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Original Article

Comparative Evaluation of Oral Melatonin with Midazolam as Premedication for Attenuation of Haemodynamic Responses to Laryngoscopy and Endotracheal Intubation in Adult Elective Surgery Patients Under General Anesthesia

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ABSTRACT

Background: Premedication is used to reduce anxiety, anaesthetic requirements, and hemodynamic fluctuations during laryngoscopy and intubation. Melatonin, when administered orally as premedication before induction of anaesthesia, provides adequate anxiolysis and arousable sedation without impairing cognitive or psychomotor function, along with stable hemodynamics and minimal side effects. Midazolam, a commonly used benzodiazepine, is valued for its rapid onset and short duration of action, and possesses anxiolytic, sedative, hypnotic, and amnesic properties. Comparative data between these agents remains limited.
Methods: This prospective, randomized comparative study included 130 adult patients (18–60 years) undergoing elective surgery under general anaesthesia. Patients received either oral melatonin (6mg) (n = 65) or oral midazolam (7.5mg) (n = 65) 90 minutes before induction. Hemodynamic parameters (HR, SBP, DBP, MBP), Ramsay sedation score, amnesia score, and SpO_2 were recorded at defined intervals (T1–T5).
Results: Both groups showed significant reductions in HR and BP from baseline to 9 minutes post-intubation. However, melatonin produced significantly lower HR, SBP, DBP, and MBP at key timepoints compared to midazolam ($p < 0.05$). Sedation scores were higher in the midazolam group, while amnesia scores were lower, indicating greater memory preservation with melatonin. SpO_2 remained stable across groups.
Conclusion: Oral melatonin was more effective than midazolam in attenuating hemodynamic responses to laryngoscopy and intubation, while providing adequate anxiolysis with less sedation and amnesia. These findings support melatonin as a safe and effective alternative premedication in elective surgical patients. Larger multicentre trials are warranted to confirm its role in perioperative care.

Keywords: *Melatonin, Midazolam, Premedication, Hemodynamic response, Sedation, Amnesia.*

INTRODUCTION

"No one, however phlegmatic, can contemplate the prospect of an operation without some nervousness or apprehension." – Rendell Baker

The perioperative period is inherently stressful for most patients undergoing surgery. Preoperative anxiety, often triggered by concerns about the procedure, postoperative pain, and hospitalization, can significantly impact anesthetic induction and recovery. If left unaddressed, it may lead to hemodynamic disturbances during laryngoscopy and endotracheal intubation, increased postoperative pain, agitation during emergence, and higher analgesic requirements [1].

Endotracheal intubation, though routine, is invasive and activates the sympathetic nervous system, resulting in transient hypertension and tachycardia [2,3]. These changes peak within 1–2 minutes post-intubation and may persist for up to 10 minutes. Such responses can be particularly harmful in patients with compromised cardiovascular status, including those with hypertension, cerebrovascular disease, pregnancy-induced hypertension, or poor cardiac reserve [4,5,6].

Untreated anxiety may also contribute to postoperative behavioral disturbances such as irritability, sleep disorders, appetite changes, and psychological effects that can persist for months.

To mitigate these perioperative challenges, both pharmacological and non-pharmacological interventions have been explored. While cognitive-behavioral therapy and aromatherapy offer benefits, pharmacological premedication remains more time-efficient and equally effective. It facilitates smoother induction, reduces emotional trauma, and promotes intraoperative hemodynamic stability [1].

Premedication prior to anesthesia aims to reduce anxiety and pain, stabilize hemodynamics during laryngoscopy and intubation, decrease anesthetic requirements, induce anterograde amnesia, and minimize postoperative nausea and vomiting. An ideal agent should offer sedative, anxiolytic, analgesic, and antisialagogue effects, with rapid onset, short duration, non-parenteral administration, and minimal systemic side effects [7].

Melatonin (N-acetyl-5-methoxytryptamine), an endogenous neurohormone secreted by the pineal gland, has gained attention for its anxiolytic and analgesic properties without impairing cognitive or psychomotor function. It acts via MT1 and MT2 receptors in the central nervous system, modulating circadian rhythms, vascular tone, immune responses, and neuronal activity [8].

Melatonin’s antioxidant, anti-inflammatory, sedative, and hypnotic properties have been demonstrated in both experimental and clinical settings. Its advantages include low overdose risk, high patient acceptability, and minimal residual sedation due to its short half-life. Administered orally or sublingually in doses of 3–15 mg, melatonin reaches peak effect within 60–150 minutes, making it suitable for premedication 90–120 minutes before anesthesia [9,10,11].

Benzodiazepines, particularly midazolam, are widely used for preoperative anxiolysis due to their rapid onset and short duration. Midazolam acts on GABA_A receptors to produce sedation, anxiolysis, amnesia, and muscle relaxation. However, its use is associated with adverse effects such as paradoxical reactions, oversedation, hypotension, and respiratory depression [12].

