Original Research

COMPARATIVE EVALUATION OF ORAL MELATONIN AND ORAL PREGABALIN AS PREMEDICATION FOR PREOPERATIVE ANXIETY AND ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND TRACHEAL INTUBATION: A PROSPECTIVE RANDOMISED STUDY

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ABSTRACT

Introduction: Preoperative anxiety is a common concern among surgical patients and is associated with adverse perioperative outcomes, including exaggerated hemodynamic responses during laryngoscopy and tracheal intubation. Pharmacological premedication plays a key role in alleviating anxiety and maintaining hemodynamic stability. Melatonin, a neurohormone with anxiolytic and sedative properties, and pregabalin, a GABA analogue with anxiolytic and analgesic effects, have been increasingly studied for this purpose. This study aimed to compare the efficacy of oral melatonin and oral pregabalin in reducing preoperative anxiety and attenuating hemodynamic responses to laryngoscopy and intubation.

Material and Methods: This prospective, randomized, double-blind controlled study included 60 patients (ASA I–III) aged 30–60 years undergoing elective surgery. Patients were randomly allocated into two groups of 30 each: Group M received oral melatonin 6 mg, and Group P received oral pregabalin 75 mg, one hour before induction. Preoperative anxiety was assessed using the APAIS scale. Hemodynamic parameters (HR, SBP, DBP, MAP) were recorded at baseline, during intubation, and at 1, 5, and 10 minutes post-intubation. Data were analyzed using appropriate statistical tests with $p<0.05$ considered significant.

Results: Both groups were comparable in demographic characteristics. Melatonin showed significantly better attenuation of hemodynamic responses compared to pregabalin, with lower HR, SBP, DBP, and MAP immediately, and at 1 and 5 minutes post-intubation ($p<0.05$). Anxiety scores decreased significantly in both groups after premedication, with a greater reduction observed in the melatonin group ($p=0.002$). Oxygen saturation and $EtCO_2$ remained comparable between groups. No significant adverse effects were noted.

Conclusion: Both melatonin and pregabalin are effective premedicants for reducing preoperative anxiety and attenuating hemodynamic responses. However, melatonin demonstrated superior efficacy in maintaining hemodynamic stability and reducing anxiety, making it a preferable option for preoperative medication.

Keywords: Melatonin, Pregabalin, Preoperative Anxiety, Hemodynamic Response, Laryngoscopy and Intubation.

INTRODUCTION

Since the introduction of endotracheal anaesthesia in the late nineteenth century, endotracheal intubation has become an essential and routinely performed procedure in anaesthetic practice.

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It involves the translaryngeal placement of a tube into the trachea through the nose or mouth to secure the airway and facilitate ventilation during surgical procedures. Despite its routine nature, the procedure is associated with several physiological and psychological challenges. One of the most common concerns among patients undergoing surgery is preoperative anxiety, which affects a substantial proportion of individuals. This anxiety arises from fear of surgery, uncertainty about outcomes, and concerns regarding anaesthesia and postoperative recovery. It not only causes significant patient distress but also contributes to adverse perioperative outcomes, including increased analgesic requirements, delayed recovery, and prolonged hospital stay [1].

The management of preoperative anxiety is therefore a critical aspect of perioperative care, with pharmacological interventions playing a central role. Among the various agents available, melatonin and pregabalin have gained increasing attention due to their favourable pharmacological profiles. Melatonin, a neurohormone secreted by the pineal gland, regulates circadian rhythms and exhibits sedative and anxiolytic properties. Its ability to induce natural sleep without significant side effects makes it an attractive option for premedication. Pregabalin, a structural analogue of gamma-aminobutyric acid (GABA), acts by inhibiting voltage-gated calcium channels, thereby reducing the release of excitatory neurotransmitters. It possesses anxiolytic, analgesic, and anticonvulsant properties, which further support its use in the perioperative setting. Although both agents are effective in reducing anxiety, their comparative efficacy and safety, particularly in relation to hemodynamic stability during airway manipulation, remain areas of ongoing research [2,3].

Direct laryngoscopy and endotracheal intubation are known to provoke significant hemodynamic responses due to stimulation of the sympathetic nervous system. These procedures interfere with protective airway reflexes and trigger the release of catecholamines such as adrenaline and noradrenaline. The afferent impulses are transmitted via the glossopharyngeal (IX) and vagus (X) cranial nerves from the epiglottis and infraglottic regions to the vasomotor centre, leading to a reflex sympathetic response. This results in tachycardia, hypertension, and occasionally cardiac arrhythmias. While these changes are generally transient and well tolerated in healthy individuals, they can pose serious risks in patients with underlying cardiovascular or cerebrovascular conditions [4].

