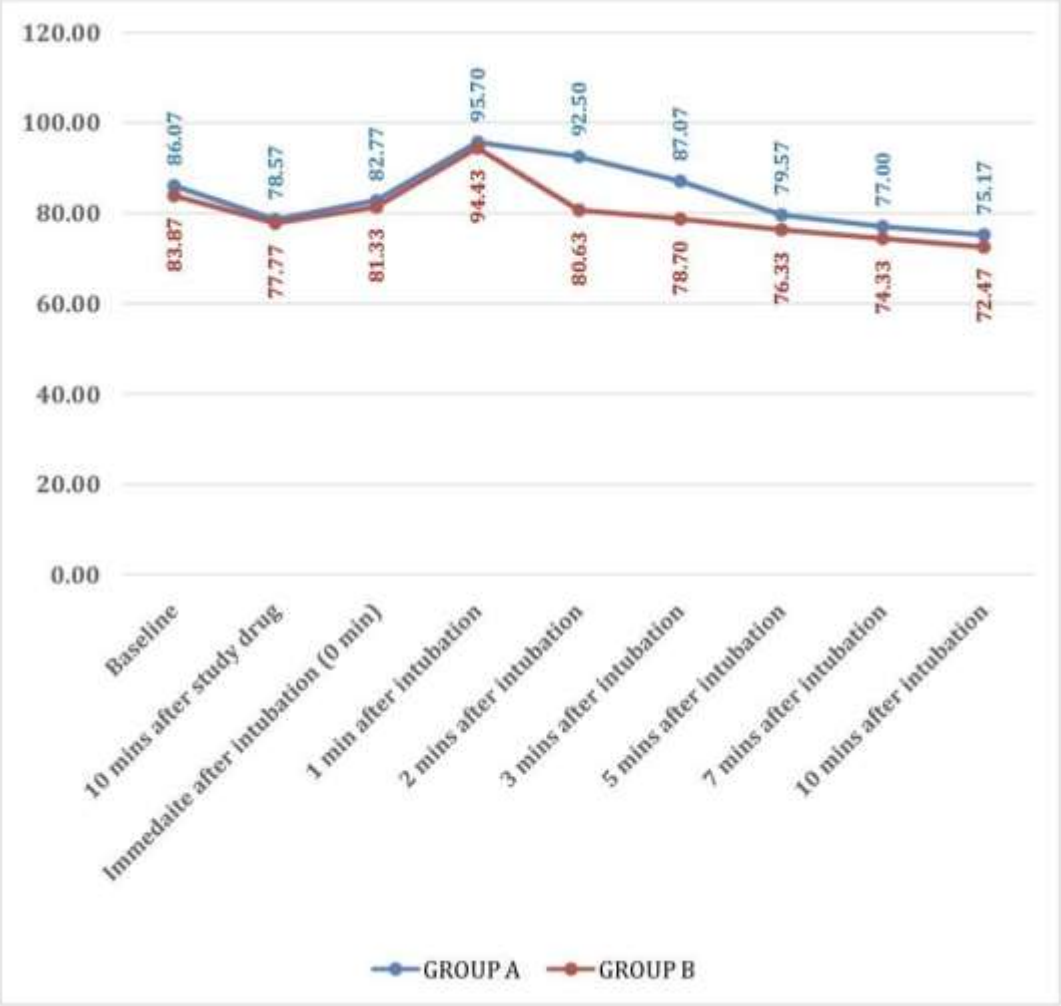
As per table-2, In the present study the mean sedation score 10 mins after study drug in group A is 1.17 ± 0.38 as compared to 1.23 ± 0.43 in group B which is non-significant ($p>0.05$). There was no statistically significant difference between the two groups with respect to RR (14.23 ± 1.01 per minute in group A vs 14.30 ± 0.92 per minute in group B) and SpO2 at 10 mins after study drug($p>0.05$).

