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SAFETY AND SIDE-EFFECT PROFILE OF ORAL PREGABALIN AND MELATONIN PREMEDICATION FOR LARYNGOSCOPY AND INTUBATION: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Laryngoscopy and endotracheal intubation trigger sympathetic surges that can be hazardous in susceptible patients. Pregabalin and melatonin are attractive oral premedicants with potential to blunt these responses.

Objective: To compare the safety and side-effect profile of oral pregabalin (150 mg) and melatonin (6 mg) with placebo in elective surgical patients undergoing general anaesthesia.

Methods: In this randomized, parallel-group trial conducted at a tertiary centre, 90 ASA I–II adults (18–65 years) scheduled for surgeries >30 min under general anaesthesia were allocated to pregabalin 150 mg, melatonin 6 mg, or placebo, administered orally 120 min pre-induction. Standardized anaesthesia was used. Primary outcomes were haemodynamic responses (HR, SBP, DBP, MAP) at baseline, induction, and 1/3/5/10 min after intubation. Safety/side-effect profile included SpO_2 trends, postoperative pain (VAS), and sedation (Ramsay score), with adverse effects monitored. Analysis used ANOVA.

Results: Groups were comparable in demographics/ASA/Mallampati. Compared with placebo, both pregabalin and melatonin significantly attenuated HR, SBP, DBP, and MAP elevations at induction and at 1–10 min post-intubation (all $p < 0.0001$). Melatonin showed stable haemodynamics at all time points; pregabalin showed early attenuation with return toward baseline by 5–10 min. SpO_2 remained comparable across groups. VAS pain scores were lower with pregabalin and melatonin vs placebo ($p < 0.0001$). Sedation was higher with pregabalin vs melatonin/placebo ($p < 0.0001$). No clinically important adverse events were observed; sedation with pregabalin was considered acceptable.

Conclusion: Oral pregabalin (150 mg) and melatonin (6 mg) are safe and effective premedicants for blunting pressor responses to laryngoscopy and intubation; pregabalin yields greater sedation, while melatonin maintains haemodynamic stability with minimal sedative effect.

Keywords: pregabalin; melatonin; laryngoscopy; intubation; haemodynamic response; premedication.

INTRODUCTION

Preanesthetic medication remains a cornerstone of modern anaesthetic practice, intended to reduce anxiety, provide sedation, improve analgesia, and ensure haemodynamic stability during induction of anaesthesia and airway instrumentation[1]. Laryngoscopy and tracheal intubation, though essential for maintaining airway control, are potent noxious stimuli associated with sympathetic

activation, resulting in tachycardia and hypertension[2]. While these responses are generally tolerated by healthy individuals, they may precipitate complications in patients with limited cardiovascular reserve, such as those with coronary artery disease, arrhythmias, hypertension, or advanced age[3]. Numerous pharmacological strategies including β-blockers, vasodilators, opioids, lidocaine, and calcium channel blockers have been evaluated to blunt the pressor response to laryngoscopy and intubation. However, their inconsistent efficacy and risk of adverse effects such as bradycardia, hypotension, or respiratory depression limit their widespread use[4]. This has generated interest in alternative premedicants with better safety and tolerability profiles.

Pregabalin, a structural analogue of γ-aminobutyric acid (GABA), exerts anxiolytic, anticonvulsant, and analgesic effects through modulation of calcium channel activity. Its favourable pharmacokinetics, oral bioavailability, and minimal hepatic metabolism make it suitable for perioperative use, with evidence suggesting a role in attenuating haemodynamic responses to airway instrumentation[5,6]. Melatonin, an endogenous neurohormone secreted by the pineal gland, has gained recognition for its sedative, anxiolytic, and sympatholytic effects, along with its ability to preserve natural sleep patterns without impairing cognition[7,8]. Its perioperative benefits extend beyond anxiolysis to include potential attenuation of haemodynamic responses during laryngoscopy and intubation, with fewer cardiovascular adverse effects compared to agents like dexmedetomidine[9,10].

Given these properties, pregabalin and melatonin appear to be promising oral premedicants for elective surgical patients undergoing general anaesthesia. The present study was designed to compare their safety and side-effect profiles with placebo, focusing on haemodynamic stability, sedation, analgesia, and overall tolerability during laryngoscopy and intubation.

