Original Article

Indian Journal of Anaesthesia and Analgesia
2017, 4 (3, Part-II), 753-759
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.4317.33

Use of Oral Clonidine for Attenuation of Pressor Response of Laryngoscopy and Intubation Associated with IV Ketamine Induction

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Abstract

Background: Premedication is used to provide sedation and anxiolysis and to enhance the quality of induction, maintenance and recovery from anaesthesia. The present study was carried out to study the pressor responses to laryngoscopy and intubation during induction with ketamine and scoline, using prior diazepam and clonidine as premedication. *Method:* A total of 60 normotensive patients of ASA grade I of both genders, aged 20 to 50 years, were randomized for this prospective study and divided into two groups of 30 patients each. Group I patients received Tab. Diazepam 0.2 mg/kg body weight and Group II patients received Tab. Clonidine 3 microgram/kg body weight. Both groups were assessed for changes in pulse rate, blood pressure and sedation. Scoring was taken every 15 minutes after giving this medication till induction. *Result:* The pulse rate rise, systolic blood pressure and diastolic blood pressure were more in control group as compared to clonidine group. There was statistically significant difference between mean pulse rate change, systolic blood pressure and diastolic blood pressure of both the groups during 1st min of intubation. And also there was significant difference between the two groups for sedation score ($p<0.001$) and pain score ($p<0.001$). *Conclusion:* Oral clonidine premedication 3 microgram/kg body weight given 90 minutes prior to induction of anaesthesia with ketamine is an effective and safe method for controlling the rise in pulse rate and rise in blood pressure associated with laryngoscopy and intubation. It also gives adequate analgesia in the immediate postoperative period without undue sedation.

Keywords: Clonidine; Ketamine; Laryngoscopy; Hemodynamic Response.

Introduction

Premedication is used to provide sedation and anxiolysis and to enhance the quality of induction, maintenance and recovery from anaesthesia. The ideal premedicant should be effective orally, should have analgesic and antiemetic properties. It should minimize side effects of the inducing agent and should not impair cardiovascular stability or depress respiration.

The cardiovascular instability could be produced either due to anaesthetic agent [1,2] or as a result of reflexes such as intubation. The former can be achieved by reducing the requirement of anaesthetic agents [3] for the same desired depth of anaesthesia and the latter can be achieved by suppression of sympathetic outflow induced by airway interference.

Clonidine is one such drug, which possesses all the above mentioned desired effects. Moreover it is superior to intravenous lidocaine plus fentanyl for blunting rise in pulse rate following intubation. It also decreases heart rate and blood pressure in hypertensive patients [4].

Postoperative hypertension and tachycardia which results from sympathetic stimulation associated with emergence from anaesthesia is also ameliorated by clonidine [4].

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Received on 03.05.2017, **Accepted on** 16.05.2017

Lack of effect on bronchomotor tone and analgesic property makes it unique for use in hypertensive patients with advanced bronchospastic disease where narcotics are not desired. Sharing the antianginal effect of beta-blocker is desirable in cardiac patients.

In susceptible patients like patients with known hypertension, preeclampsia, thyrotoxicosis or history of angina pectoris the responses following endotracheal intubation may cause serious arrhythmias, myocardial ischaemia, left ventricular failure [5] and cerebral haemorrhaage [6]. The frequency and degree of these responses is less in case of normotensive patients. The hypertension and tachycardia are transient and may be less harmful in normal subjects. But if the patient has coronary artery disease, an intracranial aneurysm or increased intracranial tension the pressor response may prove fatal. Normal healthy patients are not totally free from these risks. This can be achieved by blocking the pressor response to laryngoscopy and intubation. In principal this may be modified either locally, centrally or peripherally, using different methods.

Regional and topical anaesthesia have been used to block afferent impulse. I.V. lidocaine, I.V. short acting narcotics like fentanyl and deeper planes of inhalational anaesthesia have been used to modify the response at central nervous system level. Trimethaphan and phentolamine have been used for their peripheral effects.

Calcium channel blockers attenuate pressure responses but have no protective effects on heart rate. Beta-blockers on the other hand reduce only pulse rate without attenuating blood pressure [7].

The results of oral clonidine premedication on haemodynamic modifications all through the complete route of ketamine anaesthesia and concluded that oral clonidine 2.5 microgram/kg and 5 microgram/kg attenuate cardiostimulatory effects related to ketamine induction [8].