TABLE-2: RESPIRATORY RATE, SEDATION SCORE and SpO2 (Mean ± SD)

PARAMETERS	GROUP A		GROUP B			p-VALUE INFERENCE
	MEAN	SD	MEAN	SD		
RR (/min) Baseline	14.40	1.00	14.43	0.97	>0.05	NS
RR (/min) 10 mins after study drug	14.23	1.01	14.30	0.92	>0.05	NS
Sedation Score	1.17	0.38	1.23	0.43	>0.05	NS
SpO2 (%) 10 mins after study drug	99.23	0.86	99.33	0.61	>0.05	NS

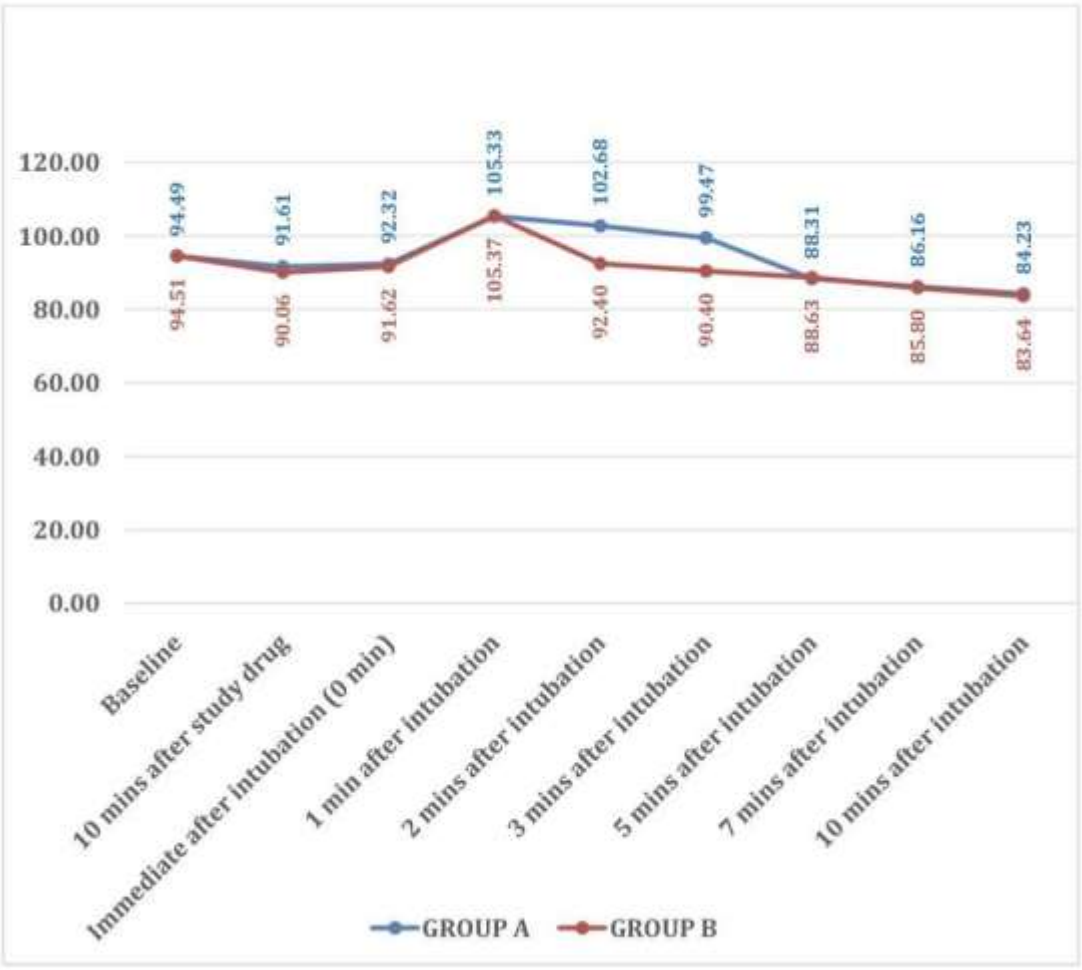
As per figure-1 baseline heart rate was comparable in both groups and no significant difference was seen (p value>0.05). 1 min after laryngoscopy and intubation, there was maximum increase in heart rate in both groups (11.19% and 12.60% from baseline in group A and group B respectively) which was statistically non-significant (p value>0.05). At 2 and 3 mins after intubation there is an increase in HR of 7.47% and 1.16% respectively in group A from baseline while there is 3.86% and 6.16% fall in HR respectively in group B from baseline and it becomes statistically highly significant(p<0.001).

