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Original Article

Anaesthesia Section

Comparison of Oral Pregabalin and Clonidine Premedication in Attenuating Pressor Response to Laryngoscopy and Intubation: A Prospective Interventional Study

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ABSTRACT

Introduction: Laryngoscopy and intubation during the induction of general anaesthesia can lead to sympathetic system-mediated haemodynamic pressor response, which, if exaggerated, may lead to hazardous complications like myocardial ischaemia, arrhythmias, and cerebral haemorrhage. Although several pharmacological and technical methods are available to attenuate this stress response, the search for an ideal agent continues.

Aim: To compare the effects of orally administered clonidine and pregabalin in attenuating the haemodynamic pressor response to airway instrumentation during the administration of general anaesthesia.

Materials and Methods: The present prospective interventional study was conducted between June 2020 and July 2021 at Government Medical College, Kozhikode, Kerala, India. A total of 176 American Society of Anaesthesiologists (ASA) Physical Status I patients aged between 18 and 65 years were included. Patients were categorised into two groups: Group P received oral pregabalin 150 mg and Group C received oral clonidine 200 mcg, 60 minutes before the induction of GA. Haemodynamic parameters {Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP)} and Ramsay sedation scores were recorded at predefined intervals. Statistical analysis was performed using International Business Machine (IBM) Statistical Packages of Social Sciences (SPSS) software, with data expressed as mean±Standard Deviation (SD). Differences between groups were assessed using the Chi-square test, independent samples t-test, and Mann-Whitney U test, with a p-value of <0.05 considered statistically significant.

Results: Demographic variables and baseline parameters were comparable between the groups. A statistically significant reduction in HR was observed in the clonidine group compared to the pregabalin group ($p<0.05$) at multiple time intervals post-drug administration. SBP, DBP, and MAP values showed reductions in both groups, with no significant intergroup differences ($p>0.05$). A higher incidence of bradycardia and hypotension was noted in the clonidine group ($p<0.05$). Sedation scores, compared using the Mann-Whitney U test, revealed significantly higher sedation in the pregabalin group at one hour after drug administration and 15 minutes after extubation.

Conclusion: Both clonidine 200 mcg and pregabalin 150 mg, when administered orally one hour before the induction of anaesthesia, are effective in attenuating the haemodynamic pressor response. Clonidine is superior to pregabalin in reducing tachycardia; however, clonidine carries a higher risk of bradycardia and hypotension, whereas pregabalin results in greater postoperative sedation.

Keywords: Alpha-2 agonists, Gabapentinoids, General anaesthesia, Haemodynamic response, Ramsay sedation score, Sympathetic stimulation

INTRODUCTION

Direct laryngoscopy and intubation during the induction of general anaesthesia can lead to a haemodynamic pressor response due to the intense noxious stimuli ascending via the vagal and glossopharyngeal afferents. This results in reflex autonomic activation, manifested in the form of tachycardia and hypertension in adults. This response is mediated through the cardioaccelerator fibres and the sympathetic chain ganglia [1]. Plasma concentrations of catecholamines increase, which can precipitate arrhythmias, myocardial ischaemia, and cerebral haemorrhage. This response peaks immediately following intubation and lasts for 5 to 10 minutes. Many technical and pharmacological methods have been evaluated and are currently in practice, either in premedication or during induction, to attenuate this response. These methods include airway blocks, deepening the anaesthesia, and premedication using vasodilators, beta blockers, alpha agonists, calcium channel blockers, topical or intravenous (i.v.) lignocaine, and opioids [2-8]. Each of these methods has its own adverse effects, prompting the search for an ideal agent that can effectively suppress both the rise in heart rate and blood pressure with minimal adverse effects.

Clonidine is a centrally acting alpha-2 adrenergic agonist. It is well absorbed when administered orally, with a bioavailability of 70-80%. Clonidine has several applications in anaesthesia practice. It exhibits analgesic properties and reduces opioid requirements. Additionally, it decreases the volume of gastric contents, reduces postoperative nausea and vomiting, shortens induction time, improves haemodynamic stability, prevents postoperative shivering, and may reduce blood loss [9-12].