MATERIAL AND METHODS

After institutional ethics approval and written informed consent, this randomized controlled study was conducted in the Department of Anaesthesiology and Intensive Care. Inclusion criteria: ASA I–II, age 18–65 years, BMI 18–30 kg/m² or weight 45–90 kg, and surgeries >30 min under general anaesthesia. Exclusions included uncontrolled diabetes/hypertension, psychiatric illness or psychoactive/antiepileptic use, sleep disorders, obesity, drug allergy, ASA III–IV, pregnancy/lactation, coagulopathy/anticoagulants, and anticipated difficult intubation (or >1 attempt/>20 s). Participants were randomized (computer-generated) to:

Group P (n = 30): pregabalin 150 mg PO 120 min pre-induction

Group M (n = 30): melatonin 6 mg PO 120 min pre-induction

Group C (n = 30): placebo PO 120 min pre-induction

Standard pre-anaesthetic assessment was performed; all patients fasted 6 h and received night-before alprazolam 0.25 mg and pantoprazole 40 mg. Pre-OT monitoring included HR, SBP/DBP/MAP. Anaesthesia: fentanyl 1 μg/kg, propofol 2 mg/kg, rocuronium 0.6 mg/kg; maintenance with O_2/N_2O/isoflurane; reversal with neostigmine/glycopyrrolate. Post-anaesthesia care included routine monitoring and oxygen. Outcomes: HR, SBP, DBP, MAP at baseline/induction/1/3/5/10 min after intubation; SpO_2; postoperative pain (VAS 0–10); sedation (Ramsay scale). Adverse effects (e.g., vomiting, visual blurring, excessive sedation) were recorded.

RESULTS

Ninety adults were randomized equally to pregabalin 150 mg (Group P, n=30), melatonin 6 mg (Group M, n=30), or placebo (Group C, n=30). Groups were comparable at baseline for age (mean ± SD years: 42.43 ± 11.32 vs 46.06 ± 13.89 vs 40.53 ± 13.67; ANOVA F=1.39, p=0.25), sex distribution (male:female 11:19 vs 13:17 vs 14:16), ASA class (ASA I/II: 56.7%/43.3% vs 60%/40% vs 56.7%/43.3%), Mallampati grade (MPG I/II 76.7%/— vs 83.3%/— vs 80.0%/—), and surgical diagnoses. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) did not differ among groups (all p>0.05).

Following induction and during 1–10 min after intubation, between-group differences were highly significant for HR (ANOVA $p<0.0001$ at all time points), SBP ($p<0.0001$ at all time points), DBP ($p<0.0001$ at all time points), and MAP ($p<0.0001$ at all time points). Compared with placebo, melatonin consistently showed the lowest HR and BP values across time points, while pregabalin attenuated the pressor response vs placebo but to a lesser extent than melatonin.

Peripheral oxygen saturation (SpO_2) remained stable and comparable among groups at baseline, induction, and 1/3/5/10 min after intubation ($p\geq0.07$ at all time points), indicating no clinically meaningful desaturation episodes attributable to study drugs. Mean VAS pain scores were significantly lower with pregabalin and melatonin compared with placebo (3.3 ± 0.46; 3.4 ± 0.49; 4.1 ± 0.66, respectively; $p<0.0001$). Sedation (Ramsay Sedation Scale) was higher with pregabalin than with melatonin or placebo (3.63 ± 0.49 vs 1.53 ± 0.50 vs 1.50 ± 0.50; $p<0.0001$). Melatonin's sedation profile was similar to placebo.

In elective surgical patients under general anaesthesia, both pregabalin (150 mg) and melatonin (6 mg) improved peri-intubation haemodynamic stability versus placebo, with melatonin showing the greatest attenuation; oxygenation remained comparable across groups; analgesia improved with both agents; and increased sedation was observed with pregabalin but not with melatonin.