In susceptible individuals, the exaggerated sympathetic response associated with laryngoscopy and intubation may precipitate life-threatening complications such as myocardial infarction, arrhythmias, left ventricular failure, or even rupture of a pre-existing aneurysm. Therefore, attenuation of this stress response is a key objective in anaesthetic management. Various strategies, both pharmacological and non-pharmacological, have been employed to achieve this goal. Non-pharmacological approaches include gentle and skillful intubation techniques, minimizing the duration of laryngoscopy, use of alternative airway devices such as laryngeal mask airway (LMA), and regional nerve blocks like glossopharyngeal and superior laryngeal nerve blocks. These methods aim to reduce the intensity of the stimulus and thereby limit the sympathetic response [5].

Pharmacological methods, however, remain the mainstay for controlling hemodynamic fluctuations during airway manipulation. A wide range of drugs has been used for this purpose, including inhalational anaesthetic agents, intravenous and topical lidocaine, opioids, beta-blockers, calcium channel blockers, and vasodilators. These agents act through various mechanisms such as suppression of sympathetic activity, reduction of catecholamine release, and direct cardiovascular effects. Despite the availability of these options, no single agent has been found to be ideal, as each carries its own limitations and potential side effects [6,7].

In this melatonin and pregabalin offer promising alternatives due to their dual benefits of anxiolysis and potential stabilization of hemodynamic responses. Their role in attenuating the stress response to laryngoscopy and intubation is being increasingly explored. By reducing preoperative anxiety and modulating neuroendocrine responses, these agents may contribute to improved perioperative stability and patient outcomes. Further comparative studies are essential to establish their efficacy, optimal dosing, and safety profiles in different patient populations [8].

This prospective randomized study aims to address this gap in the literature by comparing the effects of oral melatonin and oral pregabalin as premedication for preoperative anxiety, focusing on their abilities to attenuate hemodynamic responses to laryngoscopy and tracheal intubation. By elucidating the comparative efficacy and safety profiles of these pharmacological agents, this study seeks to inform evidence-based practices in preoperative anxiety management and optimize patient outcomes in the perioperative period.

MATERIAL AND METHODS

This prospective observational study was conducted at the Department of Anaesthesiology, B.J. Medical College Civil Hospital, Ahmedabad from March 2024 till sample size is achieved. Ethical approval has been obtained from the Ethical Approval Committee of B.J. Medical College Civil Hospital, Ahmedabad.

Study Population

Study population included patients aged 30 to 60 years, classified as ASA grade I, II, or III, who provided informed consent and were scheduled for elective surgery. Patients were excluded if they had uncontrolled diabetes or hypertension, heart disease, severe anaemia, were on antipsychiatric medication, had an anticipated difficult airway, required more than 20 seconds or multiple attempts for intubation, or had known allergies to anaesthetic drugs used in the study.

Data Analysis

Data analysis was performed by recording all patient information in a structured study proforma. Data were expressed as mean values with standard deviation. Quantitative variables were analyzed using the t-test, while qualitative variables were assessed using the chi-square test. Statistical calculations were conducted using Microsoft Office Excel 365. Changes in hemodynamic variables from baseline and comparisons of means at different time intervals were evaluated using paired t-tests, with p-values less than 0.05 considered significant.

RESULTS

The demographic characteristics of patients in both groups were comparable. The mean age in Group M was 40.70±9.70 years, while in Group P it was 41.57±9.65 years, showing no statistically significant difference (p=0.750). Similarly, the mean weight was 59.70±8.64 kg in Group M and 57.37±6.56 kg in Group P, with no significant difference (p=0.244). Gender distribution was also similar, with males comprising 56.67% and females 43.33% in Group M, and 53.33% males and 46.67% females in Group P, indicating demographic comparability between groups.

Table 1: Comparative Changes in Heart Rate (/min)

HR	Group M		Group P		p Value
	Mean	SD	Mean	SD	
Baseline	85.90	6.17	86.10	5.82	0.898
After premedication	79.27	9.94	82.20	7.73	0.207
At the time of intubation	76.67	4.70	76.40	5.91	0.847
After intubation	71.97	4.48	75.20	3.03	0.002
1 min after intubation	72.23	3.07	77.77	8.37	0.001
5 min after intubation	71.67	3.02	75.00	5.35	0.004
10 min after intubation	75.40	5.28	75.20	6.04	0.892

Heart rate was comparable between both groups at baseline, after premedication, and at intubation (p>0.05). However, after intubation and at 1 and 5 minutes, Group M showed significantly lower heart rate than Group P (p<0.05), indicating better hemodynamic stability. By 10 minutes, heart rate differences were no longer significant, suggesting both groups eventually returned to similar levels, though Group M demonstrated superior early control of heart rate response.