Pregabalin, a gabapentinoid compound, produces inhibitory modulation of neuronal excitability, particularly in the neocortex, amygdala, and hippocampus of the Central Nervous System (CNS). Gabapentinoids act via the alpha-2-delta subunit of presynaptic calcium channels, resulting in the modulation of the release of excitatory neurotransmitters from activated nociceptors, thus inhibiting pain transmission. Pregabalin possesses analgesic, anticonvulsant, and anxiolytic activities by reducing the neurotransmitters glutamate, noradrenaline, serotonin, dopamine, and substance P. It has been used as premedication to alleviate anxiety, achieve perioperative sedation, provide haemodynamic stability, and offer postoperative analgesia. Furthermore, it displays opioid-sparing properties [13-15].

Pregabalin and clonidine have been extensively studied for postoperative analgesia [16-21] as well as their effects on the stress response [22-26]. A few studies are available that compare their use as oral premedication for the attenuation of the pressor response [27-30]. In the present study, authors compared the effects of oral clonidine and pregabalin in attenuating the haemodynamic response during intubation. Given that both drugs exhibit desirable properties such as analgesia, anxiolysis, and good oral bioavailability, a comparative study assessing their ability to suppress the pressor response with minimal complications would be helpful in identifying an optimal oral premedication prior to the induction of general anaesthesia.

MATERIALS AND METHODS

This prospective interventional study was conducted between June 2020 and July 2021 at Government Medical College, Kozhikode, Kerala, India. Ethical clearance was obtained from the Institutional Ethical Committee (approval number GMCKKD/RP2020/IEC/369).

Sample size calculation: Sample size calculation was performed using the formula:

$$n=(Z\alpha/2+Z\beta)^2\times SD^2\times 2/d^2$$

Here, Zα/2 is the critical value of normal distribution for a confidence interval of 95%, its numerical value is 1.96. Zβ is the critical value of normal distribution at β. The power of the study was set at 80% and Zβ is 0.84. SD is the mean of all the SDs of MAP, calculated from the study by Chandra A et al., [27]. It was 11.86. In the formula, d represents the effect size, it was fixed as 5 mmHg of MAP. Substituting the values in the formula, sample size was calculated as $n=(1.96+0.84)^2\times 11.86^2\times 2/5^2=88.2$, rounded off and taken as 88 in each group.

Inclusion criteria: A total of 176 ASA PS I (American Society of Anaesthesiologists Physical Status) patients aged between 18 and 65 years, who were scheduled for elective general surgical procedures with a duration of three hours or less under General Anaesthesia (GA), were included in the study.

Exclusion criteria: Patients with an anticipated difficult airway, those weighing 100 kg or more, those who were pregnant or lactating, individuals who had previously taken clonidine or pregabalin, and those with a known allergy to any of the drugs used were excluded from the study.

Study Procedure

All patients were assessed by a detailed pre-anaesthetic check-up and were counselled about the study. Informed written consent was obtained from the participants in their native language. All patients were kept Nil Per Os (NPO) for eight hours for solid foods and two hours for clear fluids before surgery. They received ranitidine 150 mg and metoclopramide 10 mg orally on the night before the surgery and on the morning of the surgery, as well as alprazolam 0.25 mg on the night before.

On the day of the surgery, patients were brought to the premedication room, where baseline HR, SBP, DBP, and MAP were recorded. The preoperative level of sedation was assessed using the Ramsay sedation scale.

A total 88 patients were assigned to the Pregabalin group (Group P) and 88 to the Clonidine group (Group C) using consecutive sampling, alternating the allocation of patients to either group. Patients in Group P received oral pregabalin 150 mg, while those in Group C received oral clonidine 200 mcg as premedication 60 minutes before induction, accompanied by a sip of water.

The HR, SBP, DBP, and MAP were measured and recorded 30 minutes after drug intake. In the operating room, after attaching monitors that included electrocardiogram, pulse oximetry, and non-invasive blood pressure measurement, an 18G intravenous (i.v.) cannula was secured, and normal saline i.v. infusion was started at a rate of 6 to 8 mL per kg per hour. Each patient was administered midazolam 0.02 mg/kg, ondansetron 0.08 mg/kg, and morphine 0.1 mg/kg intravenously.

Anaesthesia was induced with intravenous injection of propofol at a dose of 2 mg/kg. For muscle relaxation, succinylcholine was administered intravenously at a dose of 2 mg/kg, and the patient was mask ventilated. After one minute, laryngoscopy and intubation were performed by the most experienced anaesthesiologist available in the operating room.

