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Clonidine Infusion as Premedication in Hypertensive Patients: A Randomised Controlled Study

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Abstract

Background and Aims: Integral components of general anesthesia are endotracheal intubation and Laryngoscopy. However hemodynamic responses, such as tachycardia and hypertension, occur immediately and often lasts for 5 to 10 minutes. Hemodynamic responses are exaggerated in hypertensive patients. This study aimed to assess the efficacy of clonidine infusion as a premedication for attenuating hemodynamic reactions of hypertensive patients to laryngoscopy and endotracheal intubation.Methods: This prospective, randomized, controlled study enrolled 60 hypertensive patients of either sex scheduled for surgery under general anesthesia and endotracheal intubation. Patients in clonidine group (C group, n = 30) received intravenous clonidine (4 μg kg-1), diluted in 50 ml normal saline, over 15 minutes by syringe pump pre-operatively, at rate of 200 ml / hr and those in the control group (NS group, n = 30), were given 50 ml normal saline as a placebo in the same manner. The Sedation score of each patient was recorded 15 min after infusion completion. General anesthesia was subsequently given to the patients in both groups in accordance with a prescribed protocol. Hemodynamic parameters were recorded before induction, during laryngoscopy, and at various intervals after laryngoscopy, and statistical analyses were performed. Results: Compared to the control group, the study group had a significantly lower heart rate in all of the recorded readings. There was a significant attenuation of systolic blood pressure and mean arterial pressure in group C compared to those in the NS group. The sedation score after 15 min was significantly higher in Group C than Group NS ($p < 0.001$). There were no significant variations noticed between the two groups regarding complications that occurred after the operation. Conclusion: Intravenous 4 μg kg-1 clonidine infusion is effective in preventing exaggerated hemodynamic responses during laryngoscopy and tracheal intubation in patients with hypertension.

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1. Introduction

"Direct laryngoscopy and passage of the endotracheal tube through the larynx are noxious stimuli that can provoke untoward responses in the cardiovascular, respiratory, and other physiological systems" [1], thus causing increased morbidity and mortality. It frequently causes tachycardia and hypertension due to sympathoadrenal activation, which is usually transient and lasts for up to 5-10 minutes. Patients with hypertension exhibit an increased hemodynamic reaction, even though it is rendered normotensive preoperatively by antihypertensive medications. The hemodynamic reactions brought on by tracheal intubation and laryngoscopy are not sufficiently or consistently suppressed by intravenous (IV) anaesthetic induction drugs. Hence, a suitable induction technique that is not associated with an increased sympathetic response to laryngoscopy and tracheal intubationis needed [2]

Various techniques and drugs have been used to attenuate circulatory responses during laryngoscopy and intubation ,such as a with inhalation agents, topical anesthesia with lidocaine spray prior to laryngoscopy of the upper respiratory tract, intratracheal and translaryngeal nerve blocks, etc.[3] "Vasodilators such as nitroprusside, hydralazine, and nitroglycerine have been used to attenuate these hemodynamic responses with varying degrees of success".[4] Hemodynamic reactions have been mitigated through the use of different combinations of dosages of beta blockers, calcium channel blockers, as well as opioids such as fentanyl, alfentanil, and remifentanil.[5,6] Modifications of instruments (use of different types of laryngoscope blades) and supraglottic intubating devices (e.g. laryngeal mask airway) have also been attempted to alter these hemodynamic responses[7] . So far, there is no agreement on the most effective approach to eliminate or reduce these reflex hemodynamic changes.

In the recent decade, there has been a focus on a newer group of drugs such as dexmedetomidine and clonidine which is α-2 adrenergic agonists. A reduction in sympathetic outflow from the central nervous system as a result of clonidine's stimulation of α_{2A} subtype of α_2 adrenergic receptors in the brainstem lowers arterial pressure by influencing peripheral resistance and cardiac output.[8] The analgesic, sedative, and anxiolytic properties of Clonidine may improve the process of inducing, maintaining, and recovering from anesthesia. "It also tends to attenuate the hemodynamic response to surgical nociceptive stimuli and improve overall peri anesthetic cardiovascular stability" [6].

