

*Research Article***Melatonin versus pregabalin for attenuation of stress response to endotracheal intubation****Ahmed K. Mohamed, Jozef Z. Attia and Ahmed R. Ali Ahmed**

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Abstract

Introduction: Endotracheal intubation is one of the most invasive stimuli in anesthesia which can lead to detrimental effects. Hemodynamic responses to laryngoscopy and laparoscopy should be attenuated due to associated risk of myocardial ischemia or cerebral hemorrhage(1). **Aim of the work:** Aim of this study is to evaluate the effect of oral melatonin versus oral pregabalin in attenuating the hemodynamic responses to endotracheal intubation, in addition, comparing their effect on preoperative anxiety. **Patients and methods:** After approval of the university ethical committee and obtaining informed consent from all patients, this prospective, randomized, double blinded, and placebo controlled study was conducted in El-Minia University Hospital during the period from December 2018 to May 2019. A total of 90 women aged between 18 and 40 years with American Society of Anesthesiologists grade I and II patients scheduled to undergo elective laparoscopic surgery under general anesthesia with endotracheal were included in the study. Patients were randomly divided into three equal groups. 2 hours before operation, the control group (C) received vit D orally as a placebo, group (M) receive 6 mg of melatonin orally and group (P) received 150 mg of pregabalin orally. Anesthetic technique was standardized in all the 3 groups. The following variables (SBP, DBP, MAP, HR, SpO₂) were recorded just before medications (baseline), 2 hours after medications (just before induction of anesthesia), after induction (just before intubation), 1 min, 3 min, 5 min, and 10 min after intubation. Also, RASS score was recorded just before medications (baseline) and 2 hours after medications (just before induction of anesthesia). Adverse effects such as tachycardia, bradycardia, arrhythmias, hypertension, hypotension, respiratory depression, headache, nausea, vomiting, restlessness, or stridor were reported and compared among the three groups. **Results:** Hemodynamic response to endotracheal response and anxiety were the least in group M followed by group P while it was the highest in group C. **Conclusion:** oral administration of 6 mg of melatonin or 150 mg of pregabalin 2 hours before operation were effective in attenuation but not complete abolishment of the pressor response to endotracheal intubation and preoperative anxiety when compared to the control with superiority of melatonin over pregabalin in both aspects.

Key Words: Melatonin, pregabalin, stress response, anxiety, norepinephrine, premedications.**Introduction**

Endotracheal intubation is one of the most invasive stimuli in anesthesia which can lead to detrimental effects. Hemodynamic responses to laryngoscopy and laparoscopy should be attenuated due to associated risk of myocardial ischemia or cerebral hemorrhage⁽¹⁾. If no specific measures are taken to prevent hemodynamic response, HR can increase from 26% to 66%, and SBP can increase from 36% to 45%. These hemodynamic changes can be detrimental in elderly and hemodynamically compromised patients^(1,2).

Various methods and pharmacological measures have been sought in literature to control these hemodynamic responses to laryngoscopy, intubation, and laparoscopy. Among these, opioids, beta-blockers, vasodilators, calcium channel blockers, and sodium channel blockers have been used in past⁽¹⁾. These agents had their own side effects, and hence, the quest to search for an ideal agent still continues.

Melatonin is a pineal gland hormone which controls the circadian rhythm. It has been used for sleep disorders; jet lag. Pregabalin is a structural derivative of the Inhibitory neuro-

transmitter γ -aminobutyric acid (GABA). Pregabalin is structurally related to gaba-pentin and has a similar pharmacological profile and anticonvulsant and analgesic activity⁽⁵⁾. The predominant mechanism of action is thought to be through its presynaptic binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels which in turns leads to reduced release of neurotransmitters, eg, glutamate, substance P, and calcitonin gene-related peptide⁽⁶⁻¹⁰⁾.

Aim of the work

The Primary aim of this study is to evaluate the effect of oral melatonin versus oral pregabalin in attenuating the hemodynamic responses to endotracheal intubation. The secondary aim of this study is comparing their effect on preoperative anxiety.

Materials and methods

After approval of the university ethical committee and obtaining informed consent from all patients, this prospective, randomized, double blinded and placebo controlled study was conducted in El-Minia University Hospital during the period from December 2018 to May 2019. A total of 90 women aged between 18 and 40 years with American Society of Anesthesiologists grade I and II patients scheduled to undergo elective laparoscopic surgery under general anesthesia with endotracheal intubation were included in the study.

Patients were randomly divided into three equal groups. 2 hours before operation, the control group (C) received oral vitamin D as a placebo, group (M) receive 6 mg of melatonin orally and group (P) received 150 mg of pregabalin orally. Anesthetic technique was standardized in all the 3 groups.