Table 2: Comparative Changes in Systolic Blood Pressure (mmHg)

SBP	Group M		Group P		p Value
	Mean	SD	Mean	SD	
Baseline	123.97	9.79	125.33	10.72	0.608
After premedication	122.80	12.91	128.37	16.11	0.145
At the time of intubation	121.97	8.44	126.07	13.02	0.153
After intubation	109.50	7.15	115.07	6.15	0.002
1 min after intubation	114.33	7.27	121.13	9.19	0.002
5 min after intubation	115.43	6.54	120.47	6.19	0.003
10 min after intubation	119.43	9.10	118.27	10.23	0.643

Systolic blood pressure was comparable between both groups at baseline, after premedication, during intubation, and at 10 minutes (p>0.05). However, after intubation and at 1 and 5 minutes, Group M showed significantly lower SBP than Group P (p<0.05), indicating better control. Overall, Group M demonstrated superior attenuation of systolic blood pressure response in the immediate post-intubation period compared to Group P.

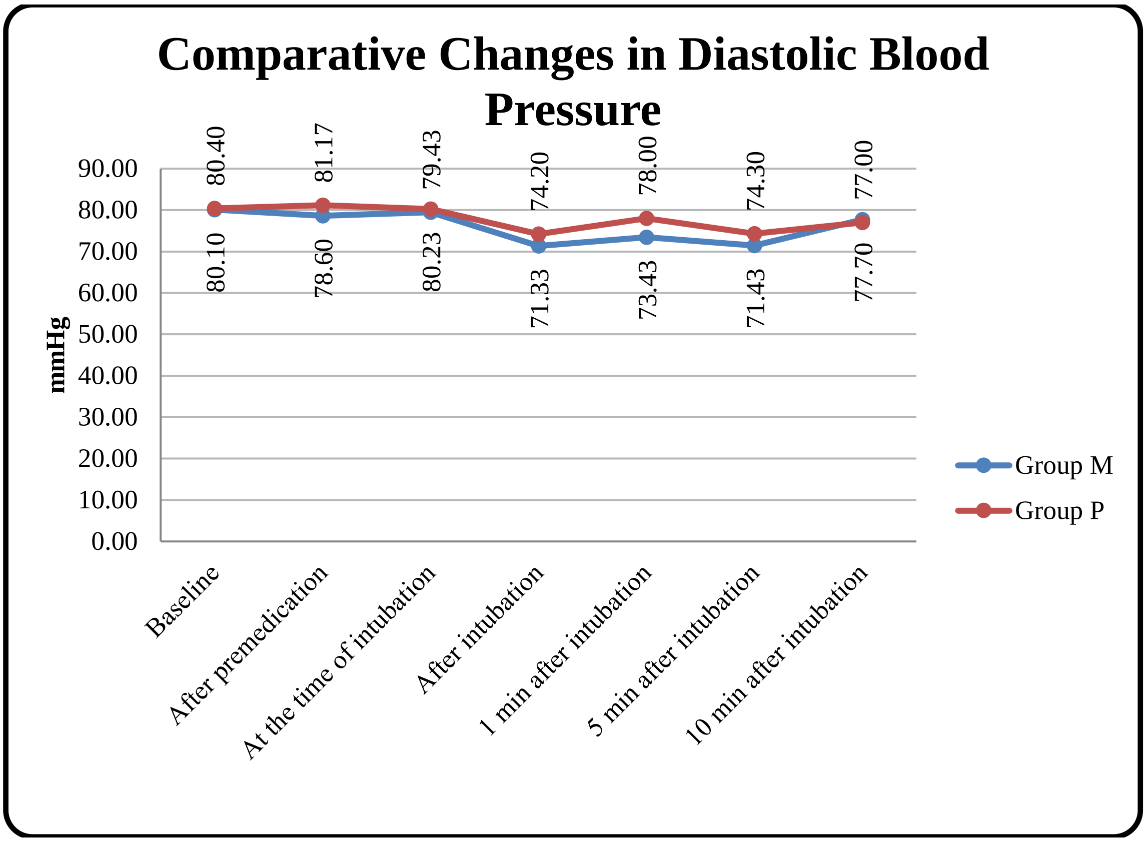

Figure 1: Comparative Changes in Diastolic Blood Pressure (mmHg)

Diastolic blood pressure was comparable between both groups at baseline, after premedication, during intubation, and at 10 minutes ($p>0.05$). However, after intubation and at 1 and 5 minutes, Group M showed significantly lower DBP than Group P ($p<0.05$), indicating better control. Overall, Group M demonstrated superior attenuation of diastolic blood pressure response in the immediate post-intubation period compared to Group P.