Thus, this study aimed specifically assess the efficacy of clonidine infusion as a premedication for attenuating hemodynamic responses to laryngoscopy and endotracheal intubation in hypertensive patients.

2. Methods

This randomized, prospective, controlled study was conducted after obtaining approval from the Institutional Ethics Committee. Sixty patients with American Society of Anesthesiologists (ASA) physical status II and III, known hypertensive patients aged between 20 and 70 years, of either sex, undergoing elective surgical procedures, and requiring general anesthesia (GA) and orotracheal intubation, were included in the study. Patients were advised to continue the morning dose of antihypertensive medication on the day of surgery at 6:30 a.m. with a sip of water. The baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressures (MAP) were recorded. The Patients were then randomly divided into two groups of 30 patients each. The patients belonging to the clonidine group (C group, n=30) received IV clonidine (4 μg kg^{-1}) diluted in 50 ml normal saline over 15 min using syringe pump at rate of 200 ml/hr and those in the control group (group NS, n=30) were given 50 ml normal saline as a placebo in the same manner. The sedation score of each patient was recorded before induction, 15 min after completion of infusion, and after the operation as follows:

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Score 0: Awake and alert
Score 1: Minimally sedated with appropriate response to verbal commands.
Score 2: Moderately sedated, easily arousable with tactile stimulation.
Score 3: Unarousable
Score 4: Intensely sedated and can only be awakened by a painful stimulus .

The patients were then administered GA for both groups in accordance with a standardized protocol that comprised intravenous injections of nalbuphine (0.3 mg kg-1) for analgesia.. Induction was performed with IV injection of propofol at a rate of 40 mg/10 s until the eye lash reflex was lost. Propofol dose required for induction was recorded for each patient. Endotracheal intubation was facilitated by the injection of succinylcholine (2 mg kg^{-1}). Laryngoscopy and intubation were performed 1 min later. Patients requiring >20 seconds of intubation were excluded from the study. HR, SBP, DBP, and MAP were observed in both groups and were recorded as basal (before premedication: T_0), before induction(T_1), during laryngoscopy (T_2), and at specific timings following intubation: immediately after intubation (T_3), and at 1(T_4), 2(T_5), 3(T_6), 5(T_7), and 10(T_8) minutes after intubation. No surgical stimuli were provided during the study period. Monitoring included ECG, SpO_2 and $EtCO_2$.

Based on the intraoperative characteristics, the anaesthesia was kept at 33% oxygen in nitrous oxide and 0.5-1.5% isoflurane, with muscle relaxation being provided by injection vecuronium (0.06 mg kg^{-1}) bolus followed by 0.015 mg kg^{-1}intermittently for continued neuromuscular blockade. Supplementary analgesia was administered intravenously with an injection of diclofenac sodium (1 mg kg^{-1}) and paracetamol infusion (15 mg kg^{-1} based on the intraoperative parameters and recorded. Hypotension (SBP < 90 mmHg) was treated with a 6 mg bolus dose of Mephentermine sulfate. Bradycardia (HR < 50 beats/min) was treated with an injection of atropine (0.6 mg). An IV injection of neostigmine (0.05 mg kg-1) and glycopyrrolate (0.01 mg kg-1) was administered to reverse the residual neuromuscular block. Patients were extubated when all extubation criteria were fulfilled and were transferred to the post anesthesia care unit (PACU). In the PACU, Patients were watched closely for any indications of problems or unfavorable occurrences, such as nausea, vomiting, sedation, and respiratory depression etc. for four hours. The sedation scores were recorded in the PACU. The study has been presented with a tabular representation of the results, accompanied by a statistical analysis. A P-value of 0.05 is regarded as being on the threshold of statistical significance. If the p-value was < 0.01, the results were considered statistically significant, and p < 0.001 was considered statistically highly significant.