Figure -1: Mean Heart Rate (beats/min)



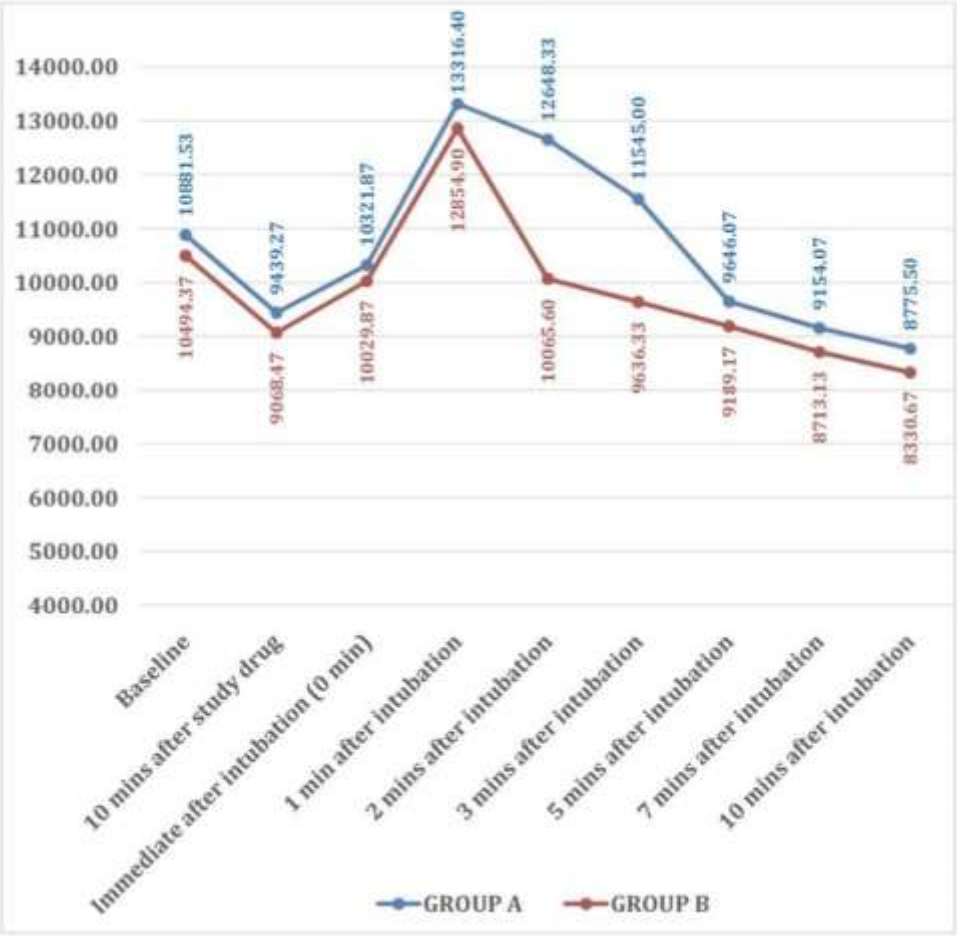
As per figure-2, baseline MAP was comparable in both groups and no significant difference was seen (p value>0.05). 1 min after laryngoscopy and intubation, there was maximum increase in MAP in both groups, which was statistically non-significant (p value>0.05). At 2 and 3 mins after intubation there is increase in MAP in group A from baseline while there is no significant increase in MAP with group B, instead there is fall at 2 and 3 mins after intubation as compared to baseline and it becomes statistically highly significant (p<0.001). At 5, 7 and 10 min, the decrease in MAP did not show statistical significance (p-value>0.05).

Figure-2 Mean Arterial Pressure (mm hg)



As per figure-3, In our study baseline RPP was comparable in both groups and no significant difference was seen (p value>0.05). 1 min after laryngoscopy and intubation, there was maximum increase in RPP in both groups, which was statistically non-significant (p value>0.05). At 2 and 3 mins after intubation there is increase in RPP in group A from baseline while there is no significant increase in RPP with group B, instead there is fall at 2 and 3 mins after intubation respectively as compared to baseline and it becomes statistically highly significant($p<0.001$). At 5, 7 and 10 min, the decrease in RPP did not show statistical significance($p>0.05$).

FIGURE-3: RATE PRESSURE PRODUCT (Mean ± SD)



DISCUSSION:

Laryngoscopy is a basic and essential step during tracheal intubation under general anaesthesia but both laryngoscopy and intubation are associated with haemodynamic changes. These hemodynamic responses were first recognized in 1940 by **Reid and Brace**[12] and in 1950, **Burstein et al.**[13], studied ECG changes and suggested pressor responses are due to increase in sympathetic and sympathoadrenal activity when sensitive receptor areas of epiglottis are mechanically stimulated by instrumentation. Measurements of the plasma catecholamine have demonstrated an increase in noradrenaline following laryngoscopy.

