The Influence of Administration of Intravenous Clonidine on Dosage of Thiopentone and Cardiovascular Response to Laryngoscopy and Intubation

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ABSTRACT

Introduction: Various techniques and drugs have been used to attenuate the stress response to laryngoscopy and intubation. So the present study was designed to know the influence of intravenous clonidine on dosage of thiopentone and cardiovascular response to laryngoscopy and intubation.

Material and Methods: one hundred male patients randomized to two groups belonging to class I and II, Group I (n=50) received 10ml Normal saline intravenously over 120seconds 15minutes before laryngoscopy and intubation. Group II (n=50) received clonidine 2.5µgm/kg intravenously over 120seconds 15minutes prior laryngoscopy and intubation. Values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxyhaemoglobin saturation (SpO_2) was recorded before test drug, before induction of anaesthesia (pre-induction), after induction (before airway instrumentation), at the time of laryngoscopy and intubation (T0) and at 1, 3, 5 and 8 minutes after intubation.

Results: There was marked increase in HR, SBP, DBP and MAP 1minute following laryngoscopy and intubation in the control group. However, in clonidine group there was a rise in HR, SBP, DBP and MAP values, at 1, 3, 5 and 8minutes after intubation in clonidine group which was clinically not significant though statistically significant. Also there was significant reduction in dose of thiopentone requirement.

Conclusion: clonidine in the dose of 2.5µg/kg I.V, given 15minutes before laryngoscopy and intubation can be safely given to attenuate the haemodynamic response to laryngoscopy and intubation without any side effects. Clonidine also reduces the dose of thiopentone requirement to induce sleep during induction.

Keywords: Sympathetic response, cardiovascular response, tracheal stimulation, airway instrumentation, α_2-agonist, eyelash reflex, sleep.

INTRODUCTION

Laryngoscopy and tracheal intubation provoke a marked sympathetic response which may result in tachycardia, hypertension and arrhythmias. Such cardiovascular responses, although transient but may be dangerous in patients suffering from cardiovascular and cerebrovascular disease. These changes are produced by lifting of base of tongue and epiglottis by the laryngoscope blade and tracheal stimulation during laryngoscopy and intubation.[1] Airway instrumentation is accompanied by 25-50% increase in mean arterial pressure (MAP) and heart rate (HR) beginning with laryngoscopy, peaking at 1-2 minutes and returning to base line within 5-10 minutes. The cardiovascular response to laryngoscopy has been of great interest to the investigators during last four decades.

Recently, few studies have evaluated the effect of intravenous local anaesthetics namely lignocaine and bupivacaine on the dose of commonly used intravenous anaesthetics[2,3] and cardiovascular response to laryngoscopy and tracheal intubation.[3]

Intravenous clonidine is a central alpha-2 agonist (α_2) has become a popular agent for obtunding haemodynamic response to laryngoscopy and intubation. Further clonidine has sedative, analgesic and antihypertensive actions in addition to reducing the anaesthetic drug requirements. Intravenous clonidine given before induction has been shown to reduce the dose of thiopentone needed for induction.

The controlled human investigations to evaluate the influence of intravenous clonidine on dosage of thiopentone and cardiovascular response to intubation are scarce and the full clinical significance of intravenous clonidine used with general anaesthetics has not been realized. Moreover, in Indian literature no definitive study has been done to evaluate the influence of intravenous clonidine on the induction dose of thiopentone and haemodynamic response to intubation. Hence, further clinical trials are warranted.

Thiopentone is still the most widely used agent as pleasant and effective means of inducing anaesthesia. Such popularity is because of ease of administration, rapidity of action, smooth onset, compatibility with catecholamines, rapid recovery, etc. To avoid hazards associated with thiopentone overdosage we used method of Dundee and coworkers (1982)[4] which uses abolition of eyelash reflex as the end point and which employs a standard method of administration and offers an acceptable compromise, has not been used in the above studies, but the method used by Dundee and coworkers was adopted in the present study.