3. Results

Patient demographic data are presented in Table 1. The mean age of both groups was comparable. In the NS group, there were 76.7% female patients compared to 23.3% male patients. Nonetheless, the majority of participants in the study group (63.3%) were men, and the remaining individuals (36.7%) were women. Thus, gender difference was obvious.

Table 1: Age wise distribution of study subjects

Age in years	Group C (n=30)		Group NS (n=30)		Total (n=60)	
	No.	%	No.	%	No.	%
Upto 40 years	6	20.0	6	20.0	12	20.0
41-60 years	14	46.7	18	60.0	32	53.3
>60 years	10	33.3	6	20.0	16	26.7

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Table 2 : Comparison of Mean age between both groups

Gender	Group C (n=30)		Group NS (n=30)		P value
	No.	%	No.	%	
Male	19	63.3	7	23.3	
Female	11	36.7	23	76.7	<0.01

A comparison of HR at different time intervals is shown in Table 3. There was a significant decrease in HR in group C immediately before induction (T_1), immediately after intubation (T_3), and from 2 to 10 min after intubation. Comparisons of SBP, DBP, and MAP at different time intervals are presented in Tables 3, 4, and 5, respectively. There was a significant decrease in SBP just before induction and all readings after 1 min in group C compared with group NS. Although there was a greater fall in SBP during laryngoscopy and immediately after intubation in group C than in group NS, it was not clinically significant. There was a highly significant decrease in DBP immediately before induction in group C ($P < 0.001$). A clinically significant decrease in DBP was also observed after 2 and 10 min in group C. At other time intervals, the falls were not clinically significant. Likewise, MAP was significantly lower just before induction, and at 1–10 min in group C cases. However, there was no statistically significant difference between Group NS and Group C for MAP at T_2 and T_3 [$P = 0.1$ & 0.18, respectively], although all readings were higher in the NS group.

Table 3 –Comparison of heart rate between both groups at different intervals

Heart rate	Group C (n=30)	Group NS (n=30)	P value
Basal (before premedication) (T_0)	86.87±13.31	79.23±8.92	0.01
Before induction (T_1)	76.03±20.39	91.13±12.22	<0.01
During Laryngoscopy (T_2)	90.47±21.10	101.67±11.92	0.01
Immediately after intubation(T_3)	98.17±15.55	107.50±8.62	<0.01
At 1 minute (T_4)	91.80±13.93	97.90±10.88	0.06
At 2 minutes (T_5)	84.57±11.77	92.90±9.39	<0.01
At 3 minutes(T_6)	80.07±12.06	88.47±8.78	<0.01
At 5 minutes (T_7)	75.90±12.18	83.93±8.06	<0.01
At 10 minutes (T_8)	73.03±12.08	80.37±8.10	<0.01

Table 4 –Comparison of systolic blood pressure between both groups at different intervals

SBP (mm Hg)	Group C (n=30)	Group NS (n=30)	P value
Basal (before premedication) (T_0)	142.67±12.18	135.47±11.77	0.02
Before induction(T_1)	117.60±15.31	144.57±11.29	<0.01

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During Laryngoscopy(T_2)	144.13±20.88	151.77±14.74	0.10
Immediately after intubation(T_3)	149.30±11.61	158.13±14.35	0.01
At 1 minute(T_4)	140.10±10.66	148.80±10.06	<0.01
At 2 minutes(T_5)	129.37±10.20	140.57±11.10	<0.001
At 3 minutes(T_6)	122.47±10.07	132.57±9.80	<0.001
At 5 minutes(T_7)	114.10±7.42	126.33±11.24	<0.001
At 10 minutes(T_8)	105.30±10.10	118.63±12.23	<0.001