Clonidine, α2 adrenergic receptor agonist, has been studied as a premedication in a dose of 1-3 μg/ kg due to its beneficial effect on the hyperdynamic response to endotracheal intubation[14]. The haemodynamic effects of clonidine are both peripheral and central. Centrally, it stimulates α2 adrenergic inhibitory neurons in the medullary vasomotor center[15]. As a result, there is a decrease in sympathetic nervous system outflow from central nervous system to peripheral tissues. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and decrease in systemic blood pressure, HR and cardiac output[16]. Clonidine doses up to 4-5 μg/kg have been investigated frequently,

primarily for their anaesthetic-sparing effects in the intraoperative period and for their opioid sparing effects in the postoperative period[17].

Sakshi Arora et al.[15]in their study observed that in the control group fentanyl 2µg/kg was unable to attenuate the hemodynamic response to laryngoscopy and intubation as the increase in HR was 11.62% from baseline. Clonidine 1µg/kg and 2µg/kg significantly attenuated the hemodynamic response to laryngoscopy and intubation. In group B (Clonidine 1µg/kg) at intubation HR decreased 2.81% below baseline; and in group C (Clonidine 2µg/kg) HR decreased 8.1% below baseline.

Carabine et al.[18] demonstrated that clonidine at doses of 0.625 and 1.25 µg/kg administered IV 15 minutes prior to induction of anaesthesia attenuated the increase in pulse rate after laryngoscopy and endotracheal intubation. On the contrary, **Wright et al.**[19] noted, under almost identical conditions, that clonidine 1.25 µg/kg IV was not effective in preventing this response.

Sandeep Sharma et al.[20] observed that in control group A with 20ml normal saline was unable to attenuate the hemodynamic response to laryngoscopy and intubation. In Group B (Clonidine 1µg/kg) and C(Clonidine 2µg/kg), the mean HR showed progressively lesser increase 36.67% and 10.02% respectively as compared to Group A (58%) but the increase was statistically highly significant in all three groups. The mean heart rate returned to baseline values at 5 and 2 minutes in group B and C respectively but it remained high even till 10 min in the control group. While in Group D (Clonidine 3µg/kg), the mean HR showed a significant fall with 9.40% than baseline throughout the intraoperative period.

Kulka PJ et al.[21] had noted that clonidine 2 µg/kg decreased the rise in pulse rate after laryngoscopy and endotracheal intubation but this was not statistically significant. However, they noted that clonidine at doses of 4 µg/kg and 6 µg/kg equally attenuated the tachycardia seen after laryngoscopy and endotracheal intubation.

Sedation is a well-known side effect of clonidine. Caution must be exercised before administering this higher dose of clonidine to elderly patients. In our study, in both the groups patients were calm and comfortable throughout the study period and required no airway management before induction due to lower doses (Clonidine 1µg/kg and 2µg/kg) indicating well maintained airway and oxygenation. In a study conducted by **Ghignone M et al**.[22], they observed that patients were better sedated in the clonidine group as compared to the diazepam group. Similarly **Rudra Segal et al.**[23]found the sedative effect of clonidine better than in the placebo group.
Intraoperatively, none of the patients in group A and B had episodes of bradycardia. **Ambrose C et al.** [24]didn't find bradycardia with clonidine infusion (0.1-2 µg/kg) in critically ill children. However, their study was conducted on the pediatric population. No evidence of rebound hypertension after clonidine withdrawal was seen in this study. **Wing L.M.H.**[25] had noted similar findings and concluded that no evidence of an increased sympathetic nervous system activity was seen after a single dose of clonidine. Rebound phenomenon after the sudden withdrawal of clonidine is seen only after treatment for 6-30 days.

CONCLUSION:

From observations of our study, while comparing two different doses of IV clonidine (1 µg/kg and 2 µg/kg) given 10 mins prior to intubation for attenuating the sympathetic response to laryngoscopy and intubation, we found that Clonidine 2 µg/kg as premedication provides early and better attenuation of hemodynamic responses to laryngoscopy and intubation without causing clinically significant sedation, respiratory depression, bradycardia or hypotension.

In conclusion, Clonidine 2 µg/kg was found to be marginally superior to Clonidine 1 µg/kg for attenuation of sympathetic response without any adverse effects.

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