For the reasons as stated above, we carried out a study in a double blind randomized and controlled manner to evaluate the influence of intravenous clonidine on induction dose of thiopentone and cardiovascular response to laryngoscopy and intubation in normotensive patients.

Aims and objectives of the study were to evaluate the effect of premedication with intravenous clonidine on cardiovascular response to laryngoscopy and intubation and to investigate the influence of intravenous clonidine premedication on dosage of

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thiopentone required to induce sleep.

MATERIAL AND METHODS

One hundred normotensive male patients of ASA class I and II were included in this study after approval of the ethical committee of our institute. The patients were randomized to one of the two groups between age group of 20 to 50years, weighing between 40 to 55kilograms and comparable with respect to all other independent identifiable variables known to affect the sensitivity to thiopentone and undergoing elective surgery under general anaesthesia.

Exclusion Criterion

1. Patients suffering from cardiorespiratory problems major systemic illnesses, hypertension, hepatic dysfunction, renal, psychiatric and neurological disorders.
2. Allergy to barbiturates and taking drug treatment known to affect heart rate and pressure.
3. Patients in whom thiopentone is contraindicated. For e.g. Allergic to sulphur drugs, porphyria etc.
4. Patients in whom difficult intubation is anticipated.
5. Uncooperative patients.
6. Alcoholics and smokers.

Pre-operative Visit

All the patients were visited day before surgery and examined thoroughly. Written and informed consent taken from all the patients and after explaining the procedure. Patients were advised nil per orally six hours to solids and three hours for clear fluids prior to surgery. No sedatives and hypnotics were advised night before surgery.

Anaesthetic Technique

The study population were randomly divided into two groups, 50 patients in each group.

Group I - Control group (n=50) received 10ml of normal saline intravenously over 120seconds, 15minutes prior to laryngoscopy and intubation.

Group II - Study group (n=50) received injection clonidine 2.5µgmkg^{-1} (to the nearest 10 µgm), diluted in 10ml normal saline, intravenously over 120seconds, 15minutes prior to laryngoscopy and intubation.

On arrival of patient in operating room, an 18 gauge intravenous cannula was inserted and infusion of normal saline started. Patients were connected to multichannel monitor to record the baseline heart rate (HR), electrocardiogram (ECG), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxyhaemoglobin saturation (SpO_2).

The Heart rate and rhythm also monitored from continuous visual display of electrocardiogram (lead II). After recording the baseline readings, patients received clonidine 2.5microgram per kg diluted in 10ml normal saline intravenously over 120 seconds, 15minutes before laryngoscopy and intubation, and in control group normal saline 10ml given intravenously over 120seconds. The study drug was prepared by the senior anaesthetist who was not involved with the study. The observer as well as patient was blinded to the study. All the observations were made by same observer to eliminate subjective error.

All the patients were premedicated with injection glycopyrrolate 0.2mg intravenously before pre-oxygenation and pre-oxygenated for 3minutes prior to induction.

For the purpose of this study, the endpoint "sleep" was taken as the moment when the eyelash reflex was abolished. A clear freshly prepared and adequately mixed solution of thiopentone in a concentration of 2.5% administered to all patients in this study; 2.0mgkg^{-1} (to the nearest 25mg) was given over 10seconds and after a further 30seconds the eyelash reflex was tested. If present, again a 25mg incremental dose was given over 1-2seconds and the eyelash reflex was again tested after 15seconds. Further increments of 25mg were given over 1-2seconds every 15seconds as necessary until the eyelash reflex was abolished. The total dose found necessary to abolish the eyelash reflex was recorded and this dose referred to as the "induction dose". Additional dose of thiopentone might be given, if necessary, to allow endotracheal intubation. This additional dose was not be recorded.