This study aims to compare the efficacy of oral melatonin and midazolam as premedication in attenuating hemodynamic responses to laryngoscopy and endotracheal intubation in adult patients undergoing elective surgery under general anesthesia. The primary objective was to evaluate and compare the hemodynamic parameters—heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure—following laryngoscopy and intubation in patients premedicated with oral melatonin versus midazolam. The secondary objective was to assess and compare the sedative effects of oral melatonin and midazolam using the Ramsay Sedation Score prior to induction, and to evaluate their impact on perioperative amnesia in adult elective surgery patients under general anaesthesia.

MATERIALS AND METHODS

This prospective, randomized, comparative study was conducted over a period of 18 months in the Department of Anaesthesiology and Intensive Care at a tertiary care centre. Prior to initiation, ethical clearance was obtained from the Institutional Ethics Committee, and written informed consent was secured from all participating patients. A total of 130 adult patients aged 18 - 60 years of either gender, scheduled for elective surgery under general anaesthesia, were enrolled.

Inclusion Criteria: Adult patients aged 18 - 60 years of either gender belonging to American Society of Anaesthesiologists (ASA) grade I or II undergoing elective surgery under general anaesthesia requiring endotracheal intubation were included in the study.

Exclusion Criteria: Patients with anticipated difficult airway, known allergy to any of the study drugs, uncontrolled hypertension, cardiac disease, diabetes mellitus, any pulmonary illness, pregnancy, renal, hepatic, neurological disease, and psychiatric disorder were excluded from the study.

Randomisation and Group Allocation: Participants were randomized using a computerized technique (RANDBETWEEN function in Excel; range 1–2). If 1 is generated, melatonin group will be allocated and if 2 is generated, midazolam group will be allocated. Once any of group got 65 samples rest of the samples will be allocated to another group to make 65 samples in that group too.

- Group 1 (Melatonin, n = 65): Received 6 mg of melatonin orally 90 minutes before induction of general anaesthesia.
- Group 2 (Midazolam n = 65): Received 7.5mg of midazolam orally 90 minutes before induction of general anaesthesia.

Preoperative Preparation

All patients underwent a detailed pre-anaesthetic evaluation and were instructed to follow standard fasting guidelines. Baseline vitals—heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO_2)—were recorded in the preoperative room. Sedation was assessed using the Ramsay Sedation Scale. To assess amnesia, patients were shown five standardized images (ball, apple, dog, aeroplane, tree).

Melatonin group: Patients received 6 mg of melatonin orally 90 minutes before induction of general anaesthesia.

Midazolam group: Patients received 7.5 mg of midazolam orally 90 minutes before induction of general anaesthesia.

Patients were shifted to the operative room. All routine monitors were attached. Inside the operative room, following parameters were recorded and compared between both the groups

a) Haemodynamic parameters (SBP, DBP, MBP, HR, SPO2) before induction, at 2, 5 and 9 minutes after endotracheal intubation
b) Sedation score using Ramsay Sedation Scale [13] before induction
c) Amnesia score before induction

Preoxygenation was performed with 100% oxygen for 3 minutes. Induction was done with inj. fentanyl (2 mcg/kg iv), inj. propofol (2 mg/kg iv), inj. Vecuronium (0.1 mg/kg iv). Patients were ventilated with oxygen and nitrous (50:50) and isoflurane for 3 minutes. Endotracheal intubation was performed using an appropriately sized cuffed tube under direct laryngoscopy. Tube placement was confirmed via capnography and bilateral auscultation. Anaesthesia was maintained with oxygen and nitrous oxide (40:60), isoflurane, vecuronium, and fentanyl. Reversal of muscle relaxant was done using inj. neostigmine (0.5 mg/kg iv) and inj. Glycopyrrolate (0.1 mg/kg iv). Patients were extubated after confirming adequate recovery from anaesthesia. Patients were shifted to post-operative room and vital parameters were monitored. Any adverse effects were noted and treated accordingly. In the post-operative room, sedation using Ramsay Sedation Score27 was compared between the two groups.

Statistical Analysis

Patient data were recorded using a pre-designed study proforma and entered into a microsoft excel spreadsheet. Descriptive statistics were used to summarize the data:

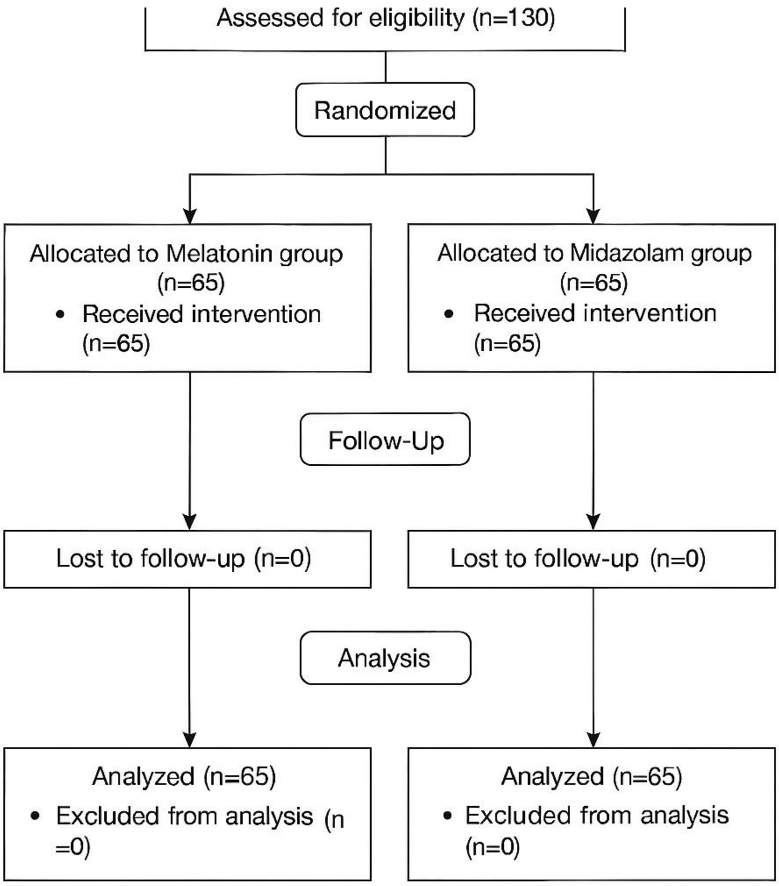
- Quantitative variables were presented as range (minimum–maximum), mean ± standard deviation (SD), or median with interquartile range (IQR), depending on data distribution.
- Qualitative variables were expressed as frequencies and percentages across both study groups.
- Comparative Analysis: Appropriate statistical tests were applied based on the type and distribution of data:

1. Between-group comparisons
   - Categorical variables: Pearson's Chi-square test or Fisher's Exact test
   - Continuous variables: Unpaired t-test for normally distributed data; Mann–Whitney U test for non-normally distributed data

2. Within-group comparisons
   - Categorical variables: McNemar test
   - Continuous variables: Paired t-test for normally distributed data; Wilcoxon Signed-Rank test for non-normally distributed data

A p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

CONSORT FLOW DIAGRAM



RESULTS

A total of 130 adult patients aged 18–60 years, classified as ASA physical status I or II, were enrolled and randomly assigned to one of two groups:

- Melatonin Group (n = 65): Received 6 mg oral melatonin 90 minutes prior to induction
- Midazolam Group (n = 65): Received 7.5 mg oral midazolam 90 minutes prior to induction

Parameters assessed heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), Oxygen saturation (SpO_2), Sedation score assessed using the Ramsay Sedation Scale and Amnesia score based on recall of pre-induction visual stimuli

Hemodynamic parameters were recorded at five distinct time intervals:

- T1: Before premedication
- T2: Before induction
- T3: 2 minutes after endotracheal intubation
- T4: 5 minutes after endotracheal intubation
- T5: 9 minutes after endotracheal intubation

Comparison of Age Between Groups

The variable Age (years) was normally distributed in both study groups, allowing for parametric comparison using the independent samples t-test. There was no statistically significant difference in age between the melatonin and midazolam groups ($t = 1.070$, $p = 0.287$). The strength of association, measured by point-biserial correlation, was 0.09, indicating little to no association between age and group allocation.

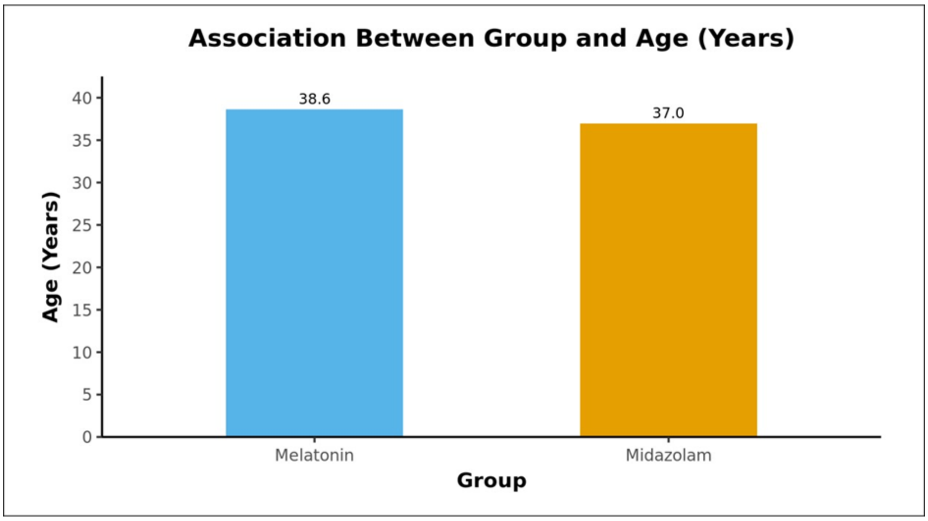


Figure 1: Bar diagram illustrates the mean age in both groups, showing comparable distributions.

🟦 Melatonin Group — Patients who received 6 mg oral melatonin (n = 65)

🟧 Midazolam Group — Patients who received 7.5 mg oral midazolam (n = 65)

Each bar represents the mean age (in years) of participants in the respective group. Error bars (if included) denote ± standard deviation.