Table 3: Comparative Changes in Mean Arterial Pressure (mmHg)

MAP	Group M		Group P		p Value
	Mean	SD	Mean	SD	
Baseline	94.72	7.15	95.38	8.57	0.749
After premedication	93.33	8.93	96.87	11.76	0.195
At the time of intubation	93.61	6.80	95.47	9.62	0.392
After intubation	84.32	2.61	87.64	4.23	0.001
1 min after intubation	85.03	5.36	89.90	4.99	0.001
5 min after intubation	83.63	2.80	86.40	3.43	0.001
10 min after intubation	91.61	7.70	89.46	6.66	0.251

Mean arterial pressure was comparable between both groups at baseline, after premedication, during intubation, and at 10 minutes ($p>0.05$). However, after intubation and at 1 and 5 minutes, Group M showed significantly lower MAP than Group P ($p<0.05$), indicating better control. Overall, Group M demonstrated superior attenuation of mean arterial pressure response in the immediate post-intubation period compared to Group P.

Table 4: Comparative Changes in SpO2 (%)

SpO2	Group M		Group P		p Value
	Mean	SD	Mean	SD	
Baseline	98.50	0.63	98.60	0.50	0.498
After premedication	98.80	0.48	98.53	0.63	0.071

At the time of intubation	98.93	0.37	98.80	0.48	0.233
After intubation	98.97	0.18	98.63	0.49	0.001
1 min after intubation	98.63	0.49	98.67	0.48	0.791
5 min after intubation	98.60	0.50	98.97	0.18	0.000
10 min after intubation	98.63	0.49	98.60	0.56	0.808

Oxygen saturation (SpO_2) remained stable and comparable between both groups at most time intervals, with no clinically significant differences observed ($p>0.05$). Overall, both groups maintained adequate oxygenation throughout the study, indicating that neither drug adversely affected respiratory status.

Table 5: Comparative Changes in EtCO2 (cmH2O)

EtCO2	Group M		Group P		p Value
	Mean	SD	Mean	SD	
After premedication	28.67	2.25	29.03	2.30	0.535
At the time of intubation	28.53	2.19	28.90	2.17	0.518
After intubation	28.80	2.23	29.13	1.78	0.525
1 min after intubation	28.50	1.78	28.47	1.76	0.942
5 min after intubation	28.97	2.11	28.40	1.67	0.254
10 min after intubation	29.20	2.17	28.53	2.16	0.238

End-tidal CO_2 ($EtCO_2$) levels were comparable between both groups at all measured intervals, with no statistically significant differences observed ($p>0.05$). Overall, both groups maintained stable ventilation parameters throughout the study, indicating no adverse effect of either drug on respiratory function.

Table 6: Comparative Changes in Anxiety Score

Anxiety Score	Group M		Group P		p Value
	Mean	SD	Mean	SD	
1hr Before of Premedication	9.50	1.80	9.60	1.30	0.806
After Premedication	6.73	0.87	7.70	1.42	0.002

Anxiety scores were comparable between both groups before premedication ($p>0.05$), indicating similar baseline anxiety levels. After premedication, Group M showed a significantly greater reduction in anxiety score compared to Group P ($p<0.05$). Overall, Group M demonstrated more effective reduction of preoperative anxiety than Group P.

DISCUSSION

Preoperative anxiety is a frequently encountered issue among patients awaiting surgery, arising from fear of the unknown, concerns about surgical outcomes, anticipated postoperative pain, and the overall hospital experience. Its prevalence ranges widely from 11% to 80%, depending on patient characteristics and the type of surgical procedure performed. Uncontrolled anxiety not only affects psychological well-being but also contributes to physiological disturbances, including increased sympathetic activity, which may complicate perioperative management. Consequently, effective control of preoperative anxiety has become an essential component of modern anesthetic practice [9].