The endotracheal intubation was facilitated with suxamethonium chloride (1.5mgkg^{-1}). Steps were taken to ensure that laryngoscopy and intubation completed within 15seconds. Any patient who strains and takes more than 15seconds to intubation, or required a second attempt of intubation was excluded from the study.

Anaesthesia was maintained with 66% nitrous oxide (N_2O) in oxygen (O_2), 0.5% halothane and inj. pentazocine 30mg and intermittent uses of adequate doses of inj. vecuronium and intermittent positive pressure ventilation (IPPV) to maintain normocarbia.

Pentazocine was given to the patient 8minutes after intubation but before start of the surgery. At the end of surgical procedure, residual neuromuscular blockade antagonized with neostigmine 0.05mgkg^{-1} and atropine 0.02mgkg^{-1}. After successful reversal, trachea was extubated.

Any episode of hypertension (>30% of pre-induction levels), hypotension (<90 mmHg systolic), tachycardia (>30% of preinduction heart rate) and bradycardia (< 50 beats per minute) noted. Untoward side effects like nausea, vomiting, dryness of mouth, vertigo, etc. either complained of or observed was noted.

Values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxyhaemoglobin saturation (SpO_2) recorded before test drug, before induction of anaesthesia (pre-induction), after induction (before airway instrumentation), at the time of laryngoscopy and intubation (T0) and at 1, 3, 5 and 8minutes after intubation.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the statistical analysis. Descriptive statistics like mean, SD and percentages were used for interpretation of data.

RESULTS

Intergroup Comparison of mean heart rate changes in response to laryngoscopy and intubation.

Statistical comparison between two groups showed that the increase in mean HR observed in group I was statistically highly significant when compared to increase in mean HR in group II (p<0.01) at baseline, preinduction, induction, intubation and 1, 3, 5 and 8minutes following intubation (Table-1).

Intergroup comparison of mean systolic blood pressure (SBP) changes in response to laryngoscopy and intubation at different intervals.

Increase in mean SBP observed in group I was statistically highly significant when compared to increase in mean SBP in the group II (p<0.01) at baseline, pre induction, induction, intubation, 1, 3, 5 and 8 minutes following intubation (table-2).

Intergroup comparison of Mean Diastolic Blood Pressure (DBP in mmHg) changes in response to laryngoscopy and intubation at different time intervals.

Increase in mean DBP observed in group I was statistically highly significant when compared to increase in mean DBP in the group II (p<0.01) at induction, intubation, 1, 3, 5 and 8minutes following intubation (Table-3).

Intergroup comparison of mean arterial pressure (MAP) changes in response to laryngoscopy and intubation at different time intervals.

Increase in MAP observed in group I was statistically highly significant when compared to increase in MAP in the group II (p<0.01) at pre induction, induction, intubation, 1, 3, 5 and 8 minutes following intubation (Table-4).

Dose of thiopentone required for induction in control and clonidine group.

Statistical evaluation shows, in group I mean dose of thiopentone required for loss of eye lash reflex is 223.0±26.5 (Mean±SD) mg i.e (4.26mg/kg) and in group II mean dose is 133.5±16.5 (Mean±SD)mg (2.56mg/kg). Statistical comparison between the groups showed that the statistically significant reduction in dose of thiopentone required for induction in group II p<0.05.

Mean Heart Rate	Group I (control) (mean±SD)	Group II (clonidine) (mean±SD)	t-value	*p*-value
Baseline	84.48±9.86	86.10±13.44	0.687	0.494*
Preinduction	89.10±10.56	85.74 ± 12.93	1.423	0.158*
Induction	93.16±12.09	84.68±12.21	3.489	0.001*
Intubation	119.20±11.16	90.60±11.86	12.410	0.000*
1 minute	125.08±9.31	95.56±12.66	13.275	0.000*
3 minute	116.14±8.69	90.60±11.06	12.833	0.000*
5 minute	109.88±8.97	87.82±10.76	11.130	0.000*
8 minute	97.48±9.49	85.96±10.01	5.904	0.000*

Table-1: Showing intergroup comparison of mean heart rate changes in response to laryngoscopy and intubation.