The dexmedetomidine premedication correctly attenuated the ketamine brought on haemodynamic pressor response and postanaesthetic delirium outcomes [9].

We thought of using clonidine 3 microgram/kg, orally 90 min before induction with ketamine and scoline as it has quite a few ideal properties of a premedicating agent.

Objectives

The present study was carried out to study of pressor responses to laryngoscopy and intubation during induction with ketamine and scoline, using prior diazepam premedication

Materials and Methods

The study was carried out in the department of Anaesthesiology, subjects included ASA grade I patients healthy, normotensive (resting blood pressure less than 140/90 mmHg) males and females between the age group 20-50 years with average weight (weight range 45- 60 kgs) were taken.

In all subjects preoperative examination was done a day prior to surgery. Information regarding medications was given to all the patients and all patients had given consent to the performance of the investigation. Institutional ethical committee clearance was obtained prior to start the study. Obese patients, patients with hypertension E.C.G. abnormalities, patients with other systemic illness as well as edentulous cases and those with gross anatomical changes predicting difficult intubation were not included in this study.

A total of 60 patients were studied in two groups of 30 each. Group I was control group and Group II was clonidine group. Clonidine group patients were given Tab. Clonidine 3 microgram/kg (approximately 0.15mg) body weight 90 minutes before induction and the control group patients were given Tab. Diazepam 0.2 mg/kg body weight (approximately 10 mg) 90 minutes before induction in the preoperative room and were observed for the immediate possible side effects. Pulse rate, blood pressure and sedation scoring was taken every 15 minutes after giving these medication till induction.

Patient was taken on operation table. I.V. line secured with Ringer lactate solution. A multipara monitor with ECG, pulseoximeter, NIBP and ETCo2 is applied to the patient. Preoperative readings of pulse rate and blood pressure were taken.

Preoxygenation with 100% O_2 for 5 minutes was done, then induction done with Inj. ketamine 2 mg/kg body weight over 30 seconds. Inj. Scoline 2 mg/kg body weight was given over next 5 seconds. Pulse rate and blood pressure readings were noted.

Light IPPV with O_2 mask was given till laryngoscopy. Gentle laryngoscopy was done at 1 minute after scoline and intubation was done in 15-20 seconds. The procedure was done by one person in all the cases. Pulse rate and blood pressure reading were taken during 1st minute of intubation, 3rd minute, 5th minute and at 10th minute after intubation. Pulse

rate and blood pressor readings were taken recorded During this period patient was ventilated with O_2 +N_2O (-30:70) and sevoflurane 2% at a rate of 12/ minute on Datex Ohmeda anaesthesia machine ventilator. After 10 minutes Inj. Fortwine 0.5 mg/kg body weight was given to the patients of both groups.

Anaesthesia was maintained on O_2 +N_2O + Sevoflurane+ Pancuronium 0.02 mg/kg body weight and ventilated on Datex Ohmeda anaesthesia machine ventilator with tidal volume of 10 ml/kg with rate of 12/minute. Postoperatively, immediately after reversal and extubation sedation score and analgesia score was noted. Sedation scoring was done on five point sedation scale (Segal IS et al, 1991) [10] and pain score [11].

All the patients were observed for the dryness (appearance of was tongue was noted) of mouth and other side effects (bradycardia and vomiting)

Result

From the table-1, it is observed that both the groups are comparable for age wise distribution and the age difference is not significant. It is also observed that both the groups are comparable for duration of surgery and the difference is not significant.

The pulse rate rise was more in control/diazepam group as compared to study/ clonidine group. During 1st minute of intubation the pulse rate in group I was 109.46 beats/min as compared to 79.93 beats/min in group II which is statistically significant ($p<0.05$) (Table 2).

From Table 3, it was observed that, the rise in mean systolic blood pressure was more in control group as compared to clonidine group. In clonidine group, 30 min after medication with clonidine the systolic blood pressure decreased which was statistically significant when compared with basal mean systolic pressure.

The maximum rise in systolic pressure in both the groups was during 1st min of intubation when both the groups were compared, the mean systolic blood pressure is statistically not significant at all time points. The decrease in systolic blood pressure, 30 min after medication was significant when both the groups were compared.

The mean systolic pressure in control group did not decrease up to basal value even at 10 the min of intubation suggests that the decrease in systolic pressure after intubation was earlier in study group as compared to control group.