Comparison of Gender Distribution Between Groups

The association between study group and gender was assessed using the Chi-squared test.

There was no statistically significant difference in gender distribution between the melatonin and midazolam groups (χ^2 = 0.068, p = 0.795). The strength of association, measured by Cramer's V, was 0.02, indicating little to no association between gender and group allocation.

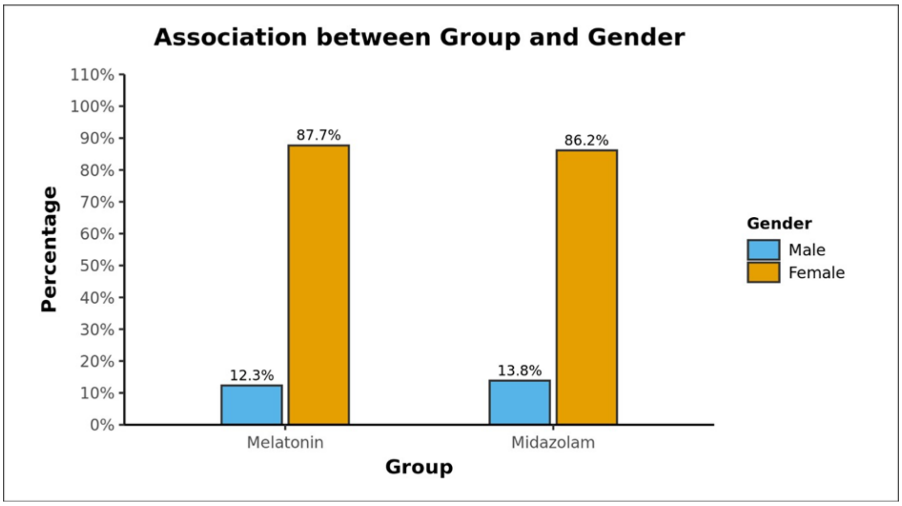


Figure 2: Bar diagram illustrates the proportional distribution of male and female participants in each group.

The bar graph above shows distribution of gender between the two groups.

12.3% of the participants in the group Melatonin were males and 87.7% were females. 13.8% of the participants in the group Midazolam were males and 86.2% were females.

Comparison of heart rate in two groups

- In Melatonin group, the mean heart rate decreased from a maximum of 87.38 at the T1 timepoint to a minimum of 65.08 at the T5 timepoint. This change was statistically significant (Friedman Test: $\chi2$ = 208.7, p = <0.001).
- In Midazolam group, the mean heart rate decreased from a maximum of 86.06 at the T1 timepoint to a minimum of 71.77 at the T5 timepoint. This change was statistically significant (Friedman Test: $\chi2$ = 128.5, p = <0.001).

The overall change in Heart Rate over time was compared in the two groups using the Generalized Estimating Equations method. There was a significant difference observed in the trend of Heart Rate over time between the two groups (p = <0.001).

There was a significant difference observed between the two groups in terms of Heart Rate at the following timepoints: T3, T4, T5. The mean Heart Rate was lower in the melatonin group at these time intervals as compared to the midazolam group. There was no significant difference between the two groups at the following timepoints: T1, T2. (Table 1)

Table 1: Comparison of the two Groups in Terms of change in Heart Rate (BPM) over time (n = 130)

Heart Rate (BPM)	Group		P value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	Melatonin	Midazolam	
	Mean (SD)	Mean (SD)	
T1	87.38 (7.96)	86.06 (10.07)	0.588
T2	82.32 (8.61)	82.55 (11.57)	0.903
T3	78.98 (8.54)	84.09 (11.91)	**0.014**
T4	72.45 (8.95)	76.34 (11.16)	**0.033**
T5	65.08 (8.71)	71.77 (11.95)	**0.001**
P Value for change in Heart Rate (BPM) over time within each group (Friedman Test)	**<0.001**	**<0.001**	
Overall P Value for comparison of change in Heart Rate (BPM) over time between the two groups (Generalized Estimating Equations)	**<0.001**		

Comparison of the two groups in terms of changes in Systolic, diastolic and Mean blood pressure.
Systolic Blood Pressure (SBP): In Melatonin group, the mean Systolic BP (SBP) decreased from a maximum of 122.17 (T1) to minimum of 95.82 (T5). This change was statistically significant (Friedman Test: $\chi 2 = 235.4$, p = <0.001).

In Midazolam group, the mean SBP decreased from a maximum of 124.65 (T1) to a minimum of 98.60 (T5). This change was statistically significant (Friedman Test: $\chi 2 = 201.2$, p = <0.001).

The overall change in SBP over time was compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of SBP over time between the two groups (p = 0.004). Significant difference observed between the two groups in terms of SBP at T2, T3 &T4. The mean SBP was lower in the melatonin group at these time intervals as compared to the midazolam group.