Table 1: Baseline characteristics

Characteristic	Pregabalin 150 mg (n=30)	Melatonin 6 mg (n=30)	Placebo (n=30)	P value
Age, years (mean ± SD)	42.43 ± 11.32	46.06 ± 13.89	40.53 ± 13.67	0.252
Sex: Male, n (%)	11 (36.67)	13 (43.33)	14 (46.67)	0.727
Sex: Female, n (%)	19 (63.33)	17 (56.67)	16 (53.33)	
ASA I, n (%)	17 (56.67)	18 (60.00)	17 (56.67)	0.955
ASA II, n (%)	13 (43.33)	12 (40.00)	13 (43.33)	
Mallampati I, n (%)	15 (50.00)	11 (36.67)	13 (43.33)	0.205
Mallampati II, n (%)	8 (26.67)	14 (46.67)	11 (36.67)	
Mallampati III, n (%)	7 (23.33)	2 (6.66)	5 (16.67)	
Mallampati IV, n (%)	0 (0.00)	3 (10.00)	1 (3.33)	

Table 2: Heart rate at different time intervals

Time	Pregabalin 150 mg (mean ± SD)	Melatonin 6 mg (mean ± SD)	Placebo (mean ± SD)	p-value
Baseline	82.16 ± 7.41	82.43 ± 9.26	82.00 ± 5.76	0.9758
Induction	97.80 ± 4.04	83.90 ± 10.61	87.40 ± 8.89	<0.0001
1 min	93.52 ± 5.78	79.00 ± 10.02	89.87 ± 11.65	<0.0001
3 min	87.68 ± 4.28	75.43 ± 9.05	86.57 ± 8.83	<0.0001
5 min	82.88 ± 5.91	74.03 ± 9.02	84.03 ± 8.10	<0.0001
10 min	81.52 ± 7.64	74.60 ± 8.87	83.27 ± 7.08	0.0001

Table 3: Mean Arterial Pressure across time

Time	Pregabalin 150 mg (mean ± SD)	Melatonin 6 mg (mean ± SD)	Placebo (mean ± SD)	p-value
Baseline	95.51 ± 8.60	94.27 ± 5.58	95.10 ± 4.71	0.7548
Induction	108.31 ± 3.45	93.10 ± 6.65	104.27 ± 4.49	<0.0001
1 min	104.49 ± 5.42	86.27 ± 5.97	110.33 ± 6.99	<0.0001
3 min	100.63 ± 5.37	78.97 ± 6.35	102.87 ± 4.25	<0.0001
5 min	97.09 ± 5.81	78.47 ± 5.72	100.17 ± 4.19	<0.0001
10 min	95.88 ± 4.72	78.97 ± 5.45	98.97 ± 3.91	<0.0001