On arrival at the operating room, electrocardiogram, pulse oximetry, and non-invasive arterial blood pressure were applied. Vital signs were obtained and subsequent values were recorded throughout surgical procedure. Then an intravenous 18G cannula was inserted and preloading with Ringer's solution (10-15 ml/kg) was started. The patients were preoxygenated for 3 minutes before anesthetic induction, and balanced anesthesia was induced with fentanyl 1.5 μ g/kg, propofol 2.5-3.5 mg/kg in incremental

doses till loss of verbal contact and atracurium 0.5 mg/kg.

Laryngoscopy was attempted 2 minutes after induction of anesthesia by an experienced anesthetist. The patients who required more than 1 attempt at intubation or in whom laryngoscopy and intubation took > 30 sec were excluded from the study. After confirmation of endotracheal tube position, Anesthesia was maintained using 100% O₂ and isoflurane (1.2-1.5%). Recovery from anesthesia was done by discontinuation of isoflurane and reversal of neuromuscular blockage by atropine 0.01mg/kg then neostigmine 0.03-0.05 mg/kg. Then extubaion was done, after the airway reflexes were regained. Duration of surgery was defined as the time from surgical incision till closure of the wound.

The following variables (SBP, DBP, MAP, HR, SpO₂) were recorded just before medications (baseline), 2 hours after medications (just before induction of anathesia), after induction (just before intubation), 1 min, 3 min, 5 min, and 10 min after intubation. Also, RASS score was recorded just before medications (baseline) and 2 hours after medications (just before induction of anesthesia).

Adverse effects such as tachycardia, bradycardia, arrhythmias, hypertension, hypotension, respiratory de pression, headache, nausea, vomiting, restlessness, or stridor were reported and compared among the three groups. Hypertension was defined as SBP >30% of baseline value or > 140 mmHg and hypotension was defined as a decrease in the systolic arterial pressure <90 mmHg or a decrease of >30% from baseline values. Tachycardia and bradycardia were defined as HR >100 bpm or <60 bpm respectively.

Results

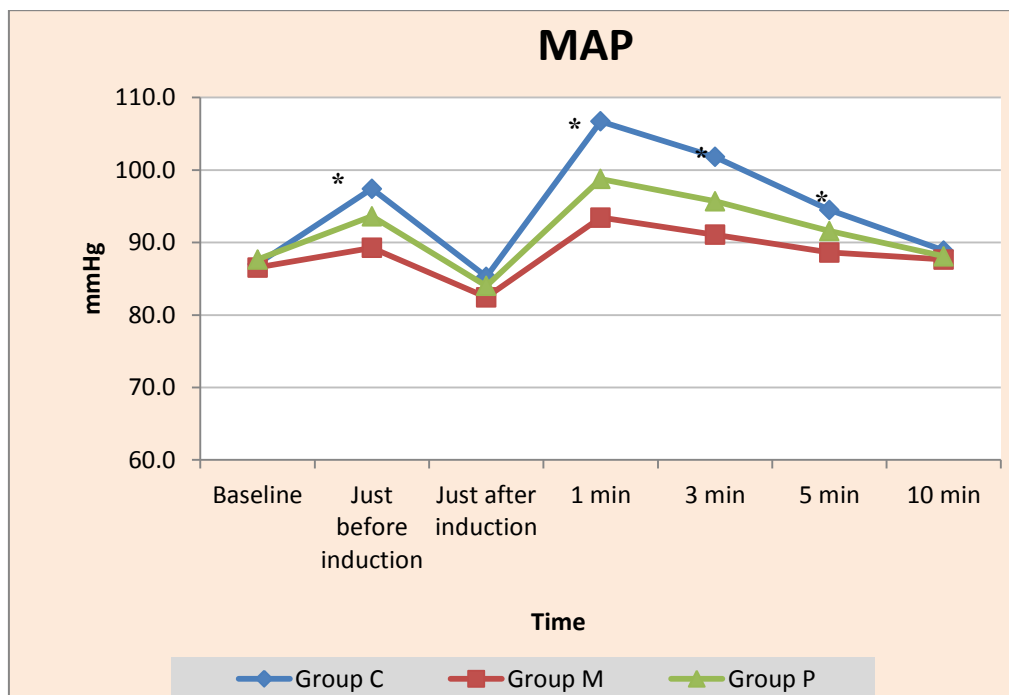
Basic characteristics:

The 3 groups were comparable with respect to age, gender, weight, ASA grade, type of surgery, mean time of intubation and duration of surgery with no clinical significance between the 3 groups. All patients were successfully intubated within 30 seconds at the first attempt.