Table 2: Comparison of the two Groups in Terms of change in SBP (mmHg) over time

Systolic BP (mmHg)	Group		P value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	Melatonin	Midazolam	
	Mean (SD)	Mean (SD)	
T1	122.17 (9.62)	124.65 (7.87)	0.086
T2	116.23 (9.05)	122.97 (10.45)	**<0.001**
T3	108.26 (7.87)	115.35 (11.91)	**<0.001**
T4	101.54 (6.75)	106.00 (10.65)	**0.001**
T5	95.82 (6.34)	98.60 (9.29)	0.050
P Value for change in Systolic BP (mmHg) over time within each group (Friedman Test)	**<0.001**	**<0.001**	
Overall P Value for comparison of change in Systolic BP (mmHg) over time between the two groups (Generalized Estimating Equations)	**0. 004**		

Diastolic Blood Pressure (DBP): In Melatonin group, the mean DBP decreased from a maximum of 77.06 (T1) to a minimum of 60.85 (T5). This change was statistically significant (Friedman Test: $\chi2 = 227.0$, p = <0.001).

In Midazolam group, the mean DBP decreased from a maximum of 78.06 (T1) to a minimum of 62.88 (T5). This change was statistically significant (Friedman Test: $\chi2 = 133.7$, p = <0.001).

The overall change in DBP over time was compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of Diastolic BP over time between the two groups (p = 0.024). There was significant difference observed between the two groups in terms of DBP at the following timepoints: T2, T3. The mean DBP was lower in the melatonin group at these time intervals as compared to the midazolam group.

Table 3: Comparison of the two Groups in Terms of change in DBP (mmHg) over time

Diastolic BP (mmHg)	**Group**		**P value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)**
	Melatonin	**Midazolam**	
	Mean (SD)	**Mean (SD)**	
T1	77.06 (6.78)	78.06 (5.30)	0.603
T2	74.14 (5.82)	77.68 (7.25)	**0.004**
T3	69.83 (5.45)	74.55 (10.32)	**0.001**
T4	65.12 (5.73)	67.17 (9.58)	0.261
T5	60.85 (4.86)	62.88 (9.72)	0.670
P Value for change in Diastolic BP (mmHg) over time within each group (Friedman Test)	**<0.001**	**<0.001**	
Overall P Value for comparison of change in Diastolic BP (mmHg) over time between the two groups (Generalized Estimating Equations)	**0. 024**		

Mean Blood Pressure (MBP): In Melatonin group, the mean MBP decreased from a maximum of 92.11 (T1) to a minimum of 72.43 (T5). This change was statistically significant (Friedman Test: $\chi2 = 227.9$, p = <0.001). In Midazolam group, the mean MBP decreased from a maximum of 93.60 (T1) to a minimum of 75.97 (T5). This change was statistically significant (Friedman Test: $\chi2 = 148.8$, p = <0.001). The overall change in MBP over time was compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of MBP over time between the two groups (p = 0.006). There was significant difference observed between the two groups in terms of MBP at the following timepoints: T2, T3, T4. The mean MBP was lower in the melatonin group at these time intervals as compared to the midazolam group.

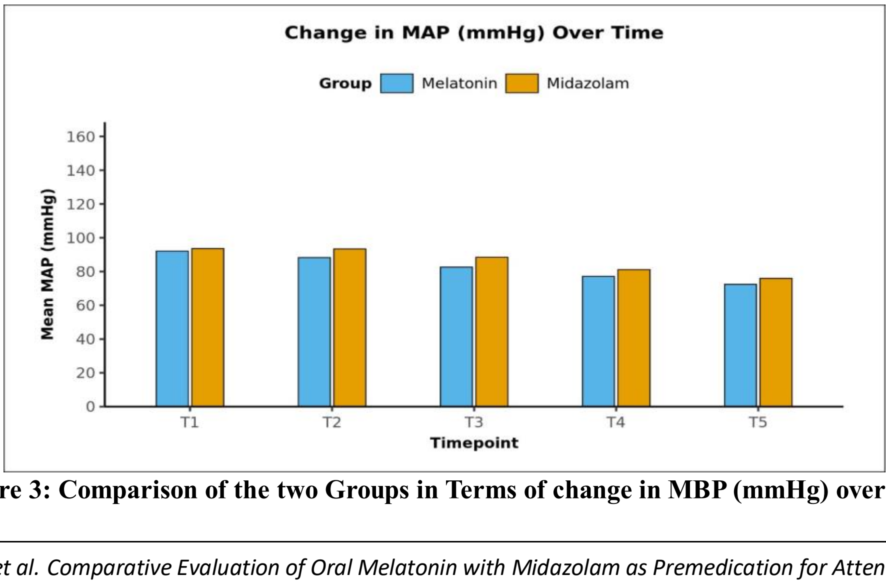


Figure 3: Comparison of the two Groups in Terms of change in MBP (mmHg) over time

Peripheral Oxygen saturation (SpO2): In Melatonin group, the mean SpO2 increased from a minimum of 99.32% at the T1 timepoint to a maximum of 100.00% at the T5 timepoint. In Midazolam group, the mean SpO2 increased from a minimum of 98.66% at the T1 timepoint to a maximum of 100.05% at the T4 timepoint, and then decreased to 99.77 at the T5 timepoint. The overall change in SpO2 over time was compared in the two groups using the Generalized Estimating Equations method. There was no significant difference in the trend of SpO2 over time between the two groups (p = 0.094).