Mean SBP (mmHg)	Group I (control) (Mean±SD)	Group II (clonidine) (Mean±SD)	t-value	*p*-value
Baseline	127.90±5.62	122.74±9.25	3.371	0.001*
Preinduction	130.84±5.86	122.12±7.29	6.590	0.000*
Induction	127.26±5.72	120.48±7.28	5.177	0.000*
Intubation	145.34±4.58	127.30±8.60	13.087	0.000*
1min	158.02±4.50	132.46±10.24	16.147	0.000*
3min	149.16±8.27	126.56±9.06	13.024	0.000*
5min	139.24±8.02	124.54±8.42	8.938	0.000*
8min	128.58±5.91	122.80±7.94	4.126	0.000*

Table-2: Intergroup comparison of mean systolic blood pressure (SBP) changes in response to laryngoscopy and intubation at different intervals.

Mean DBP (mmHg)	Group I (control) (Mean±SD)	Group II (clonidine) (Mean±SD)	t-value	*p*-value
Baseline	77.00±6.10	77.70±7.58	0.508	0.612
Preinduction	80.80±6.49	78.68±7.75	1.482	0.142
Induction	78.30±6.88	76.22±8.09	1.384	0.170
Intubation	94.04±3.46	82.66±7.81	9.413	0.000*
1min	98.78±3.45	85.20±8.00	11.017	0.000*
3min	92.12±7.24	82.32±6.99	6.881	0.000*
5min	86.10±8.04	80.10±8.29	3.672	0.000*
8min	80.00±8.07	79.00±7.77	0.631	0.530

Table-3: Intergroup comparison of Mean Diastolic Blood Pressure (DBP in mmHg) changes in response to laryngoscopy and intubation at different time intervals.

MAP (mmHg)	Group I (control) (Mean±SD)	Group II (clonidine) (Mean±SD)	t-value	*p*-value
Baseline	93.62±5.05	91.84±6.59	1.515	0.133
Preinduction	97.28±5.33	93.00±6.87	3.480	0.001*
Induction	93.66±5.35	90.68±6.75	2.448	0.016*
Intubation	110.86±2.82	97.58±7.17	12.176	0.000*
1min	118.12±3.32	100.54±7.55	15.057	0.000*
3min	110.28±7.01	96.96±6.97	9.518	0.000*
5min	102.96±7.05	94.60±7.61	5.696	0.000*
8min	96.12±6.41	93.42±6.70	2.058	0.042*

Table-4: Intergroup comparison of mean arterial pressure (MAP) in (mmHg) changes in response to laryngoscopy and intubation at different time intervals.

DISCUSSION

Changes in heart rate (HR) at various time intervals

In the present study, following laryngoscopy and intubation at 1,3 and 5minutes mean HR increased by 40.6bpm vs. 9.46bpm, 31.6bpm vs. 4.5bpm and 25.4bpm vs. 1.7bpm in control and clonidine group respectively which was statistically highly significant (p<0.01). (Table-1)

Various authors have found a similar response to I.V. clonidine at 1min after intubation. Zalunardo MP et al.[8] used clonidine 3µg/kg and found that following laryngoscopy and intubation at 1min HR increased by 23bpm in control group and by only 6bpm in the clonidine pre-medicated group. Altan A et al.[10] used clonidine 3µg/kg and found that, following laryngoscopy and intubation, HR increased by 10 bpm in the control group, whereas in the clonidine group, HR decreased by 10bpm, which was statistically highly significant (p<0.01). Ray M et al.[11] used clonidine 3µg/kg and found that following laryngoscopy and intubation, HR at 1min increased by 19bpm in control group and only 1bpm in clonidine group, the difference was statistically significant.