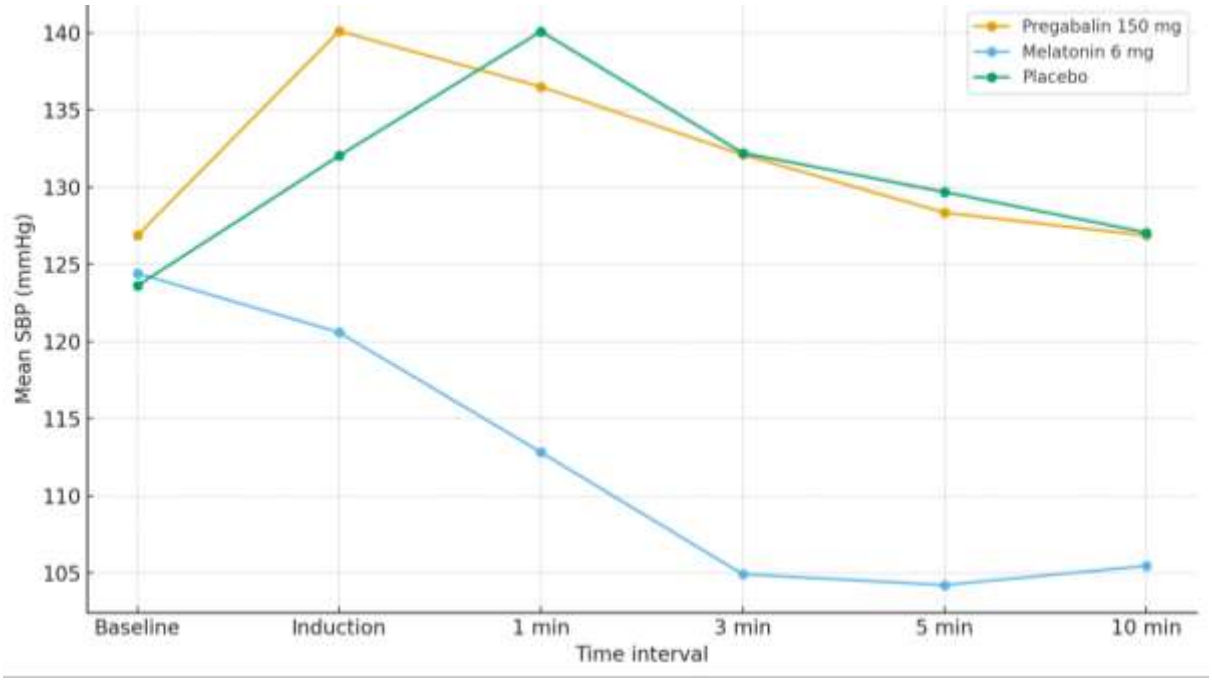

Figure 1: Systolic blood pressure (mmHg) across time

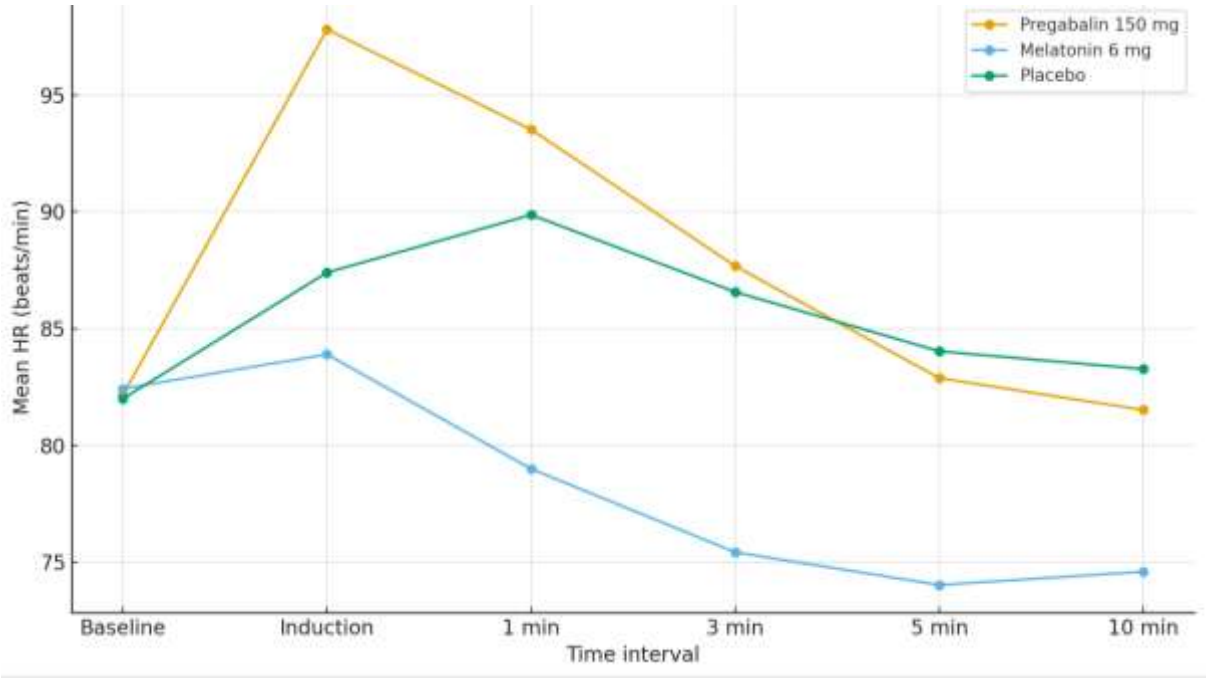

Figure 2: Heart rate (bpm) across time

DISCUSSION

The haemodynamic pressor response during laryngoscopy and intubation is common laryngoscopy elevates arterial pressure and catecholamines, and intubation increases heart rate potentially causing harmful sequelae; despite many agents, the ideal premedicant remains uncertain[11].