Female patients were intubated with an endotracheal tube of 7.5 mm Internal Diameter (ID), while male patients received a tube of 8.5 mm ID. Anaesthesia was maintained with a mixture of 66% nitrous oxide in oxygen and isoflurane. All patients were given intravenous paracetamol at a dose of 15 mg/kg after intubation. Muscle relaxation was continued using vecuronium at 0.02 mg/kg i.v.

The HR, SBP, DBP and MAP were monitored throughout the procedure and recorded at specific time points, as detailed below, for the purposes of the study. Patients were also monitored for any complications like hypotension, hypertension, tachycardia, bradycardia, arrhythmias, hypercapnia, and bronchospasm. If hypotension (defined as MAP <30% from baseline) occurred, it was recorded and managed by increasing the i.v. infusion rate and administering vasopressors. Bradycardia (HR <50 beats/min), if present, was managed with intravenous atropine at a dose of 0.02 mg/kg.

Upon completion of the surgery, throat suctioning was performed, and isoflurane was discontinued. When the patient regained spontaneous ventilation, residual muscle relaxation was reversed with intravenous neostigmine at a dose of 0.05 mg/kg and glycopyrrolate at 0.01 mg/kg. The train-of-four monitoring was not performed. Extubation was carried out once adequate reversal was achieved, regular respiration was established, appropriate muscle tone was regained, and the patient was awake. The patient was then transferred to the recovery room.

The haemodynamic parameters were recorded at different predefined intervals as follows:

- T1: Before administering the test drug (baseline recordings)
- T2: 30 minutes after administering the test drug
- T3: Before induction (60 minutes after administering the drug)
- T4: Immediately after induction
- T5: 1 minute after intubation
- T6: 5 minutes after intubation
- T7: 10 minutes after intubation

Pre- and postoperative sedation scoring was conducted using the Ramsay sedation scale at T2 and 15 minutes after extubation.

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel and analysed using IBM SPSS software version 28. Qualitative data were analysed using proportions and the Chi-square test. Quantitative data were analysed using means, Standard Devaition (SD) and the Independent samples t-test. Sedation scores were compared using the Mann-Whitney U test.

RESULTS

Both groups were comparable in terms of demographic variables such as age and weight (p>0.05). All patients were classified as ASA physical status class I. The study included a higher proportion of female patients (64.8%), with comparable gender distribution in both groups. The mean duration of surgery was also comparable in both groups [Table/Fig-1]. There was no statistically significant difference in the time taken for intubation between the clonidine and pregabalin groups, with a p-value of 0.07. Most patients in the study group had a Mallampati (MP) Class II airway (54%) [Table/Fig-2]. The two groups exhibited similar ease of intubation, as evidenced by

comparable Mallampati class and time taken for intubation [Table/Fig-1,2]. Both groups were comparable with respect to the type of surgery undergone by the study subjects [Table/Fig-3]. All surgeries lasted less than three hours.

Variables	Clonidine group	Pregabalin group	t value	p-value
Age (years)	44.89±13.342	46.64±11.844	0.920	0.359
Weight (kg)	58.15±9.269	58.06±8.429	0.068	0.946
Number of females	56 (63.6%)	58 (65.9%)		0.875
Number of males	32 (36.4%)	30 (34.1%)		
Time taken for intubation (seconds)	17.44±2.154	18.23±3.463	1.803	0.073
Duration of surgery (hours)	113.01±15	117.44±16.383	1.818	0.071

[Table/Fig-1]: Age, weight, gender distribution, time taken for intubation and the duration of surgery (compared using Chi-square test of independence).

MP class*	Group		Total
	Clonidine	Pregabalin	
MP class 1	33 (37.5%)	33 (37.5%)	66 (37.5%)
MP class 2	47 (53.4%)	48 (54.5%)	95 (54.0%)
MP class 3	8 (9.1%)	7 (8.0%)	15 (8.5%)
Total	88 (100%)	88 (100%)	176 (100%)

[Table/Fig-2]: Mallampati class of study group *Mallampati airway classification.

