

A Randomized Placebo-Controlled Trial Investigating the Effects of Melatonin on Hemodynamic Changes during Intubation and Laryngoscopy

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Abstract: Background: Laryngoscopy and endotracheal intubation are critical components of general anesthesia during surgical procedures. While most patients' hemodynamic responses to the stress caused by these procedures are normal, those with cardiac problems are more likely to experience hemodynamic instability during anesthetic induction and endotracheal intubation. This frequently presents as increased blood pressure and heart rate. Melatonin has been offered as a way to reduce these hemodynamic reactions.

Aims: This study attempted to explore changes in blood pressure and heart rate during endotracheal intubation in patients undergoing general anesthesia, comparing two groups: one given sublingual melatonin and the other given a sublingual placebo.

Methods: Eighty patients, designated as American Society of Anesthesiologists grade I or II and aged 20 to 45 years old, scheduled for elective surgical procedures under general anesthesia, were divided evenly into two groups: Group C (control) and Group M (melatonin). They got either an oral placebo or sublingual melatonin tablets (6 mg) 120 minutes before surgery. Hemodynamic parameters were measured before surgery, during laryngoscopy and endotracheal intubation, and at 1, 3, 5, 10, and 15 minutes afterward.

Results: During laryngoscopy and intubation, the control group experienced a significant increase in heart rate and blood pressure, which persisted for up to 10 minutes after intubation. In contrast, the melatonin group experienced a non-significant increase in heart rate during laryngoscopy and intubation, which returned to normal within 1 minute of intubation.

Conclusion: Melatonin is effective at reducing the cardiovascular reactions to endotracheal intubation and laryngoscopy.

Keywords: Laryngoscopy, intubation; sublingual melatonin, premedication, hemodynamic response.

1. Introduction:

In 1878, British surgeon William McEwen pioneered orotracheal intubation for human anesthesia using a metal tube. O'Dwyer[1] suggested employing short, curved metal tubes to treat upper airway blockage in croup and diphtheria. Elsborg[2] reported on the use of intubation for thoracic surgery in 1910, which led to its acceptance for anesthesia. During World War I, Magill and Macintosh greatly improved the use of intubation for anesthesia. PVC tubes with inflatable cuffs were first marketed in 1964, followed by high-volume, low-pressure cuffs in 1970.

Bergstrom reported the first case of long-term intubation in 1962. The ASA Task Force on the Management of the difficult airway[3][4]

Endotracheal intubation (ETI) is the preferred airway management technique for administering general anesthesia. Mechanical ventilation is used in severely ill patients to relieve airway blockage, respiratory failure, prevent aspiration, and provide airway protection. The Macintosh laryngoscope remains the standard for ETI, however, newer versions have emerged due to scientific advancements.[5][6] Limiting the hemodynamic response during laryngoscopy and intubation (L&I) is a debated topic in anesthetic research, so numerous methods and medications have been employed to reduce these stress reactions, but each one has drawbacks, therefore, there is constantly a quest for a novel treatment approach[7].

In order to determine the best time to provide oral melatonin to maintain stable vital signs during induction and intubation, we carried out a prospective, double-blind, randomized controlled clinical experiment.

We hypothesized that oral melatonin premedication would reduce the induction dose of propofol and intraoperative fentanyl consumption, as well as the hemodynamic response to intubation. Seeing how hemodynamics changed throughout laryngoscopy and intubation was the main goal of this investigation.

1.1 Complications of endotracheal intubation

Laryngoscopy and endotracheal intubation can cause a significant increase in heart rate and blood pressure[8]. This is presumably of no relevance in healthy people. Individuals with poor myocardial reserve, such as those with coronary artery disease, cardiac dysrhythmias, congestive heart failure, hypertension, cardiomyopathy, or geriatric age group, are particularly vulnerable to these situations.

Tachycardia and hypertension are among the numerous stress responses induced by laryngoscopy and intubation. These are connected with an increase in plasma adrenaline concentration following intubation.

1.2 Medications on induction:

1. For quick sequence intubation, Etomidate is the most often utilized induction drug. It is a sedative that is not a barbiturate and works by activating gamma-aminobutyric acid (GABA) receptors to decrease central nervous system activity.
2. Ketamine exhibits analgesic, sympathomimetic, and amnestic effects. Its bronchodilator characteristics are used to treat acute and severe asthma. Ketamine has a short onset of action of 1 to 2 minutes and a half-life of 5 to 15 minutes. It can create unsettling nightmares, hallucinations, and emotional distress.
3. A fast-acting benzodiazepine called midazolam facilitates endotracheal intubation by causing anxiolysis and mild amnesia.
4. When the endotracheal tube is being inserted, fentanyl can help patients feel less pain and discomfort.

