A Comparative Study of Clonidine and Lignocaine for Attenuating Pressor Responses to Laryngoscopy and Endotracheal Intubation in Neurosurgical Cases

Vinay Marulasiddappa, H. N. Nethra
Department of Anaesthesia, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

Abstract

Background and Aims: Laryngoscopy and endotracheal intubation are associated with reflex sympathetic stimulation, known as pressor response and can cause major complications. We compared the attenuating effect of time-tested lignocaine versus clonidine on the hemodynamic response to laryngoscopy and intubation in neurosurgical cases. Design: A prospective, randomized, comparative, double-blind study with a sample size of sixty patients. Methods: Sixty patients undergoing elective neurosurgery were randomly allocated into one of the two groups: Group L (n = 30) received lignocaine 1.5 mg/kg intravenous (i.v.) before induction and Group C (n = 30) received clonidine 2 μg/kg i.v. before induction. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded at baseline, after drug, after induction and 1, 2, 3, 5, 10, and 15 min after intubation. Statistical Analysis: Statistical software, namely, SPSS, version 15.0 by SPSS Inc., Chicago, USA was used for the analysis of data with Chi-square test to compare intergroup hemodynamic parameters. Results: Mean HR remained above baseline at all times after intubation in lignocaine group but decreased at 2 min after intubation and remained below baseline at all times in the clonidine group. SBP, DBP, and MAP all increased above baseline at 1 min after intubation in lignocaine group, and decreased below baseline at 2 min after intubation, whereas in the clonidine group they all decreased below baseline after drug administration and remained below baseline at all times. Therefore, clonidine is very effective in attenuating pressor responses and this difference between the groups is statistically very significant with \( P < 0.001 \). Conclusion: Clonidine is more effective than lignocaine for attenuating the pressor responses to laryngoscopy and endotracheal intubation in neurosurgical cases.

Keywords: Clonidine, hemodynamic response, lignocaine, neurosurgery

INTRODUCTION

Laryngoscopy and endotracheal intubation, which are a basic and integral part of general anesthesia (GA), are associated with reflex sympathetic stimulation, manifested by tachycardia and hypertension.\(^1\) This is known as pressor response and has the potential to cause major complications such as myocardial ischemia, ventricular arrhythmia, left ventricular failure, and cerebral hemorrhage.\(^1,2\)

This response is harmful in neurosurgical cases as it may cause an increase in intracranial pressure, intracranial bleed, adverse hemodynamic effects, increasing the morbidity, and prolonged hospital stay\(^3,4\) and therefore has to be attenuated. We are comparing attenuating effect of lignocaine versus clonidine on the pressor response to laryngoscopy and endotracheal intubation in neurosurgical cases.

In a similar study by Vyankatesh et al., the attenuating effect of oral clonidine was compared with intravenous (i.v.) lignocaine on hemodynamic effects of laryngoscopy and endotracheal intubation.\(^5\) However, we are comparing attenuating effects of different routes of lignocaine and clonidine.

Address for correspondence: Dr. Vinay Marulasiddappa, Department of Anaesthesia, Bangalore Medical College and Research Institute, KR Road, Bengaluru - 560 002, Karnataka, India. E-mail: drvinaym@gmail.com

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of i.v. clonidine with i.v. lignocaine and specifically in neurological cases.

Other drugs such as dexmedetomidine have been compared with esmolol for attenuation of the hemodynamic effects of laryngoscopy and intubation in neurological cases by Srivastava et al.\textsuperscript{[3]}

There are also studies comparing clonidine with other drugs for attenuating pressor response, such as comparison with fentanyl by Sameenakousar et al.\textsuperscript{[5]} and comparison of oral clonidine premedication with oral gabapentin by Montazeri et al.\textsuperscript{[4]} but there are no studies currently specifically comparing i.v. clonidine with i.v. lignocaine for attenuation of pressor responses, especially in neurological cases.