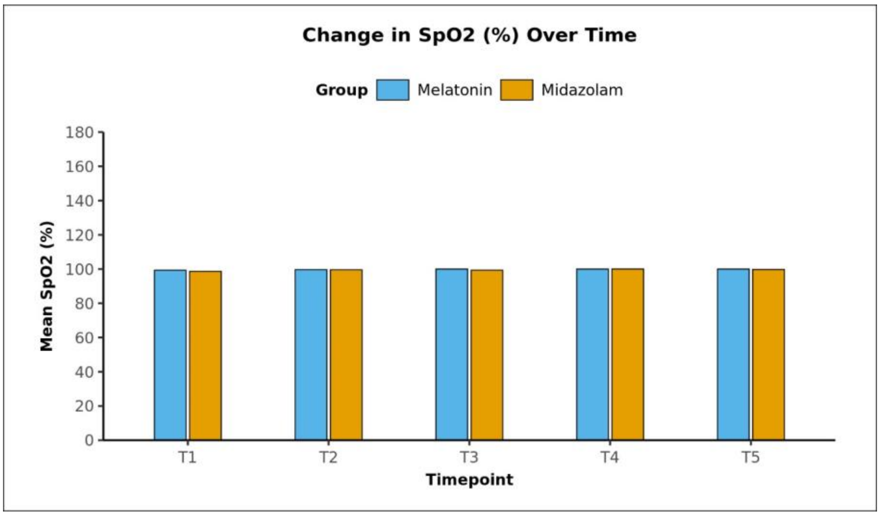


Figure 4: Comparison of the two groups in terms of change in SpO2 over time

Ramsay Sedation Score (RSS): The mean (SD) of Ramsay Sedation Score (after premedication, before induction) in Melatonin group was 1.89 (0.40) and in Midazolam group was 2.26 (0.54). This difference was statistically significant (W = 1419.500, p = <0.001). The mean RSS being highest in the midazolam group means patients of midazolam group had more sedation as compared to patients of melatonin group.

Table 4: Comparison of the two groups in Terms of Ramsay Sedation Score (90 min after premedication, before induction). (n = 130)

Ramsay Sedation Score (Before Induction)	**Gr oup**		**Wilcoxon-Mann-Whitney U Test**	
	Melatonin	**Midazolam**	**W**	**p value**
Mean (SD)	1.89 (0.40)	2.26 (0.54)	1419.500	**<0.001**

Amnesia Score: The mean (SD) of Amnesia Score after premedication and before induction in melatonin group was 4.85 (0.36) and in midazolam group was 4.54 (0.56). This was a statistically significant difference (W = 2707.500, p = <0.001). Mean Amnesia Score (number of remembered pictures) being highest in the Melatonin group means patients of melatonin group had less amnesia as compared to patients of midazolam group.

Table 5: Comparison of the two groups in Terms of Amnesia Score (90 min after premedication, before induction) (n = 130)

Amnesia Score (Before Induction)	**Group**		**Wilcoxon-Mann-Whitney U Test**	
	Melatonin	**Midazolam**	**W**	**p value**
Mean (SD)	4.85 (0.36)	4.54 (0.56)	2707.500	**<0.001**

DISCUSSION

Anxiety is an unpleasant state of fear, tension, and nervousness. In surgical patients, it often arises from concerns about disease, hospitalization, and the planned procedure, and is termed as preoperative anxiety. Common causes include prolonged fasting, waiting for surgery, fear of outcomes, separation from family, postoperative pain, and the surgery itself. If untreated, preoperative anxiety can lead to intraoperative hemodynamic disturbances, greater postoperative pain, higher analgesic requirements, and emergence agitation. It may also result in psychological and behavioural issues such as sleep disturbance and appetite changes. Both pharmacological and non-pharmacological strategies have been explored to mitigate these effects [14].

Premedication is administered to reduce anxiety, lower anaesthetic requirements, and maintain stable intraoperative hemodynamic. An ideal agent should provide anxiolysis, sedation, analgesia, and anti-sialagogue effects, with rapid onset, short duration, non-parenteral administration, and minimal systemic adverse effects. Numerous studies have evaluated its role in reducing preoperative anxiety.

This prospective, randomized comparative study included 130 patients aged 18–60 years, allocated to receive either oral melatonin (n = 65) or oral midazolam (n = 65) as premedication, administered 90 minutes before induction. The primary aim was to compare hemodynamic responses during elective surgery under general anaesthesia.

Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and SPO2 were recorded at five timepoints: T1 (before premedication), T2 (before induction), T3 (2 minutes after intubation), T4 (5 minutes after intubation), and T5 (9 minutes after intubation). Ramsay sedation score and amnesia score were assessed before premedication and 90 minutes after, just prior to induction.

Demographics:
The randomization in the present study ensured that the demographic characteristics (age, gender) were comparable in the two study groups.