Table 5 –Comparison of diastolic blood pressure at different intervals between both groups

DBP (mm Hg)	**Group C (n=30)**	**Group NS (n=30)**	**P value**
Basal (before premedication)(T_0)	88.30±9.24	83.13±10.21	0.04
Before induction(T_1)	75.30±12.94	88.43±9.41	<0.001
During laryngoscopy(T_2)	89.47±11.62	92.47±9.52	0.27
Immediately after intubation(T_3)	91.47±9.86	96.03±7.43	0.04
At 1 minute(T_4)	85.47±8.50	90.50±7.01	0.01
At 2 minutes(T_5)	78.20±7.37	83.87±6.01	<0.01
At 3 minutes(T_6)	76.40±6.73	80.50±7.39	0.02
At 5 minutes(T_7)	74.10±8.12	77.40±8.00	0.12
At 10 minutes(T_8)	67.93±8.96	75.83±8.42	<0.01

Table 6 – Comparison of mean arterial pressure which was measured at various intervals for both groups

MAP (mm Hg)	**Group C (n=30)**	**Group NS (n=30)**	**P value**
Basal (before premedication)(T_0)	106.27±9.82	100.53±9.49	0.02
Before induction(T_1)	88.93±12.58	107.37±9.70	<0.001
During laryngoscopy(T_2)	106.70±12.77	111.80±11.08	0.10
Immediately after intubation(T_3)	110.53±9.13	114.67±14.05	0.18
At 1 minute(T_4)	103.47±8.20	109.93±6.79	<0.01
At 2 minutes(T_5)	95.10±7.62	102.87±6.79	<0.001
At 3 minutes(T_6)	91.07±7.80	97.50±7.63	<0.01
At 5 minutes(T_7)	87.10±7.44	93.57±7.89	<0.01
At 10 minutes(T_8)	79.94±8.50	89.93±9.61	<0.001

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A comparison of the sedation scores in both groups is shown in Table 7. The sedation score after 15 min of infusion and post-operative was significantly higher in Group C than in Group NS ($P < 0.001$). Figure 1 shows the comparison of propofol requirements between the two groups. The mean ± SD propofol dose needed for induction was significantly higher ($P < 0.001$) in the Group NS (137.0 ± 12.08) than in Group C (89.67 ± 12.73). A comparison of side effects in both groups is shown in figure 2. In this study, four 4 (13.33%) patients had hypotension in Group C, and two (6.67%) patients had hypotension in Group NS. One patient (3.33%) in Group C and none in Group NS had bradycardia. However, the side effects were not statistically significant.

Table7: comparison of sedation score in both the groups pre and post-operatively

	Group C (n=30)		Group NS (n=30)		P value
	No.	%	No.	%	
Preop-sedation score					
0	14	46.7	30	100.0	<0.001
1	15	50.0	0	0.0	
2	1	3.3	0	0.0	
Postop sedation score					
0	0	0.0	13	43.3	<0.001
1	16	53.3	17	56.7	
2	14	46.7	0	0.0	