From the Table 4, it was observed that, the difference in mean diastolic pressure is not significant at all the time points when both the groups were compared.

The diastolic pressure in the control group increased to a higher level as compared to the study group. There was maximum rise of diastolic pressure in both the groups was during 1st min of intubation. When both the groups were compared the diastolic pressure came earlier to the basal value in the study group as compared with the control group.

Table 1: Age distribution and duration of surgery

	Control	Clonidine
Age (Yrs)	32.40 ± 8.81	36.23 ± 10.82
Duration of Surgery (Hrs)	2.20 ± 0.51	2.08 ± 00.47

Table 2: Mean pulse rate changes ± SD at various time points in two groups

	Control	Clonidine
Basal	82.86 ± 7.44	82.20 ± 7.88
15 min after medication	82.86 ± 7.44	82.20 ±7.88
30 min after medication	82.60 ± 7.20	77.66 ±7.59
45 min after medication	*82.00 ±7.04	*77.66 ±7.59
60 min after medication	*82.00 ±7.04	*74.73 ±7.39
75 min after medication	*81.26 ±6.71	*72.26 ±6.76
At 90th min/preinduction	*81.60 ±6.50	*70.13 ±5.91
Pre-intubation (35 sec after induction)	*86.90 ±6.69	*75.06 ±5.39
1st min of intubation	*109.46 ±8.50	*79.93 ±5.78
3rd min after intubation	*102.80 ±6.99	*75.06 ±5.51
5th min after intubation	*96.26 ±4.97	*74.33 ±5.54
10th min after intubation	*89.66 ±5.85	*72.80 ±5.32

Unpaired "t" test as a test of significance is used. t <2.003 is significant i.e. P<0.05

Table 3: Mean systolic blood pressure changes ±SD at various time points in two groups

	Control group (Group I)	Clonidine group (Group II)
Basal	122.73 ±8.44	122.13 ±7.16
15 Min after medication	122.73 ±8.44	122.13 ±7.16
30 Min after medication	122.46± 8.18	116.06± 7.21
45 Min after medication	122.46 ±8.20	* 117.00 ±6.90
60 Min after medication	122.46 ±8.20	*113.60 ±6.39
75 Min after medication	122.40 ±8.00	*111.46 ±6.80
At 90th min/preinduction	122.00 ±8.22	*102.40 ±6.61
Pre-intubation (35 sec after induction)	*136.53 ±7.92	*113.53 ±5.93
1st min after intubation	*152.20 ±9.83	*120.93 ±5.99
3rd min after intubation	*139.53± 8.67	*118.13 ±5.56
5th min after intubation	*133.20 ±8.11	*114.80 ±5.34
10th min after intubation	*126.65 ±7.37	*113.26 ±5.97

Unpaired "t" test as a test of significance is used. t > 2.003 is significant i.e. P < 0.05

Table 4: Mean diastolic blood pressure changes ±SD at various time points in two groups

	Control group (Group I)	Clonidine group (Group II)
Basal	80.66 ±6.30	81.46 ±6.21
15 Min after medication	80.53 ±6.28	81.46 ±6.49
30 Min after medication	79.73 ±5.81	80.40 ±6.20
45 Min after medication	18.33 ±5.69	*77.93 ±4.56
60 Min after medication	77.73 ±5.18	*75.60 ±4.07
75 Min after medication	77.53 ±5.18	*73.60 ±4.54
At 90th min/preinduction	78.13 ±5.22	*72.80 ±4.16
Pre-intubation (35 sec after induction)	*86.06 ±6.27	74.66 ±4.16
1st min after intubation	*96.93 ±6.96	*82.66 ±4.59
3rd min after intubation	*93.26 ±5.84	*77.46 ±4.95
5th min after intubation	*89.36 ±4.98	*75.40 ±4.58
10th min after intubation	*83.80 ±5.52	*74.80 ±4.85

Unpaired "t" test as a test of significance is used. t > 2.003 is significant i.e. P < 0.05

Table 5: Postoperative sedation scoring

Groups	Sedation scoring					Total
	0	1	2	3	4	
Control	18	12	0	0	0	30
Clonidine	3	6	20	1	0	30

χ^2_3= 38.06 i.e. P < 0.001

Table 6: Postoperative pain scoring

Groups	Pain scoring				Total
	0	1	2	3	
Control	2	11	12	5	30
Clonidine	8	18	3	1	30

χ^2_3= 67 i.e. P < 0.001

From the Table 5, it is observed that maximum patients i.e. 18 and 12 respectively had sedation score of 0 and 1 respectively in group I as compared to group II in which 20 patients had sedation score of 2 i.e. patients were sedated but responding to verbal stimuli 6 patients had sedation score of 1. No patient is both the groups had sedation score of 4.