Haemodynamics:
1. Heart Rate: In this study, both melatonin and midazolam produced significant reductions in heart rate from baseline (T1) to 9 minutes after intubation (T5). Between-group analysis showed significantly lower heart rates in the melatonin group at 2, 5, and 9-minutes post-intubation ($p < 0.05$), indicating better attenuation of the cardiovascular response.

Our findings are consistent with Gupta P et al. (2016) [15], who reported that heart rate remained elevated in controls after intubation but decreased rapidly in the melatonin group, concluding that melatonin effectively blunts cardiovascular reactions. Similarly, Ahmed A. Mohamed et al. (2013) [16] demonstrated that melatonin given one hour before surgery significantly reduced hemodynamic responses, with higher doses showing greater benefit. Chaudhary et al. (2020) [17] also found melatonin more effective than clonidine in reducing heart rate after intubation, without adverse effects.

Taken together, these results reinforce melatonin's role as a safe and effective premedication for attenuating hemodynamic responses to laryngoscopy and intubation. In our study, melatonin outperformed midazolam in maintaining lower heart rate trends, supporting its clinical utility in patients where cardiovascular stability is critical.

2. Blood Pressure (Systolic Blood Pressure, Diastolic Blood Pressure and Mean Blood Pressure):
In this study, both melatonin and midazolam produced significant reductions in systolic (SBP), diastolic (DBP), and mean blood pressure (MBP) from baseline (T1) to 9 minutes after intubation (T5). Between-group analysis showed significantly lower values in the melatonin group at key timepoints: SBP at pre-induction, 2 and 5 minutes; DBP at pre-induction and 2 minutes; and MBP at pre-induction, 2 and 5 minutes ($p < 0.05$).

Our findings align with Ahmed Mohamed et al. (2013), who reported significant reductions in SBP, DBP, and MBP in melatonin groups compared to controls, concluding that melatonin administered an hour before surgery attenuates hemodynamic responses to intubation. Similarly, Gupta et al. (2016) observed stable blood pressure in melatonin patients, while controls showed marked increases lasting up to 10 minutes post-intubation. In contrast, Chaudhary et al. (2020) found no differences between melatonin and clonidine groups, highlighting variability across studies.

Taken together, our results suggest that melatonin provides superior blood pressure control compared to midazolam, reinforcing its role as a safe and effective premedication for attenuating cardiovascular responses to laryngoscopy and intubation.

Peripheral Oxygen Saturation (SpO_2): SpO_2 values remained stable throughout the study, with no significant differences observed within groups or between the melatonin and midazolam groups at any timepoint.

Sedation Score: In this study, sedation was assessed using the Ramsay Sedation Scale before premedication and 90 minutes after administration. Baseline scores were comparable between groups ($p = 0.728$). After premedication, sedation was significantly higher in the midazolam group compared to the melatonin group ($p < 0.001$), indicating stronger sedative effects with midazolam.

Our findings are consistent with Naguib et al. (1998) [18], who reported greater sedation with midazolam compared to melatonin and placebo, and with Lonescu et al. (2008), who observed higher postoperative sedation in midazolam patients while melatonin provided better recovery and anxiolysis. Similarly, Patel et al. (2015) [19] found sedation scores higher in both melatonin and midazolam groups versus placebo, but midazolam produced deeper sedation and impaired psychomotor function, whereas melatonin preserved orientation. Taken together, these results suggest that while midazolam induces stronger sedation, melatonin provides adequate anxiolysis with a more favorable recovery profile, making it a safer alternative for day-care and ambulatory surgeries**.**

Amnesia Score: Amnesia was assessed using picture recall before and 90 minutes after premedication. Baseline scores were comparable, but prior to induction the melatonin group recalled more pictures than the midazolam group ($p < 0.001$), indicating that melatonin produced less amnesia.

Our findings are consistent with Naguib et al. (1998), who reported higher amnesia incidence with midazolam compared to melatonin, and with Lonescu et al. (2008) [20], who found recall consistently better in melatonin patients. These studies support the conclusion that melatonin, while providing effective anxiolysis, preserves memory function better than midazolam, making it advantageous for day-care and ambulatory surgeries where rapid recovery and cognitive integrity are important.

Limitations of the Study

• This was a single-center, hospital-based study, limiting the generalizability of results.

• Although randomization ensured comparable baseline characteristics, operator blinding was not possible, which may introduce bias.

Strengths of the Study

1. This is among the few studies in India directly comparing oral melatonin and midazolam for attenuation of hemodynamic responses (SBP, DBP, MBP, HR) and for sedation and amnesia scores in adult elective surgery patients under general anaesthesia. It provides a foundation for larger multicentred trials.
2. Many of our findings corroborate previous international and Indian studies, thereby strengthening the existing evidence base on melatonin and midazolam as premedication agents.
3. The study offers a practical evaluation across diverse age groups and genders in a real-world hospital setting, giving a fair representation of the efficacy of both drugs in routine clinical practice.