Figure.1: Comparison of requirement of propofol dose between both groups

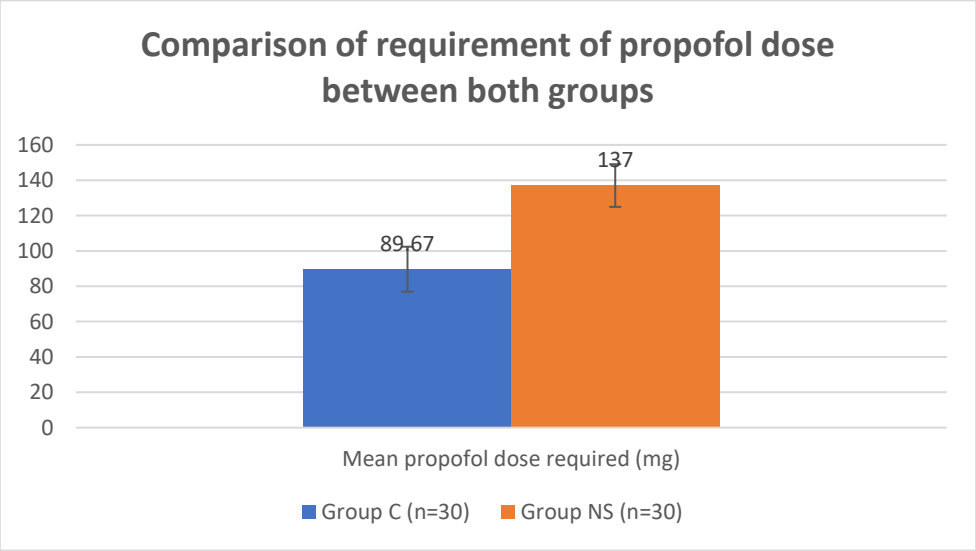

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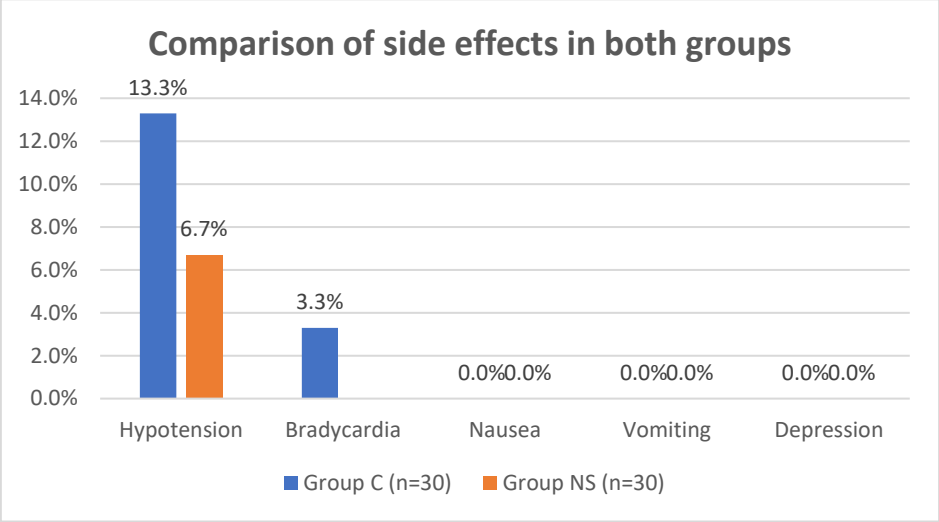
Figure 2: Comparison of side effects in both groups



4. Discussion

The key outcome of the research was that the administration of 4 µg kg-1 clonidine through preoperative infusion had a considerable impact in patients with hypertension in reducing the hemodynamic responses to laryngoscopy and intubation. It also provides hemodynamic stability, owing to its central sympatholytic action. This study also indicated that clonidine has the distinct advantage of decreasing anxiety and causing mild to moderate arousable sedation, apart from the minimal insignificant incidence of post-operative complications. It also acts as an adjuvant to decrease the propofol induction dose. Previous studies have shown that clonidine reduces the need for anesthesia [10,12]. α-2 adrenergic agonists produce noradrenergic neuron hyperpolarization, thus suppressing neuronal firing. This leads to attenuation of sympathoadrenal responses and hemodynamic stability [9]. α-2 adrenergic agonists are also effective in preventing cardiac complications [6].

Madhusudan et al. (2016) have shown that dexmedetomidine and clonidine are effective in reducing the increase in heart rate and blood pressure during laryngoscopy and intubation. In addition, they have been shown to decrease the requirements for thiopentone and morphine during surgery [10]. The sensitivity of the cardiac baroreceptor reflex was also increased by clonidine treatment. The sensitivity to systolic blood pressure is increased in the presence of clonidine; thus, it also plays a role in stabilizing BP. Owing to the long half-life of clonidine, the use of this particular drug is restricted [11], but this aspect can be helpful in the post-operative care of hypertensive patients.