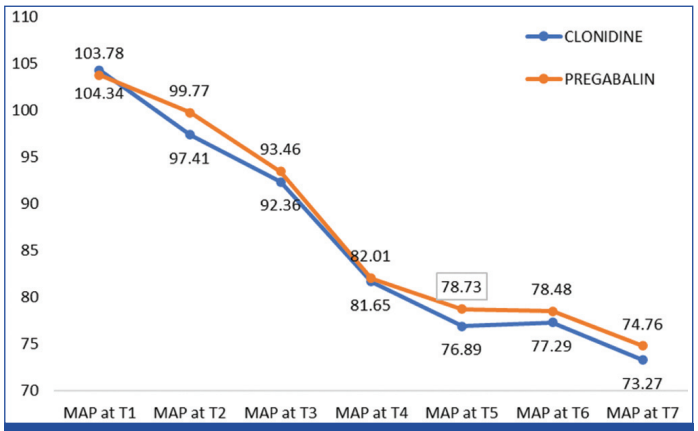
Type of surgery	Group		Total
	Clonidine	Pregabalin	
Laparoscopic appendicectomy	12 (13.6%)	11 (12.5%)	23 (13.1%)
Laparoscopic cholecystectomy	5 (5.7%)	6 (6.8%)	11 (6.3%)
Laparoscopic hernia repair	7 (8.0%)	5 (5.7%)	12 (6.8%)
MRM	32 (36.4%)	35 (39.8%)	67 (38.1%)
Superficial parotidectomy	8 (9.1%)	8 (9.1%)	16 (9.1%)
Total thyroidectomy	24 (27.3%)	23 (26.1%)	47 (26.7%)
Total	88 (100%)	88 (100%)	176 (100%)

[Table/Fig-3]: Comparison of the types of surgeries.

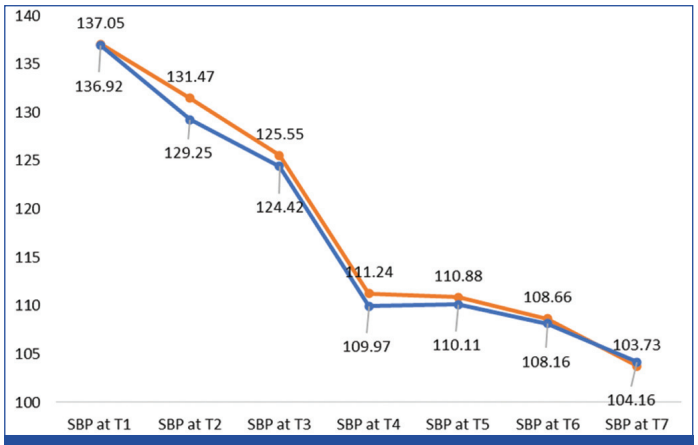
Mean baseline values of HR, MAP, SBP, and DBP were comparable in both groups, with a p-value of 0.125. In this study, authors observed that in the clonidine group, after the administration of oral clonidine, the mean HR was reduced from the baseline value after 30 minutes, after one hour, and after induction. One minute after intubation, the mean HR increased slightly, but then dropped again after five minutes and ten minutes. The pregabalin group displayed a similar trend in HR. The data indicated that both clonidine and pregabalin were effective in attenuating the tachycardia response to intubation.

The clonidine group exhibited lower HRs at all intervals compared to the pregabalin group [Table/Fig-4]. The two groups were compared using the independent samples t-test, and the p-value was found to be <0.05 for the time points T3 (p=0.021), T4 (p=0.001), T5 (p=0.001), T6 (p=0.001), and T7 (p=0.001). Thus, authors concluded that there was a statistically significant difference in the attenuation of HR between the groups, indicating that clonidine attenuates the HR response more effectively than pregabalin.

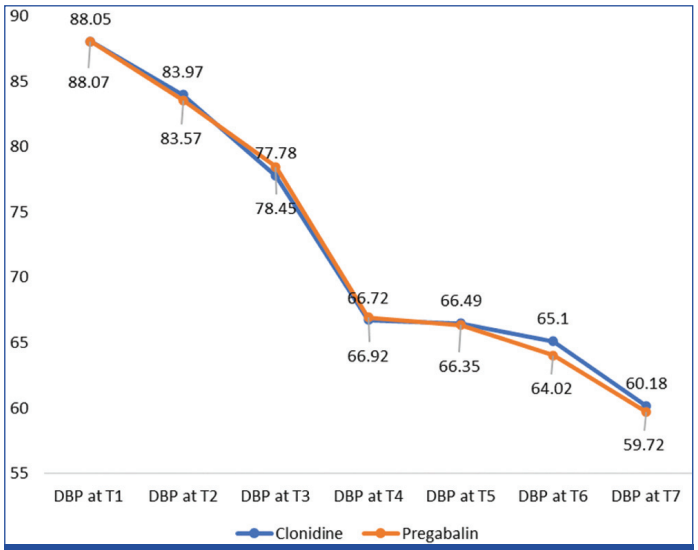
It was also observed in present study that the MAPs of both the clonidine and pregabalin groups were reduced from baseline values after premedication and at all time points. The data indicated that both clonidine and pregabalin caused blunting of the hypertensive response expected due to intubation [Table/Fig-5]. Comparing the groups, although lower mean MAP values were obtained in the clonidine group, the difference was not statistically significant, with p-values >0.05 at all monitored time points. Both SBP and DBP values were comparable to the trends observed in MAP [Table/Fig-6,7]. Clonidine was found to have