**Methods**

A prospective, randomized, comparative, double-blind study was conducted with sixty adult patients after obtaining Institutional Ethical Committee approval. These patients who were posted for elective neurological surgeries were randomly allocated into two groups of thirty each after obtaining written informed consent from the patients, using computer-generated randomization (Random Allocation Software, M. Saghaei, Isfahan, Iran). Patients were randomly allocated into one of the two groups: Group L or Group C. Group L patients received preservative-free lignocaine 1.5 mg/kg i.v. 5 min before induction and Group C patients received clonidine 2 μg/kg i.v. 5 min before induction.

All adult patients aged between 18 and 65 years, belonging to American Society of Anesthesiologists (ASA) Class 1, 2 and undergoing elective neurosurgery under GA and who are willing to participate and given written informed consent for this study were included in this study. Patients with predicted difficult intubation, laryngoscopy, and intubation time >20 s, more than one attempt of intubation, on preoperative β-blocker therapy, systemic illness such as hypertension, diabetes, hepatic failure, coronary artery disease, left bundle branch block, conduction abnormalities, congestive cardiac failure, recent myocardial infarction, and renal failure were excluded from the study.

Age <18 years and >65 years, ASA Class 3 and above, patients posted for emergency surgery and those with known hypersensitivity to these drugs were also excluded from this study.

After a detailed preanesthetic assessment and required investigations, all patients in both groups underwent the same plan of GA. All patients were fasted for 6 h. Monitoring included electrocardiogram, pulse oximetry and noninvasive blood pressure (NIBP). Group L patients received preservative-free lignocaine 2%, 1.5 mg/kg i.v. administered 5 min before induction and Group C patients received clonidine 2 μg/kg i.v. administered 5 min before induction.

After administration of either lignocaine i.v. or clonidine i.v., patients were preoxygenated with 100% O\textsubscript{2} for 5 min, and then all patients were induced with thiopentone (2.5% solution) in a dose of 5–7 mg/kg body weight and fentanyl 2 μg/kg. Neuromuscular blockade was achieved by injection vecuronium bromide 0.15 mg/kg and intubation completed with appropriate sizeduffed endotracheal tube by a single operator in all the cases. Furthermore, none of the patients in both groups required any external laryngeal manipulation to improve glottic visualization which might have caused a more laryngoscopic response. Anesthesia was maintained with oxygen and air, sevoflurane, intermittent boluses of injection vecuronium and fentanyl. Ventilation was adjusted to maintain an end-tidal carbon dioxide value between 30 and 35 mmHg. Heart rate (HR), systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) were recorded baseline, after study drug administration, after induction and 1, 2, 3, 5, 10, and 15 min after orotracheal intubation using GE Monitor (Model: USE1503A attached to Datex Ohmeda S/5 workstation).

Descriptive and inferential statistical analysis has been carried out in this study. Based on outcome variable on mean BP for a two group study, with 90% statistical power, 5% level of significance, the sample of sixty is adequate. Patients were randomly allocated into two groups by applying random allocation. Patients were randomly allocated into two groups of thirty each after obtaining written informed consent from the patients, using computer-generated randomization (Random Allocation Software, M. Saghaei, Isfahan, Iran). Patients were randomly allocated into one of the two groups: Group L or Group C. Group L patients received preservative-free lignocaine 1.5 mg/kg i.v. 5 min before induction and Group C patients received clonidine 2 μg/kg i.v. 5 min before induction. Both groups were comparable with respect to age and gender distribution [Table 1]. Furthermore, there was no significant difference between the two groups with respect to baseline HR, SBP, DBP, and MAP.

As seen in Table 2 and Figure 1, in Group L, mean HR started to rise from the baseline after drug administration, but the maximal rise was at 1 min after intubation, when it increased by 13.57 (16.31%) and continued to be higher than baseline even at 15 min after intubation. In the Group C, however, mean HR increased very slightly from baseline at 1 min after intubation, when it rose by 1.67% but started to decrease below the baseline by the 2nd min after intubation and remained lower than baseline throughout, with the maximal drop in HR at 15 min after intubation (12.46%).

When the two groups are compared, there is statistically no significant difference in the mean HR at baseline, after study
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Drug and after induction. However, there is a statistically significant difference (moderately to strongly significant) in the mean HR between the two groups at 1, 2, 3, 5, 10, and 15 min after intubation with the HR significantly lesser in the Group C than the Group L at all times after intubation, especially at 2, 3, and 5 min after intubation when there is a strongly significant difference between the two groups with $P \leq 0.001$.