"Similar to the findings of our study, Altan et al. reported that clonidine at a dose of 3 µg kg^{-1} significantly decreased the HR by 10 beats/min in the study group" [12].

Acharya and Routray (2017) evaluated the efficacy of clonidine in normotensive patients. "The results of This study showed that IV clonidine at a dose of 3µg kg^{-1} body weight effectively attenuates the hemodynamic response to laryngoscopy and intubation without any side effects" [2]. We used a _4µg kg^{-1} dose, as we were dealing with patients with hypertension. A previous study also showed that at this particular dose, clonidine is more effective in blunting catecholamine release during intubation [15].

Zalunardo et al. showed an increase in MAP of 37 mmHg in the control group compared with 5 mmHg in the study group [11]. The present study also reported a greater increase in MAP in the control group than that in the study group. However, in both groups, MAP started decreasing after 3-4 minutes.

Nayak et al. (2016) studied the effect of IV clonidine premedication on perioperative hemodynamic responses in patients undergoing laparoscopic cholecystectomy. They concluded that

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premedication with IV clonidine 1.5 μg kg^{-1} body weight) offers steady hemodynamics. It also prevents stress responses activated by pneumoperitoneum in laparoscopic cholecystectomy patients, and thus can be advocated as a routine premedication [11].

Ray et al. showed that clonidine at a dose of 3 μg kg^{-1} could effectively stabilize HR [14]. "Similarly, another study that compared the efficacy of clonidine and fentanyl showed that clonidine was better at attenuating the sympathetic response during endotracheal intubation" [5].

A study by Matot et al. showed that clonidine premedication at a dose of approximately 4–4.5 μg kg^{-1} can blunt the hemodynamic response in patients undergoing elective bronchoscopic and/or micro laryngeal surgical procedures. Alterations in arterial blood pressure were significantly higher in patients who received placebo. The SBP increased from 137 ± 11 mmHg to 166 ± 17 mmHg in the control group, and the DBP increased from 80 ± 11 mmHg to 97 ± 14 mmHg compared with the clonidine group, where a better hemodynamic response was noted [15]. Previous studies have shown that clonidine effectively improves cardiovascular stability. "Moreover, it also exerts a positive effect on cardiac oxygen delivery, and thus may prove beneficial for patients" [15-17].

Studies have shown that α2 agonists are usually associated with side effects, such as bradycardia [18] and hypotension [19]. In the current study, bradycardia and hypotension were similar in both groups and statistically insignificant. "Moreover, these side effects are easily managed using routine measures. In order to provide a bloodless surgical field during middle ear and nasal surgery, IV clonidine premedication at a dose of 4 μg kg^{-1} has been utilised safely and successfully" [20]. This can be an additional benefit, especially in patients with hypertension.

Our study had some limitations, such as the heterogeneity of patients in terms of sex distribution, age range, baseline hemodynamic variables, anxiety scale, and duration and type of surgery. The concentration of catecholamines was not measured in this study, which could provide more accurate results regarding the sympathetic attenuation of clonidine. This study was conducted in a limited number of patients, and a large cohort study would be beneficial for the implementation of the study findings.

5. Conclusion

Clonidine infusion as a premedication in hypertensive patients not only helps attenuate the sympathetic responses to intubation and laryngoscopy, but also reduces the induction dose of propofol. Minimal post-operative sedation can be considered another advantage as patients can be easily aroused. The lack of serious side effects was another distinct finding. Hence, it can be incorporated as a routine premedication in hypertensive patients owing to its sympatholytic, anxiolytic, sedative, and analgesic properties. However, further studies are required to establish its effect on post-operative analgesia and additional analgesic requirements with respect to the duration of surgery.

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Conflict of interest: None

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