Above authors, have found a statistically significant obtundation of heart rate response to intubation at 1minute in clonidine premedicated group which concurs with our study. We could not compare our results with other authors as they have not noted the haemodynamic parameters at 3 and 5 minutes after intubation.

At 8 minutes after intubation

In our study even at 8minutes after intubation, there was an increase in the HR by 13bpm compared to basal HR in the control group and in the clonidine group, there was no increase

in HR compared to basal value, this was statistically highly significant (p<0.01). (Table-1)

Ray M et al.[11] used clonidine 3µg/kg and found that, 10min following laryngoscopy and intubation HR increased by 9bpm in the control group and decreased by 16bpm in clonidine group, the difference was statistically significant (p <0.05). Our study concurs with the study by Ray M et al.[10] at 1, 3 and 5minutes following laryngoscopy and intubation. We could not compare our result as they have not noted the haemodynamic parameters at 8minute.

In the control group there is a statistically significant increase in the heart rate occurred at various time intervals, at intubation and 1, 3, 5 and 8minutes after intubation with the maximum rise of 40.6bpm at 1minute after intubation (Table-1). Similar findings were also noted by Zalunardo MP et al.[8], Altan A et al.[10], Ray M et al.[11] In the clonidine group a statistically significant increase in the heart rate occurred at 1 minute after intubation with rise of only 9.46bpm which is clinically not significant (Table-1). Similar findings were observed by Zalunardo MP et al.[8]

Changes in systolic blood pressure (SBP) at various time intervals

In the our study, following laryngoscopy and intubation at 1,3 and 5minutes after intubation SBP increased by 30.12mmHg vs. 9.72mmHg, 21.44mmHg vs. 3.82mmHg, 11.34mmHg vs. 1.8mmHg in control and clonidine group respectively which was statistically highly significant (p<0.01). (Table-2)

We could not compare our results with other investigators, as they have not documented separately the systolic blood pressure changes.

Changes in diastolic blood pressure (DBP)

In the our study, following laryngoscopy and intubation at 1,3 and 5minutes after intubation DBP increased by 21.78mmHg vs. 7.5mmHg, 15.12mmHg vs. 4.62mmHg, 8.4mmHg vs. 2.4mmHg in control and clonidine group respectively which was statistically highly significant (p<0.01). (Table-3)

When we compared the increased difference between the two groups at 1 minute after intubation the difference was statistically highly significant.(p<0.01). We could not compare our results with other investigators, as they have not documented separately the diastolic blood pressure changes.

Changes in mean arterial pressure (MAP) at various time intervals

In the our study, following laryngoscopy and intubation at 1, 3 and 5minutes after intubation in the control group MAP increased by 24.5mmHg vs. 8.7mmHg, 16.9mmHg vs. 5.1 mmHg, 9.4mmHg vs. 2.76mmHg in control and clonidine group respectively which was statistically highly significant (p<0.01). (Table-4)

Zalunardo MP et al.[8] used clonidine 3µg/kg and found that following laryngoscopy and intubation at 1minute, MAP increased by 37mmHg in the control group and only 5mmHg in the clonidine pre-medicated group. Altan A et al.[10] employed clonidine at a fixed dose of 3µg/kg found that 1minute after intubation, MAP increased by 16mmHg in control group, whereas in clonidine group MAP decreased by 10mmHg, which was statistically highly significant (p<0.05). Ray M et al.[11] employed clonidine at a fixed dose of 3µg/kg found that 1minute after intubation MAP increased by 14mmHg in control group, whereas in clonidine group MAP decreased by 18mmHg, which was statistically highly significant (p<0.01). Above authors also found statistically significant obtundation of mean arterial pressure (MAP) response to intubation at 1minute, which concurs with our study. We could not compare our results with other authors as they have not noted the haemodynamic parameters at 3 and 5minutes.