Baseline comparability: Groups were well matched for age (42.43 ± 11.32 vs 46.06 ± 13.89 versus 40.53 ± 13.67 years; p = 0.252), sex (male 36.7% vs 43.3% vs 46.7%; p = 0.727), ASA I/II (56.7/43.3% versus 60/40% vs 56.7/43.3%; p = 0.955) and Mallampati (I–IV distribution p=0.205). This mirrors earlier three-arm studies in which pregabalin/clonidine/placebo groups were also comparable at baseline[12,4].

Heart rate response: Baseline HR was similar (~82 bpm; p = 0.9758). At induction, HR rose to 97.80 ± 4.04 (pregabalin) vs 83.90 ± 10.61 (melatonin) vs 87.40 ± 8.89 bpm (placebo) (p<0.0001). After intubation, HR at 1 min was 93.52 ± 5.78 (pregabalin), 79.00 ± 10.02 (melatonin), 89.87 ± 11.65 bpm (placebo) (p < 0.0001); values trended toward baseline by 10 min (81.52 ± 7.64, 74.60 ± 8.87, 83.27 ± 7.08 bpm; p = 0.0001). These patterns agree with trials showing that pregabalin blunts the post-laryngoscopy rise in HR relative to placebo[12,13,4], while melatonin yields the most stable HR profile peri-intubation[14,15].

Systolic blood pressure: At induction, SBP averaged 140.12 (pregabalin), 120.60 (melatonin), and 132.05 mmHg (placebo); at 1 min, 136.52, 112.83, and 140.10 mmHg, with melatonin remaining lowest through 10 min. This replicates reports that pregabalin attenuates SBP surges versus placebo[12,4], and that melatonin (6–9 mg) reduces SBP around intubation via sympatholysis[14,15].

Mean arterial pressure: MAP was comparable at baseline (≈95 mmHg; p = 0.7548). At induction, MAP was 108.31 ± 3.45 (pregabalin), 93.10 ± 6.65 (melatonin), 104.27 ± 4.49 mmHg (placebo) (p < 0.0001). Post-intubation, MAP at 1 min: 104.49 ± 5.42 (pregabalin), 86.27 ± 5.97 (melatonin), 110.33 ± 6.99 mmHg (placebo) (p < 0.0001), with sustained between-group differences at 3/5/10 min (p < 0.0001 each). This agrees with prior data showing pregabalin 150 mg and melatonin attenuate MAP elevations compared with placebo[12,4,14,15].

Post-operative analgesia: Mean VAS scores were lower with pregabalin (3.3 ± 0.46) and melatonin (3.4 ± 0.49) than placebo (4.1 ± 0.66; p < 0.0001). This aligns with improved early analgesia seen with pregabalin 150 mg in laparoscopic surgery[16]; melatonin's analgesic/ sympatholytic effect also contributes to lower pain scores[14,15].

Sedation profile: Ramsay sedation was higher with pregabalin (3.63 ± 0.49) versus melatonin (1.53 ± 0.50) and placebo (1.50 ± 0.50; p < 0.0001), matching evidence that pregabalin increases peri-operative sedation relative to control or gabapentin[17] and vs placebo in other settings[18,19]. Melatonin's sedation approximated placebo, supporting its use when minimal sedation is preferred[14,15].

CONCLUSION

In elective adults under general anaesthesia, premedication with pregabalin 150 mg or melatonin 6 mg given 120 minutes pre-induction significantly attenuates the haemodynamic pressor response to laryngoscopy and intubation compared with placebo. Melatonin provided the most stable heart rate and blood pressure across induction and 10 minutes post-intubation with a sedation profile similar to placebo, while pregabalin also blunted the response and yielded greater sedation and better postoperative analgesia than placebo. Oxygenation remained comparable among groups and no clinically meaningful adverse events were observed. Choice of agent may therefore be individualized: melatonin when minimal sedation is preferred, and pregabalin when added sedation/anxiolysis and analgesic benefit are desirable.

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