It is also observed that there was significant difference between the two groups as far as sedation score is concerned.

From the Table 6, it is observed that maximum patients i.e. 11 and 12 had mild and moderate pain, 5 patients had severe pain group I and as compared to

group II in which maximum patient i.e 18 had mild pain, 8 patients had no pain and only one patient had severe pain. There was significant difference between the two groups as far as pain score is concerned.

No patient in groups I and II had nausea, vomiting, and bradycardia postoperatively.

Discussion

The main goal of premedication of producing freedom for anxiety and rendering the patient clam and co-operative is now extend to counter undesirable cardiovascular stability and smooth pain free recovery period .

Mean pulse Rate Changes

J. Pouttu et al [12] studied the effect of oral lonidine on hemodynamic responses to endotracheal intubation. They compared the effects of oral clonidine (225 to 375 microgram) with diazepam and cimetidine. They observed that the maximal increase in pulse rate at intubation was lower in clonidine group than in the cimetidine and diazepam group.

In our study there was statistically significant difference between mean pulse rate changes of both the groups during 1st minute of intubation. The study group showed lower values.

Wright et al [13] studied the intubation response and evaluated the effect of oral clonidine 0.3 mg as a premedicant in attenuating it. They compared clonidine (0.3mg) with an inert group. They observed that the pre-induction decrease of heart rate was significant in clonidine group as compared with inert group and it persisted throughout the anaesthesia. Increase in heart rate after intubation was most marked in the inert group i.e. 17 beats/min as compared to 7 beats/min in the clonidine group.

J. Pouttu et al [12] evaluated the efficacy of orally administered clonidine 4.5 microgram/kg in attenuating the hemodynamic responses to anaesthesia and surgery. They observed that clonidine attenuated the sympathoadrenal responses. The heart rate increases in association with endotracheal intubation were lower in clonidine group as compared to diazepam group of patients.

Tanaka and Nishikawa et al [14] studied the effect of oral clonidine 5 microgram/kg body weight on hemodynamic effects associated with I.V. ketamine induction (1mg/kg body weight). They observed that significant changes in heart rate from baseline values occurred only at 8 min after ketamine in clonidine group. Bradycardia before induction was observed in 20% and 35 % of patients with control and clonidine group respectively. After induction 15% of control and 30% of clonidine group of patients developed bradcardia.

Doak et al [3]studied the effect of oral clonidine 5 microgram/kg on hemodynamic effects of IV ketamine (1mg/kg) induction. They compared these with two other groups of patients receiving diazepam and placebo. They observed that heart rate increased by a maximum of 20% in clonidine group versus 41% in diazepam and in placebo group.

Kriton et al [15] studied the effect of two different oral doses of clonidine in elderly patients undergoing elective ophthalmic surgery under local anaesthesia. They observed that heart rate decreased significantly 18.5% in group III (Tab. Clonidine 4-4.5 microgram/kg) patients whereas it was 8.2% decrease in group II (Tab. Clonidine 2-2.5 microgram/kg) patients as compared to baseline. In placebo group high rate increase with approximately 5% compared to baseline value. They observed that oral clonidine in high doses produced bradycardia.

Ghignone et al [4] observed that, clonidine blunted the cardiovascular responses to intubation more effectively inpatients than lignocaine and fentanyl pretreated patients. Heart rate was consistently lower in the clonidine group as compared with group I (received lignocaine and fentanyl) throughout the operative period and in the post-anaesthesia period.

Ghignone et al [16] studied the effect of oral clonidine on intraocular pressure, perioperative hemodynamics and anaesthetic requirements for elderly patients scheduled for ophthalmic surgery under general anaesthesia and local anaesthesia. They observed that in clonidine pretreated patients there was significant reduction of IOP from 19± to 12.5± 3 mm Hg as compared with control group and it did not change following laryngoscopy and intubation in patients with clonidine. Preoperatively clonidine group of patients experienced a statistically significant reduction of heart rate. But the magnitude of changes was small. In the general anaesthesia subset clonidine premedication effectively blunted the cardiovascular responses to laryngoscopy and intubation. Both the heart rate and its co-efficient of variation were significantly less in patients receiving Clonidine as compared with the control group throughout the operative and postanaesthesia period.