At 8 minutes after intubation

At 8minutes after intubation, the increase in MAP in the control group was 2.6 mmHg and in the clonidine group increase in MAP was 1.58mmHg when compared with basal MAP, which is statistically not significant (p >0.05). (Table-4)

In control group at intubation, 1, 3 and 5minutes after intubation there was significant rise in mean arterial pressure which was statistically highly significant. Maximum rise in MAP was 24.5mmHg at 1minute after intubation. Similar findings were also noted by Zalunardo MP et al.[8], Altan A et al[10], Ray M et al.[11] In the clonidine group a statistically significant increase in mean arterial pressure occurred at intubation and 1minute after intubation with maximum rise of only 8.7mmHg at 1minute after intubation which is clinically not significant. Similar findings were observed by Zalunardo MP et al.[8] Ray M et al.[11] used clonidine 3µg/kg and found that, 10minutes following laryngoscopy and intubation MAP increased by 4mmHg in the control group and decreased by 26mmHg in clonidine group, the difference was statistically significant (p<0.05).

Action of clonidine on cardiovascular system classified as peripheral and central. Peripherally it inhibits the noradrenaline release from presynaptic α_2-adrenoreceptors at sympathetic nerve terminals causing vasorelaxation and this property contributes to bradycardiac effect of clonidine (reduced chronotropic drive). Centrally mediated mechanisms produce both hypotension and bradycardia. Mechanism involves inhibition of sympathetic outflow and the potentiation of parasympathetic nervous activity. Nucleus tractus solitarius (a site known to modulate autonomic control, including vagal activity) is an important central site for the action of clonidine where it activates post synaptic α_2-adrenoreceptors to reduce sympathetic outflow, other nuclei, including locus coerules, the dorsal motor nucleus of vagus and the nucleus reticularis lateralis also mediate hypotension and bradycardia and antiarrythmogenic actions. The ability of clonidine to decrease systemic blood pressure without paralysis of compensatory homeostatic reflexes is highly desirable. Renal blood flow and glomerular filtration rate are maintained in the presence of clonidine therapy.[5]

Dose of Thiopentone required for induction

We studied the total dose of thiopentone required for induction in each group. In control group dose of thiopentone required for induction was 223.0±26.5 (Mean±SD)mg i.e; (4.26mg/kg) and in clonidine group dose required was 133.5±16.5 (Mean±SD) mg i.e. (2.56 mg/kg) which was 40% less than control group. This was statistically highly and clinically significant (p<0.01). (Table-5)

Various authors have studied the effect of clonidine on thiopentone requirement for induction of anaesthesia. Leslie K et al.[6], studied the effect of intravenous clonidine on the dose of thiopental required to induce anaesthesia. In this study the dose of thiopentone required for induction in control group was

5.50mg/kg and in the clonidine group the dose of thiopental required to induce anaesthesia with 2.5µg/kg clonidine is 4.15 mg/kg and with 5µg/kg clonidine is 3.48mg/kg showing reduction of 25% and 36% respectively compared to control (p<0.05). Marinangeli F et al.[9] studied the haemodynamic effects of intravenous clonidine on thiopental induction. In this study the dose of thiopentone required for induction in control group was 5.80mg/kg and in clonidine group with 3µg/kg clonidine was 3.8mg/kg showing reduction of 34% compared to control (p<0.05). Sakshi Arora et al.[12] studied combination of clonidine and fentanyl. In group A clonidine 1µg/kg and fentanyl 2µg/kg, In group B clonidine 2µg/kg and fentanyl 2µg/kg. They found greater attenuation of hemodynamic response in group B. Above authors have found statistically significant reduction of thiopentone dose required for induction in the clonidine group(p<0.05), which concurs with our study.

CONCLUSION

From the above discussion it was concluded that clonidine in the dose of 2.5µg/kg I.V, given 15minutes before laryngoscopy and intubation can be safely employed to attenuate the haemodynamic response to laryngoscopy and intubation without any side effects. It also reduces the requirement of thiopental induction.

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