Thus, the attenuation of HR after intubation was much better with clonidine than lignocaine.

As seen in Table 3 and Figure 1, Using repeated measures of ANOVA, comparing SBP within the group at all times with baseline SBP, there is a statistically significant variation in SBP at 1, 2, 3, 5, 10 and 15 min after intubation with $P < 0.001$ [Table 3]. In the Group L, SBP started to increase from the baseline at 1 min after intubation, and although it slightly reduced thereafter, SBP in the Group L remained much higher than the Group C at 2, 3, 5, 10 and even at 15 min after intubation. This difference between the two groups was statistically significant at all times after intubation with $P < 0.001$. In the Group C, however, there was no rise in SBP after intubation, but on the contrary, decreased from the baseline after clonidine administration and continued to be below baseline at all times after administration and intubation. However, the fall in SBP in the Group C at all times was $<25\%$ of baseline and hence did not cause significant hypotension.

When the two groups are compared, there is no significant difference in the SBP at baseline; however, there is statistically significant difference between the two groups at all times after drug administration, with the SBP remaining lower ($P \leq 0.001$) in the Group C than the Group L. This clearly indicates that both clonidine and lignocaine are effective in attenuating SBP response after intubation, but clonidine is more effective than lignocaine.

It is evident from Table 4 and Figure 1 that, in the Group L, DBP starts to rise 1 min after intubation and returns to baseline at 3 min after intubation and thereafter drops to below baseline. The maximum rise in DBP occurs 1 min after

**Figure 1:** The comparison of heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure between the two groups

**Table 1: Demographic characteristics of both groups**

| Age in years | Group L | Group C |
|-------------|---------|---------|
| 21-30       | 6 (20.0)| 8 (26.7)|
| 31-40       | 12 (40.0)| 14 (46.7)|
| 41-50       | 4 (13.3)| 3 (10.0)|
| 51-60       | 6 (20.0)| 4 (13.3)|
| 61-70       | 2 (6.7)| 1 (3.3)|
| Total       | 30 (100.0)| 30 (100.0)|

**Table 2: Heart rate (bpm) distribution in two groups of patients studied**

| HR (bpm) | Group L | Group C | $P$ |
|----------|---------|---------|-----|
| Base line| 83.20±19.02| 86.97±17.46| 0.428|
| After study drug administration| 85.97±16.96| 82.27±17.31| 0.407|
| After induction of anesthesia| 87.90±14.05| 86.10±15.52| 0.639|
| 1 min after intubation| 96.97±16.41| 88.43±16.08| 0.046*|
| 2 min after intubation| 95.93±15.26| 83.17±13.94| 0.001**|
| 3 min after intubation| 95.97±18.25| 81.87±13.83| 0.001**|
| 5 min after intubation| 90.27±14.83| 77.70±11.28| <0.001**|
| 10 min after intubation| 89.10±19.61| 78.53±14.66| 0.021*|
| 15 min after intubation| 85.23±17.64| 76.13±10.53| 0.018*|

Repeated measures ANOVA (*Moderately significant, **Strongly significant): Between-group $F$=5.414, $P$=0.023. HR=Heart rate

Samples are age-matched with $P=0.124$ and are gender matched with $P=0.791$. SD=Standard deviation
intubation (10.28%). However, in the Group C, DBP starts to fall below baseline after drug administration and remains lower than baseline even at 15 min after intubation. The maximum fall in DBP occurs at 15 min after intubation (23.81%).

When the two groups are compared, mean DBP is very significantly lower in the Group C compared to Group L after drug administration and continues to be lower throughout the period after intubation. This difference is statistically very significant ($P < 0.001$). Thus, both lignocaine and clonidine are effective in attenuating DBP after intubation, but clonidine is much more effective than lignocaine.

As seen in Table 5 and Figure 1, in the Group L, MAP rises slightly at 1 min after intubation (5.95%) but returns to baseline 2 min after intubation and thereafter remains below the baseline. In the Group C, however, MAP never rises after intubation, but instead starts to fall after drug administration and continues to be below the baseline throughout the period after intubation, with the maximum drop at 15 min after intubation (23.36%).