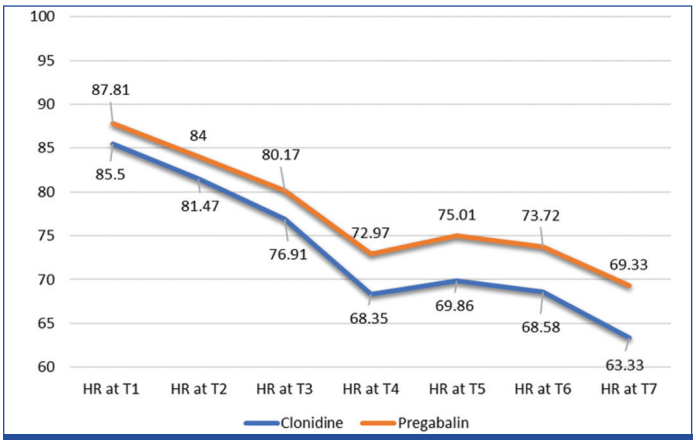
[Table/Fig-5]: Comparison of mean MAP.



[Table/Fig-6]: Comparison of mean SBP.



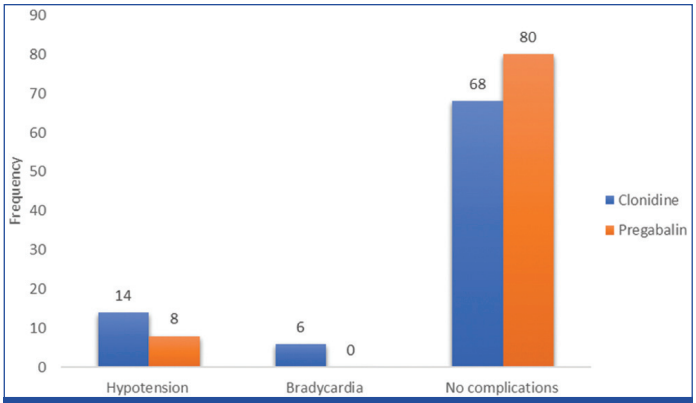
[Table/Fig-7]: Comparison of mean DBP.



[Table/Fig-4]: Comparison of Mean Heart Rate (HR).

lower SBP and DBP after one hour of drug administration, but this was not statistically significant compared to the pregabalin group. This indicates that both clonidine and pregabalin had almost similar effects in attenuating the hypertensive response to intubation.

No complications were observed during the intraoperative period in the majority of cases (84.1%). A higher incidence of complications was observed in the clonidine group, with hypotension (MAP <30% baseline) occurring in 15.9% of patients and bradycardia (HR <50/min) in 6.8%. Only 9.1% of the pregabalin group experienced hypotension [Table/Fig-8]. No incidence of bradycardia was observed in the pregabalin group. The Chi-square test was conducted to compare the incidence of complications between the two groups, yielding a p-value of 0.014. Therefore, it can be concluded that the clonidine group was associated with a significantly higher incidence of hypotension and bradycardia.



[Table/Fig-8]: Comparison of complications.

The baseline sedation scores of both groups were comparable. Higher sedation scores were observed in the pregabalin group just before induction and 15 minutes after extubation [Table/Fig-9]. When compared using the Mann-Whitney U-test, this difference was found to be statistically significant.