CONCLUSION

In this study of adult patients undergoing elective surgery under general anaesthesia, oral melatonin was better than oral midazolam in attenuating hemodynamic responses (HR, SBP, DBP, MBP) to laryngoscopy and endotracheal intubation. While sedation scores were higher with midazolam, melatonin was associated with less amnesia, indicating better preservation of memory function. Overall, melatonin emerges as a safe and effective alternative to midazolam for premedication in elective surgical patients. Given the single-center design and modest sample size, these findings should be interpreted cautiously. Larger multicenter trials are warranted to validate melatonin’s role in perioperative care and to further explore its advantages in diverse patient populations.

REFERENCES

1. Madsen BK, Zetner D, Møller AM, Rosenberg J. Melatonin for preoperative and postoperative anxiety in adults. Cochrane Database Syst Rev. 2020 Dec 8;12(12):CD009861
2. Channaiah VB, Chary K, VLK JL, Wang Y, Chnadra SBC. Low dose fentanyl: Hemodynamic response to endotracheal intubation in normotensive patients. Arch Med Sci. 2008;4:293-9.
3. Gropper MA, Miller RD. Miller‘s Anaesthesia. 9th edition. Philadelphia: Elsevier; 2015.
4. Koti VR, Cheuri SB, Pulla S, Varunchander G. Attenuation of haemodynamic response to intubation with oral clonidine and oral atenolol. Indian J Clin Anaesth. 2016;3:251-56.
5. Singh H, Vichitivejpaisail P, Gaines GY, White PF. Comparative effects of lidocaine, esmolol, and nitroglycerin in modifying the hemodynamic response to laryngoscopy and intubation. J Clin Anesth. 1995;7:5-8.
6. Chester A Ray. Melatonin attenuates the sympathetic nerve responses to orthostatic stress in humans. J Physiol. 2003;551:1043-8.
7. Yazdi B, Mombeini M, Modir H, Kamali A. Comparison the Oral Premedication of Midazolam, Dexmedetomidine, and Melatonin for Children's Sedation and Ease of Separation from Parents before Anesthesia. J Pediatr Neurosci. 2020 JulSep;15(3):231-237.
8. Shchetinin E, Baturin V, Arushanyan E, Bolatchiev A, Bobryshev D. Potential and Possible Therapeutic Effects of Melatonin on SARS-CoV-2 Infection. Antioxidants (Basel). 2022 Jan 9;11(1):140.

9. Laflı Tunay D, Türkeün Ilgınel M, Ünlügenç H, Tunay M, Karacaer F, Biricik E. Comparison of the effects of preoperative melatonin or vitamin C administration on postoperative analgesia. Bosn J Basic Med Sci. 2020 Feb 5;20(1):117-124.
10. Faghihian R, Eshghi A, Faghihian H, Kaviani N. Comparison of Oral Melatonin and Midazolam as Premedication in Children Undergoing General Anesthesia for Dental Treatment. Anesth Pain Med. 2018 Apr 16;8(2):e64236.
11. Khare A, Thada B, Jain N, Singh D, Singh M, Sethi SK. Comparison of Effects of Oral Melatonin with Oral Alprazolam used as a Premedicant in Adult Patients Undergoing Various Surgical Procedures under General Anesthesia: A Prospective Randomized Placebo-Controlled Study. Anesth Essays Res. 2018 Jul-Sep;12(3):657662.
12. Cox, R.G., Nemish, U., Ewen, A. *et al.* Evidence-based clinical update: Does premedication with oral midazolam lead to improved behavioural outcomes in children? *Can J Anesth* **53,** 1213–1219 (2006)
13. Rasheed A, Amirah M, Abdallah M, Parameaswari PJ, Issa M, Alharthy A. RAMSAY Sedation Scale and Richmond Agitation Sedation Scale (RASS): A Cross Sectional Study. J Sci Health. 2018;12:1-5.
14. Wang R, Huang X, Wang Y, Akbari M. Non-pharmacologic Approaches in Preoperative Anxiety, a Comprehensive Review. Front Public Health. 2022 Apr 11;10:854673.
15. Gupta P, Jethava D, Choudhary R, Jethava DD. Role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation. Indian J Anaesth. 2016 Oct;60(10):712-718.
16. Mohamed AA, Atef HM, El Kassaby AM, Ismail SA, Helmy AM. Effects of melatonin premedication on the hemodynamic responses and perfusion index during laryngoscopy and endotracheal intubation. Med J Cairo Univ. 2013;81:859-67.
17. Choudhary S, Sharma S, Kumari I, Kalluraya S, Meena K, Dave T. Comparative evaluation of oral melatonin and oral clonidine for the attenuation of haemodynamic response to laryngoscopy and tracheal intubation—A prospective randomised double blind study. Indian J Anaesth. 2020;64:696-99.
18. Naguib M, Samarkand AH. Premedication with melatonin: a double-blind, placebocontrolled comparison with midazolam. Br J Anaesth. 1999; 82:875-80.
19. Patel T, Kurdi MS. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. J Anaesthesiol Clin Pharmacol. 2015;31:37-43.
20. Ionescu D, Badescu C, Ilie A, Miclutia I, Iancu C, Ion D, et al. Melatonin as premedication for laparoscopic cholecystectomy: a double-blind, placebo-controlled study. South Afr J Anaesth Analg. 2008;14:8-11.