In recent years, a multimodal approach has been increasingly adopted for the management of preoperative anxiety, integrating both pharmacological and non-pharmacological strategies. This approach aims to address not only the physiological manifestations of anxiety but also the psychological and emotional needs of patients. Among pharmacological agents, melatonin and pregabalin have gained attention as effective premedicants. Melatonin, a naturally occurring hormone regulating circadian rhythms, possesses sedative and anxiolytic properties without the adverse effects commonly associated with traditional sedatives. Pregabalin, an anticonvulsant, exerts its anxiolytic effect by modulating calcium channels and reducing excitatory neurotransmitter release in the central nervous system. **Alles SR, et. al; 2020,** evaluated for their role in reducing anxiety and stabilizing hemodynamic responses during surgical procedures [10].

The hemodynamic response to laryngoscopy and endotracheal intubation remains a significant challenge for anesthesiologists. This response is characterized by tachycardia, hypertension, and arrhythmias, which may be detrimental, especially in patients with underlying cardiovascular conditions. The stress response occurs in two distinct phases. The first phase is associated with laryngoscopy, which produces a supraglottic stimulus leading to an increase in systolic and diastolic blood pressure primarily due to norepinephrine release, with minimal changes in heart rate. The second phase occurs during endotracheal intubation, where infraglottic stimulation results in a more pronounced cardiovascular response, including a 36–40% increase in blood pressure and over 20% rise in heart rate due to catecholamine discharge. **Sharma S, et. al; 2018,** highlighted the importance of differentiating between the effects of laryngoscopy and intubation in clinical practice [11].

In the study, demographic parameters such as age, sex, and weight were comparable between the melatonin and pregabalin groups, indicating homogeneity of the study population. Hemodynamic parameters including heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were also comparable at baseline. At induction, slight increases in these parameters were observed in the pregabalin group, while the melatonin group showed a mild but statistically insignificant rise in heart rate. Following intubation, the melatonin group demonstrated better hemodynamic stability, with heart rate and blood pressure returning toward baseline more rapidly. In contrast, the pregabalin group exhibited a significant increase in heart rate and blood pressure at 1 minute post-intubation, which gradually subsided over time. The differences between the two groups at 1 and 5 minutes post-intubation were statistically significant ($p<0.05$), indicating superior attenuation of the stress response by melatonin. Oxygen saturation levels remained stable and comparable in both groups throughout the study period [12,13].

Maqbool SF, et. al; 2019, reported that both melatonin and pregabalin effectively attenuated hemodynamic responses, although melatonin showed superior control in the early post-intubation period. **Maqbool SF, et. al; 2019,** demonstrated that melatonin was more effective than pregabalin and placebo in reducing heart rate and blood pressure during intubation. **Bhashyam S, et. al; 2015,** highlighted the efficacy of pregabalin in reducing hemodynamic responses, although comparative superiority was not emphasized [12,14].

Regarding anxiety scores, both melatonin and pregabalin significantly reduced preoperative anxiety, with melatonin demonstrating a slightly greater effect. **Samyukta Y & Vidhya N. 2020,** observed lower anxiety scores with melatonin administered one hour before surgery. **Nasr DA & Abdellatif AA. 2014,** confirmed the effectiveness of both drugs in reducing anxiety, although variations in the magnitude of effect have been reported across studies. Effective anxiety control is crucial, as elevated anxiety levels are associated with increased perioperative pain and delayed recovery [15,16].

In terms of safety, both drugs were well tolerated with minimal adverse effects observed in the present study. **Murari T, et. al; 2022,** reported higher sedation with pregabalin and bradycardia with clonidine. The absence of significant adverse effects in the current study reinforced the safety profile of both melatonin and pregabalin as premedicants [17].

Gupta P, et. al; 2016, supported the use of melatonin as a superior agent compared to pregabalin for controlling preoperative anxiety and attenuating hemodynamic responses to laryngoscopy and intubation, while maintaining a favorable safety profile [18].

CONCLUSION

Our study demonstrated that both melatonin and pregabalin are effective in reducing preoperative anxiety and maintaining hemodynamic stability, with melatonin showing a slightly greater effect, particularly in the immediate post-intubation period. Both agents significantly reduced heart rate and blood pressure at various intervals, contributing to stable intraoperative conditions. Anxiety scores decreased in both groups, with a marginally better reduction observed with melatonin. Both drugs exhibited favorable safety profiles with minimal adverse effects, rapid onset, and sustained action, facilitating smooth recovery and improved patient outcomes, with melatonin offering a slight clinical advantage.

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