In our study pulse rate decreased by a mean of 12 beats/min after 75 min of giving Tab. Clonidine and

increased to maximum of 79.9 beats/min during first minute of intubation and then decreased below the baseline values as compared to control group thus attenuating the response.

Mean Systolic Blood Pressure Changes

In the present study, the maximum rise in mean systolic pressure for both the control and clonidine group was during first min of intubation and difference was statistically significant. The mean systolic pressure returned to baseline values earlier in clonidine group as compare with the control group.

Pouttu et al [12] observed that the means of systolic pressure just before and immediately after tracheal intubation were lower in the clonidine group then in the control group.

Doak et al [3] observed that the peak increases in mean blood pressure was 39% in clonidine group whereas 70% in diazepam group, there is rapid control of systolic blood pressure from 166±32 to 130±16 mmHg. And clonidine also blunted the cardiovascular responses to intubation more effectively than the lidocaine-fentanyl pretreatement administered to group I.

In our study we observed (Table 3) that 75 min after giving clonidine the systolic blood pressure decreased by a mean of 10.67 mmHg and the preinduction value was 102.4 mm Hg. It then increased to a maximum of 113.53 mm Hg after induction with ketamine and further increased up to 120.93 mm Hg during first minute of intubation. But this increase was less than 30 mm Hg during first minute of intubation. But this increase was less than 30 mm Hg as compared to that of in control group.

Mean Diastolic Pressure Changes

In the present study, the maximum rise of mean a diastolic blood pressure for both the control and clonidine group was during first minute of intubation and the difference was statistically significant when both the groups were compared the return of the mean diastolic pressure to basal values was earlier in the clonidine group as compared to control group.

Kriton Filos [15] observed that the depression of systolic, diastolic and mean arterial pressure was more pronounced in group III i.e. patients received Tab. Clonidine 4-4.5 microgram/kg, ranged between 25%-34% as compared to baseline values. In group II patients with clonidine 2-2.5 microgram/kg maximum reduction of systolic, diastolic and MAP compared to baseline values observed was between 18%-19% significant hypotension was notice in group III patients and thus clonidine in 2-2.5 microgram/kg is more careliostable. A similar fall in mean SBP after premedication; but significant hypotension (SBP <25% of baseline) was not observed. This could be due to younger age and healthy status of the patients included in the study [17].

Ghingnone et al [16] observed that preoperatively clonidine group of patients experienced a statistically significant reduction in diastolic blood pressure as compared to control group.

Rudra et al [18] studied the efficacy of oral clonidine as a premedicant. They compared the clonidine group with diazepam group and placebo. They observed that both the diazepam and clonidine caused a higher decrease of blood pressure. Reduction of mean diastolic blood pressure in clonidine group was by 9 mmHg and in diazepam group by 5 mmHg. In the placebo group, the diastolic blood pressure was relatively unchanged after premedication.

In our study, the mean diastolic blood pressure was 81.46 mm Hg and it decreased to man of 73.6, 75 minutes after giving clonidine. The maximum increases were to mean of 82.66 as compared to 96.93 of control group. And this increase was less as compared to control group.

On comparison of intravenous premedication of midazolam and dexmedetomidine in ketamine anaesthesia, it is concluded that dexmedetomidine has effectively attenuated the ketamine-induced haemodynamic pressor response and psychomimetic effects. Due to its tendency to cause bradycardia, routine use of an anticholinergic drug was advised. Incidence and intensity of bradycardia were less in the present study as compared to the previous study [9].

In another study, 300 µg oral clonidine was found to be more effective than 1.5 mg/kg intravenous lidocaine in preventing the cardiostimulatory effects of ketamine. There was statistically significant increase in heart rate and arterial blood pressure after ketamine induction. The partial attenuation could be due to the smooth muscle relaxation effect of lignocaine [19].

Conclusions

Clonidine is an effective and safe premediacating agent with regard to preoperative pulse rate and blood pressure stability. Oral clonidine premedication 3 microgram/kg body weight given 90 minutes prior

to induction of anaesthesia with ketamine is an effective and safe method for controlling the rise in pulse rate and rise in blood pressure associated with laryngoscopy and intubation. It gives adequate analgesia in the immediate postoperative period without undue sedation.

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