Hemodynamic parameters:

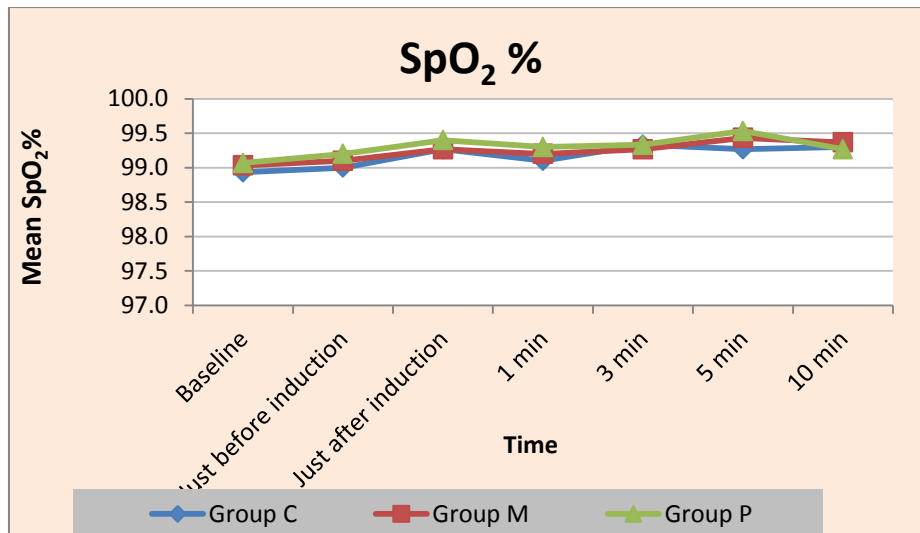
The baseline mean values for MAP were 87 ± 5.2 , 86.6 ± 6.1 , 87.7 ± 7.2 mmHg for groups C, M and P respectively, with no significant difference among the groups. There were 2 significant rises at Tb and T1 intervened by a significant drop at Ti in MAP from baseline values in between the 3 study groups which reached its peak value at T1. The drop in MAP is explained by cardiovascular depressive effect of anesthesia induction which was insignificant between the 3 study groups. On the other hand, The 2 rises in MAP interpreted as the effect of preoperative anxiety and stress response to intubation respectively, that were significant between the 3 study groups.

At 3rd minute after intubation (T3), MAP started to drop significantly through the 3 study groups. In addition, the MAP continued to drops significantly At 5 minute after intubation (T5) in between the 3 study groups but still higher than the baseline values .Upon reaching 10th minute after intubation (T10), MAP values became closer to each other with no significant difference between the 3 study groups. The changes in MAP values at T3, T5, and T10 could be demonstrated by subsidence of stress response to endotracheal intubation. Group M showed the least fluctuation in MAP followed by group P while it was the highest in group C .Changes in MAP values were noted to be similar to changes in values of SBP, DBP, and HR during the same study period.



Arterial Oxygen Saturation (SpO₂):

The baseline values of oxygen saturation were similar in the three groups. There were no significant differences concerning arterial oxygen saturation, either between the groups or within each group throughout the whole study period.



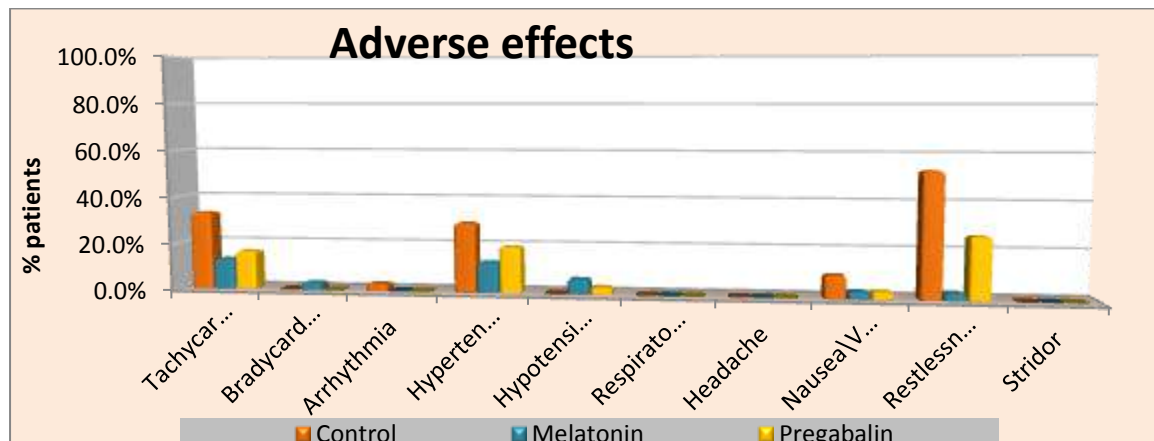
Richmond Agitation-Sedation Scale (RASS):

RASS scores of 0 was recorded in all the 90 patients of the study groups at start of the study (T₀). However, RASS score of +1 was noted in 16, 8, and 1 patients in group C, P, M respectively 2 hours after medications and just before induction (T₀) resulting in a clinical significance between the 3 study groups. Thus, group C showed the highest incidence of anxiety followed by group P while it was the least in group M.