Time point	Group	Ramsay sedation score				U statistic	p-value
		1	2	3	4		
Baseline	Clonidine	53 (60.2%)	35 (39.8%)	0	0	3916.0	0.879
	Pregabalin	54 (61.4%)	34 (38.6%)	0	0		
Before induction	Clonidine	16 (18.2%)	72 (81.8%)	0	0	3432.0	0.023
	Pregabalin	6 (6.8%)	82 (93.2%)	0	0		
After extubation	Clonidine	2 (2.3%)	69 (78.4%)	17 (19.3%)	0	1238.5	<0.0001
	Pregabalin	0	12 (13.6%)	73 (82.9%)	3 (3.4%)		

[Table/Fig-9]: Comparison of Ramsay sedation scores.

DISCUSSION

It is important to address the haemodynamic pressor response to direct laryngoscopy and intubation during the induction of GA, as it can lead to several serious consequences. In present study, authors compared the effects of oral clonidine and oral pregabalin in minimising this stress response.

The present study observed that both clonidine and pregabalin are effective in suppressing the tachycardic response to laryngoscopy and intubation. Clonidine demonstrated a significantly greater potential for lowering the HR at multiple time points compared to pregabalin. This can be explained by the fact that clonidine, as an alpha-2 agonist, decreases sympathetic outflow from the CNS, resulting in reduced HR, peripheral vascular resistance and blood pressure [31]. In a similar study, Parveen S et al., compared the effects of oral clonidine (300 mcg) and oral pregabalin (150 mcg) as premedication, observing that both clonidine and pregabalin were effective in blunting the pressor response. Here, clonidine was found to be superior to pregabalin in reducing SBP, DBP, MAP and HR responses [28]. This may be because of the higher dose of clonidine. When two different doses of pregabalin were compared by Rastogi B et al., 150 mg of the drug resulted in a significant decrease in MAP compared to 75 mg; however, there was no significant decrease in HR [32]. Similar results were obtained in a prospective randomised controlled study conducted by Kaur H et al., which compared 200 mcg of clonidine and 150 mg of pregabalin [33]. Thengumgal RG et al., also conducted a similar study using 200 mcg of clonidine and 150 mg of pregabalin, yielding comparable results: clonidine significantly outperformed pregabalin in decreasing HR, MAP, SBP, and DBP [30]. However, in present study, a significant difference was observed only in the HR component.

Prathibha H et al., compared clonidine (300 mcg) and pregabalin (150 mg) orally and measured the Rate Pressure Product (RPP) in addition to HR, SBP, DBP, and MAP. RPP, calculated as HR × SBP, is an indirect measurement of Myocardial Oxygen Consumption (MVO_2). They noted a significant attenuation of RPP in the clonidine group compared to the pregabalin group following intubation [29].

In present study, the clonidine group had a comparatively higher incidence of hypotension and bradycardia. A significantly higher incidence of bradycardia was noted in the clonidine group by Chandra A et al., in a study comparing 200 mcg of clonidine and 150 mg of pregabalin [27].

Sedation scores were significantly higher in the pregabalin group in present study. A similar observation was made by Chandra A et al., and Kaur H et al., [27,33]. Anxiety scoring was performed by Kaur H et al., and significantly lower anxiety scores were associated with pregabalin at 60 and 90 minutes after premedication [33]. Gupta K et al., observed a decrease in anxiety in those premedicated with clonidine (200 mcg) and pregabalin (150 mg) compared to the placebo group, where pregabalin demonstrated a better reduction in anxiety [34]. However, in present study, authors did not document anxiety scoring.

Limitation(s)

The study was non randomised, introducing a potential risk of selection bias. It was not blinded, which may have led to observational or assessment bias. The study was conducted at a single centre, limiting the generalisability of the findings. Only American Society of Anaesthesiologists (ASA) Physical Status I patients were included, excluding those with co-morbidities or higher perioperative risk. Future multicentre, randomised controlled trials involving patients across a broader range of ASA classifications are recommended to validate and expand upon these findings.

CONCLUSION(S)

Both oral clonidine (200 mcg) and pregabalin (150 mg), when used as premedication, were effective in attenuating the haemodynamic pressor response to laryngoscopy and endotracheal intubation. Clonidine demonstrated superior efficacy in blunting the HR response compared to pregabalin, with statistically significant lower HRs at multiple time points. However, the attenuation of MAP, SBP, and DBP was comparable between the two groups. Clonidine was associated with a higher incidence of intraoperative hypotension and bradycardia, suggesting a greater need for haemodynamic monitoring and caution. Pregabalin, on the other hand, provided stable haemodynamics but resulted in increased sedation before induction and after extubation. Based on the findings of present study, both drugs are viable options for blunting the pressor response to intubation.

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