When the two groups are compared, MAP remains significantly lower in the Group C than the Group L throughout the period after intubation and this difference is statistically very significant ($P < 0.001$). Therefore, once again although both clonidine and lignocaine are effective in attenuating the MAP after intubation, clearly clonidine is much more effective in attenuating the MAP than lignocaine. No adverse effects such as bradycardia, significant hypotension (BP <25% below baseline) were observed in both groups.

**DISCUSSION**

Various drugs have been used to reduce the pressor response, such as topical anesthesia with lignocaine, narcotics like fentanyl and alfentanil, β blockers like propranolol and esmolol, calcium channel blockers like verapamil and diltiazem and peripheral vasodilators like sodium nitroprusside and nitroglycerine.\(^{[1,2]}\) α₉ agonists like clonidine, recently used for attenuation of sympathoadrenal stimulation caused by tracheal intubation, works by stimulating α2 adrenergic inhibitory neurons in the medullary vasomotor center. As a result, there is a decrease in sympathetic nervous system outflow from central nervous system to peripheral tissues.\(^{[3]}\)

The pressor response is believed to be a reflex sympathetic response to the mechanical stimulation of pharynx and larynx and is associated with a significant increase in serum levels of epinephrine and norepinephrine.\(^{[4]}\)

Lignocaine, a time-tested drug for attenuation of pressor responses to laryngoscopy and intubation, is used in the treatment of patients with ventricular dysrhythmias and as prophylaxis in the treatment of ventricular tachyarrhythmias especially those with myocardial infarction and mechanical irritation of cardia.\(^{[5]}\)

| Table 3: Systolic blood pressure (mmHg) distribution in two groups of patients studied |
|-----------------|-----------------|-----------------|-----------------|
| SBP (mmHg)      | Group L         | Group C         | $P$              |
| Base line       | 133.77±8.34     | 120.03±16.81    | 0.615            |
| After study drug administration | 134.03±12.47    | 123.30±14.78    | 0.004**          |
| After induction of anesthesia | 115.93±15.88    | 106.60±19.26    | 0.045*           |
| 1 min after intubation | 137.80±24.38    | 112.17±12.03    | <0.001**         |
| 2 min after intubation | 127.73±20.33    | 102.73±13.08    | <0.001**         |
| 3 min after intubation | 125.40±22.75    | 101.57±15.51    | <0.001**         |
| 5 min after intubation | 114.17±15.85    | 99.97±14.52     | 0.001**          |
| 10 min after intubation | 113.23±17.51    | 102.00±16.74    | 0.014*           |
| 15 min after intubation | 111.73±14.08    | 100.77±14.30    | 0.004**          |

Repeated measures ANOVA: Between-group $F=32.523$, *$P<0.05$. **$P<0.001$. SBP=Systolic blood pressure

| Table 4: Diastolic blood pressure (mmHg) distribution in two groups of patients studied |
|-----------------|-----------------|-----------------|-----------------|
| DBP (mmHg)      | Group L         | Group C         | $P$              |
| Base line       | 83.33±6.65      | 81.03±10.23     | 0.967            |
| After study drug administration | 84.73±8.34     | 77.50±9.24     | 0.002**          |
| After induction of anesthesia | 75.77±14.09     | 67.77±13.87     | 0.031*           |
| 1 min after intubation | 91.90±17.77     | 72.60±11.15     | <0.001**         |
| 2 min after intubation | 84.00±13.39     | 66.17±11.34     | <0.001**         |
| 3 min after intubation | 80.83±16.59     | 65.03±12.07     | <0.001**         |
| 5 min after intubation | 75.67±13.22     | 63.53±13.15     | 0.001**          |
| 10 min after intubation | 75.57±15.14     | 63.70±11.06     | 0.001**          |
| 15 min after intubation | 73.40±13.58     | 61.73±11.29     | 0.001**          |