5. Propofol lowers intracranial pressure and has anti-convulsive and anti-emetic effects, which help patients with status epilepticus and traumatic brain damage.

1.3 Role of melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring hormone released by the pineal gland. Several studies have examined its hypnotic, sedative, analgesic, and anxiolytic, anti-inflammatory, and antioxidant properties. Melatonin has also been shown to lower blood pressure while decreasing norepinephrine concentrations.

Some studies have shown that melatonin has analgesic, sedative, and anxiolytic properties. On the other hand, little is known about how melatonin affects the reduction of the hemodynamic response to intubation. Our goal was to determine if oral melatonin, a preanesthetic, reduces hemodynamic reactions to intubation and anesthetic needs[9]

1.4 Aim of study

Our goal was to determine if oral melatonin, a preanesthetic, reduces hemodynamic reactions to intubation and anesthetic needs.

2. Methodology:

2.1 Study design

This prospective randomized double-blind trial was carried out following informed patient permission and clearance from the Dhi-qar Health province's Ethical Committee. According to the produced list, the pre-operative nurse gave each patient either medication in a thick, opaque packet that looked similar. Neither the patient nor the researcher knew what kind of medication was being given. Furthermore, a nurse in the pre-operative area who was also not aware of the study gave the study medications. Heart rate, systolic, diastolic, and mean blood pressure readings were taken before the study drug's administration (baseline reading), 60 minutes after it was administered, right before anesthesia was induced, during laryngoscopy and intubation, immediately following laryngoscopy and intubation, and at 1, 3, 5, 10, and 15 minutes after that. The major goal was to keep systolic blood pressure within 10% of baseline levels throughout laryngoscopy and intubation. In the post-operative period, secondary outcomes were mild respiratory depression ($\text{SpO}_2 < 90\%$, respiratory rate $< 12/\text{min}$), bradycardia (heart rate $< 20\%$ of baseline), and hypotension (systolic blood pressure $< 20\%$ of baseline).

2.2 Patient selection

Inclusion criteria: Patients with ASA physical status Grade I or II, 20-45 years old, either gender, and scheduled for surgery needing general anesthesia lasting more than 40 minutes were eligible for inclusion.

Exclusion criteria: Diabetes, hypertension, psychiatric illness, use of antipsychotics, sedatives, anxiolytics, and antiepileptic medications, sleep disorders, obesity, and drug allergies were all exclusion factors. Patients who were expected to have a difficult intubation, as well as those who needed more than one attempt or more than 20 seconds for laryngoscopy, were also excluded. Females who were pregnant or nursing were also excluded.

2.3 Induction plan

Routine monitoring began upon the patient's arrival in the operating theatre, including heart rate, ECG, arterial SpO_2 , and non-invasive blood pressure (NIBP). Two puffs of 10% lignocaine were sprayed in the larynx. Prior to induction, all patients received 100% oxygen for three minutes. Intravenous propofol (2 mg/kg) was combined with preservative-free lignocaine hydrochloride to induce anesthesia.

Succinylcholine (2 mg/kg) was given intravenously to enable endotracheal intubation using a suitably sized, well-lubricated cuffed endotracheal tube by the same person each time.

Anesthesia was maintained by inhaling isoflurane (1.2 minimum alveolar concentration). Intravenous vecuronium bromide (0.06-0.08 mg/kg) was used to promote muscle relaxation. Maintenance doses were one-fourth of the first dose.

Mechanical ventilation was performed using Pressure-Controlled Ventilation Volume-Guaranteed (PCVG).

2.4 Setting of this study

It should be noted that this study, which took place in the orthopedic and general surgery theaters of the Imam Hussein teaching hospital from October 2024 to December 2024, included 80 patients. Before anything else, the patients verbally agreed to take part in the experiment, and the responsible anesthesiologist at the "Imam Hussein Teaching Hospital" assessed each patient's anesthetic risk.

2.5 Data collection & sample size

There were 80 patients, divided into two equal groups at random ($n = 40$). A computer-generated list was used for randomization. Group M (melatonin group) was given sublingual melatonin pills (5 mg) 90 minutes before surgery, while Group C (control group) was given a sublingual placebo tablet 90 minutes prior to surgery.