Repeated measures ANOVA: Between-group $F=33.667$, *$P<0.05$. **$P<0.001$. DBP=Diastolic blood pressure

| Table 5: Mean arterial pressure (mmHg) distribution in two groups of patients studied |
|-----------------|-----------------|-----------------|-----------------|
| MAP (mmHg)      | Group L         | Group C         | $P$              |
| Base line       | 101.90±6.24     | 102.00±11.61    | 0.967            |
| After study drug administration | 103.93±7.69    | 95.17±9.66     | <0.001**         |
| After induction of anesthesia | 91.63±12.92    | 83.23±14.79     | 0.025*           |
| 1 min after intubation | 107.97±19.22    | 89.00±9.77     | <0.001**         |
| 2 min after intubation | 100.27±15.32    | 81.47±10.86     | <0.001**         |
| 3 min after intubation | 97.97±17.89    | 79.83±13.59    | <0.001**         |
| 5 min after intubation | 91.20±13.61    | 79.20±12.39    | 0.001**          |
| 10 min after intubation | 90.70±14.82    | 79.63±12.16    | 0.002**          |
| 15 min after intubation | 89.07±12.08    | 78.17±10.62    | <0.001**         |

Repeated measures ANOVA: Between-group $F=35.699$, *$P<0.05$. **$P<0.001$. MAP=Mean arterial pressure

Clonidine is mainly used as an antihypertensive agent, but has been found to have beneficial effects in attenuating hemodynamic responses to laryngoscopy and intubation, especially in i.v. route rather than oral route, in a dose of 2 μg/kg.\(^{[6,8]}\)

In this study, mean HR is significantly lower in the Group C than Group L at all times after intubation and this difference is statistically very significant ($P < 0.001$). This correlates well with the observations made in earlier studies comparing
lignocaine with clonidine for attenuation of hemodynamic response to laryngoscopy and intubation such as the study by Vyankatesh et al.,[3] who found a statistically significant difference between the HR in lignocaine and clonidine groups, with the HR being higher in the lignocaine group than the clonidine group after intubation and HR in lignocaine group returned towards baseline only at 5 min after intubation. In this study, however, HR remained high even at 15 min after intubation in the Lignocaine group.

In this study, mean HR is maximum at 1 min after intubation in both groups. This is in agreement with studies which have found that plasma catecholamine levels to be maximum at 1 min after intubation.[9]

When the two groups are compared, mean SBP, DBP, and MAP are significantly lower in the Group C than Group L at all times after intubation and this difference is statistically very significant ($P < 0.001$). Our results are similar to earlier studies comparing lignocaine with clonidine for attenuation of pressor responses, which reported a reduction in SBP and DBP following clonidine such as studies by Vyankatesh et al.,[12,10,11] In these three studies, during the postintubation period, SBP and DBP remained below baseline value producing significant attenuation of the rise in SBP due to laryngoscopy and intubation.[2,10,11] In the study conducted by Raval and Mehta[10] SBP and DBP returned to baseline 5 min after intubation. However, in this study, SBP and DBP remained below baseline even at 15 min after intubation in the clonidine group, thereby establishing that clonidine i.v. is very effective in attenuating rises in SBP and DBP even at 15 min after intubation.

The effects of clonidine on HR and BP have been studied extensively and it has been reported that reduction in the pulse rate after the clonidine administration is due to a combination of reduction in the sympathetic outflow, the simultaneous increase of the parasympathetic tone of central origin and the influence of clonidine on the neurons which receive the baroreceptor afferents. Clonidine alters HR mainly through its direct central action on the baroreceptor pathways.[12]

Clonidine has been found to be safe in neurosurgical patients by previous studies such as the study by Gupta et al.[13] In this study also, we did not observe any major side effects such as bradycardia or significant hypotension (BP <25% of baseline).

There are a few limitations of our study as we have not measured serum levels of stress markers such as cortisol and catecholamines during laryngoscopy and intubation and hence not able to compare the differences in the neuroendocrine responses to laryngoscopy and intubation between the two drugs.

**Conclusion**

We, therefore, conclude that the attenuating effect of clonidine on the pressor response is far superior to lignocaine, both in controlling the HR as well as BP.

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**Conflicts of interest**

There are no conflicts of interest.

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