2.6 Statistical analysis

The statistical analysis was performed using Excel 2010 for Windows 7 and the Statistical Package for the Social Sciences (SPSS) (version 26). The percentages, averages, and standard deviations of all research components were calculated and compared to determine whether there were any significant discrepancies. The chi-square test employed an independent P-value of 0.05 to determine statistical significance. ANOVA was also used to compare heart rate, blood pressure, respiratory rate, and blood oxygen saturation levels. All data were compared to determine the effect of the injection method on the key parameters for each person in this experiment.

3. Results and Discussion

Table 1: shows that both study groups had similar age, gender distribution, weight, ASA status, and operation time.

This table simply provides an example of the average age, weight, and gender of patients, the types of procedures, the time needed for these surgeries, and the classification of patients' diseases according to the ASA classification.

<i>Table 1: Demographics</i>			
Variable	Group C	Group M	P
ASA grade (I/II)	18/22	14/16	0.606
Gender (male/female)	21/19	18/12	0.789
Type of surgery(open/laparoscopic)	23/17	22/8	0.580
Duration of surgery (min)	68.10±10.03	66.17±11.33	0.487
Age (years)	30.57±3.31	31.30±3.41	0.401
Weight (kg)	53.10±5.47	54.37±4.49	0.331

Fisher's exact test; n – Number of patients; mean $\pm$ SD – (Standard deviation); ASA – American Society of Anesthesiologists

In Table 2: We clearly notice that systolic blood pressure increased significantly during laryngoscopy and intubation in comparison to baseline values in the control group. This rise remained consistent for 10 minutes ($P < 0.0001$). In contrast, participants in the melatonin group did not experience any rise and remained steady after receiving the study medicine ($P < 0.0001$).

This indicates that the administration of melatonin is an effective and appropriate method to lessen the known adverse effects of tracheal intubation. It had a substantial, favorable effect on blood circulation by not increasing heart rate or blood pressure, indicating that melatonin can help reduce the consequences of tracheal intubation.

Table 2: SBP at various points of time (mmHg)			
Variable	Group C	Group M	P
Before drug administration	123.63±5.79	124.43±6.65	0.621
60 min after drug administration	124.80±6.30	119.10±8.36	0.004
After induction	122.13±6.27	115.77±8.12	0.001
At Laryngoscopy and intubation	132.50±5.88	120.60±9.73	<0.0001
After intubation (min)			
1	140.10±11.54	112.83±7.52	<0.0001
2	137.57±9.73	107.30±9.13	<0.0001
3	132.23±6.85	104.93±9.56	<0.0001
5	129.70±6.86	104.23±8.63	<0.0001
10	127.07±5.92	105.47±8.39	<0.0001

Unpaired *t*-test. Mea± SD – (Standard deviation).

In Table 3: We noted that during and after laryngoscopy and intubation, diastolic blood pressure (DBP) differed significantly from baseline values in the control group. The elevation was steady throughout most reading times ($P < 0.0001$). In contrast, in the melatonin group, DBP remained reasonably consistent and closer to the baseline value, indicating patients remained stable after receiving the study medicine ($P < 0.0001$).

Table 3: DBP at various points of time (mmHg)			
Variable	Group C	Group M	P
Before drug administration	80.87±4.52	79.17±6.34	0.237
60 min after drug administration	98.43±5.54	89.97±6.45	<0.0001
After induction	95.73±5.04	88.40±6.02	<0.0001
At Laryngoscopy and intubation	104.27±4.49	93.10±6.65	<0.0001
After intubation (min)			
1 min	95.53±6.00	73.00±7.35	<0.0001
2 min	92.00±3.40	68.80±7.12	<0.0001
3 min	88.27±3.78	66.03±6.14	<0.0001
5 min	85.53±3.41	65.43±6.25	<0.0001
10 min	84.87±3.43	65.67±5.76	<0.0001

Unpaired *t*- test. SD – Standard deviation

Table 4: At laryngoscopy, the control group's heart rate jumped dramatically from baseline levels, achieving statistical significance at one minute and staying high for ten minutes. The melatonin group, on the other hand, saw a slight rise in heart rate during laryngoscopy, which was not statistically significant and went back to normal in just one minute. Table 5 shows that heart rate stayed below baseline values at all-time intervals for 10 minutes following laryngoscopy and intubation ($P < 0.0001$).

Table 4: Heart Rate at various points of time (mmHg)			
POINT OF TIME	C group	M group	P value
Before drug administration	82.00±5.76	82.43±9.26	0.829
60 min after drug administration	83.93±5.90	80.57±9.85	0.115
After induction	81.37±5.73	79.13±9.97	0.293
At Laryngoscopy and intubation	87.40±8.89	83.90±10.61	0.171
After intubation (min)			
1 min	89.87±11.65	79.00±10.02	<0.0001
2 min	89.50±10.05	76.33±9.49	<0.0001
3 min	86.57±8.83	75.43±9.05	<0.0001
5 min	84.03±8.10	74.03±9.02	<0.0001
10 min	83.27±7.08	74.60±8.87	<0.0001

Unpaired *t*- test. SD – Standard deviation

Table 5: seen that following surgery, two patients in the control group were restless and disturbed, and one patient had nausea and vomiting. After surgery, one patient in the melatonin group had nausea and vomiting. As seen in Table 5, none of the patients in either group suffered from hypotension or respiratory depression. There were no dropouts among the thirty participants in either study group.

Table 5: Complications		
Variable	Group C (n=30)	Group M (n=30)
Bradycardia	0	0
Headache	0	0
Nausea/vomiting	1	1
Restlessness	2	0
Arrhythmias	0	0
Hypotension	0	0
Respiratory depression	0	0

Discussion

This study's main goal is to assess how melatonin affects the reduction of hemodynamic responses during intubation and laryngoscopy. The pineal gland produces the hormone melatonin, also called N-acetyl-5-methoxytryptamine, which controls the body's circadian rhythm. Melatonin plays a varied role in anesthesia and critical care, as discussed extensively in the literature. Melatonin, known as a "wonder drug," has a wide range of benefits in various areas, including antioxidant and neuroprotective characteristics, as well as involvement in hypnosis, anxiolysis, and analgesia[10].

It has been used in a number of medical settings, including as treating sleep problems, reducing jet lag, reducing anxiety and sedation during surgery, and improving cognitive and psychomotor abilities. Numerous studies have postulated that its central nervous system-calming effects, which aid in sedation and anxiety reduction, might also help to lessen hemodynamic reactions to intubation and laryngoscopy [11]. Rosenberg et al.'s earlier study[12] examined how perioperative melatonin affected the body's stress response after surgery, indicating that melatonin has sympatholytic qualities. This supports our findings. Exogenous melatonin usually has its maximum effect between 60 and 150 minutes after injection[13]. We expected that providing melatonin 90 minutes before laryngoscopy and intubation would improve hemodynamic stability during major procedures. Our data revealed that utilizing 5 mg of sublingual melatonin with a 90-minute administration time before induction of anesthesia resulted in patient serenity and hemodynamic stability.

We found that in the melatonin group, systolic blood pressure remained lower than baseline values at all time intervals up to 10 minutes after intubation, whereas in the control group, there was a considerable increase. Similar patterns were found for diastolic and mean blood pressure. Melatonin has been proven in studies to lower mean blood pressure in healthy individuals [14][15]. Additionally, studies on rats have shown that pinealectomy causes severe hypertension[16]. Mohammed et al.[17] investigated the effects of oral melatonin at dosages of 6 mg and 9 mg vs a placebo given one hour before surgery on the pressure response to laryngoscopy and intubation. When compared to the placebo group, both melatonin groups showed lower systolic, diastolic, and mean blood pressures, as well as a lower perfusion index.

There are several different ways that melatonin influences circulation. Because it specifically binds to melatonin receptors in blood vessels, it can interfere with the vascular response to catecholamines, which may explain its capacity to reduce blood pressure[18]. A reduction in adrenergic outflow and consequent catecholamine levels may result from this interference, which may impact both the central and peripheral autonomic systems. Furthermore, by making more nitric oxide available, melatonin may encourage the smooth muscle of the artery wall to relax [19][20]

Our study has a few drawbacks. For example, we did not look into the effects of different doses of melatonin or how they changed over time. Second, we did not assess sedation and anxiety levels or administer psychoanalytic tests in the postoperative period. Furthermore, we did not investigate extubation responses or quantify plasma norepinephrine concentration. These limitations indicate areas that require additional research and exploration in future studies.

4. Conclusion and Recommendations

The research we conducted found that the ketamine-propofol combination significantly reduced the occurrence of propofol injection discomfort, with no discernible difference between ketamine doses used. Notably, no patients in either ketamine-propofol group reported significant discomfort. Based on our findings, we recommend administering a ketamine-propofol cocktail to patients to alleviate propofol injection pain. We advise testing various ketamine doses, taking into account their cost-effectiveness and potential to improve patient comfort. Further research is needed to determine the effectiveness of various ketamine dosages in relieving Propofol injections discomfort.

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