Adverse effects:

There was no significant difference between the 3 study groups regarding the incidence of adverse effects during the study period except for restlessness. Thus, 16, 8, and 1 patient in

group C, P, and M respectively, experienced restlessness just before induction (T₀) which was the least in group M followed by group P while it was the highest in group C.



Discussion

Several studies evaluated the efficacy of melatonin and pregabalin to obtund the hemodynamic response to endotracheal intubation and their effect on the preoperative anxiety using different drug doses, time interval

between drug administration, anxiety assessment tools, age group, or type of surgery.

In agreement with our results Gupta et al., compared the effect of 6 mg of melatonin when given orally 120 minutes before operation with

a control group on attenuation of haemodynamic responses to laryngoscopy and intubation in 60 ASA status Grade I and II patients of either gender, 20–45 years old, 40–65 kg body weight, scheduled to undergo elective surgical procedures under GA. The study concluded 6 mg melatonin administered orally 120 min before induction of anaesthesia is effective for attenuating haemodynamic responses (BP and HR) to laryngoscopy and intubation with no significant side effects indicating that melatonin has an excellent safety profile⁽³⁾. To our knowledge, this is the only study found to assess the effect of melatonin on the stressor response to endotracheal intubation uptill now.

Another study conducted by Sundar et al. which was a comparison between two groups of 30 adult patients scheduled for elective off pump coronary artery bypass surgery. In the control group, the patients were given placebo capsules, and in the pregabalin group, the patients were given pregabalin 150 mg capsule orally 1h before surgery. The patients were compared for hemodynamic changes before the start of the surgery, after induction, 1, 3, and 5 min after intubation. In agreement with our results, the study showed that a single oral dose of 150 mg pregabalin given 1h before surgery suppressed reflex tachycardia and hypertension related to laryngoscopy and intubation of trachea in patients coming for elective OPCAB grafting and does not produce dizziness or visual disturbance⁽¹¹⁾.

In partial agreement with our study, Nasr et al., performed a randomized double-blind study of 40 patients with age range of 25–35 years undergoing gynecological surgeries divided into 2 equal groups to receive either melatonin capsule 6 mg (Group M), or pregabalincapsule 150 mg (Group P) 1h before induction of general anesthesia. The acute anxiety level 1h after drug administration was assessed. The results showed that the anxiety scores decreased significantly >50% after premedication in both groups compared to baseline values ($p < 0.01$) with no statistically significant difference between the two groups⁽⁴⁾. That may be due to difference in time interval between drug administration and anxiety assessment which was 2 hours in our study compared to 1 hour in that study or usage of observer assessment of

alertness/sedation scale (OAA/S) as a sedation scale instead of Richmond agitation-sedation scale (RASS) as in our study.

In a contradiction to our results Capuzzo et. who performed a prospective, double-blind, and randomized study to compare preoperative anxiety in elderly patients receiving melatonin (M) or placebo (P). Anxiety was measured in patients aged >65years with ASA physical status I–III by a numerical rating scale (range, 0–10). Each patient was randomized to receive M 10 mg or P orally: 71 patients were in group P and 67 in group M. The median anxiety level was 5 (2–8) before and 3 (1–7) 90 min after premedication in group M and 5 (3–6) and 3 (1–5) in group P, respectively. This study showed that melatonin, compared with placebo, does not reduce anxiety and depression in elderly patients undergoing surgery⁽¹²⁾. The difference between our results and this one could be explained by differences in populations (age, gender, and types of surgery) or methodologies.

Our study had several limitations as it had been conducted in normotensive females undergoing elective laparoscopic surgery, not cardiac and with easy airway. Our finding cannot be extrapolated in both genders, different types of surgery, patients with hypertension, IHD or difficult airway.

We concluded that oral administration of 6 mg of melatonin or 150 mg of pregabalin 2 hours before operation were effective in attenuation but not complete abolishment of the pressor response to endotracheal intubation and preoperative anxiety when compared to the control with superiority of melatonin over pregabalin in both aspects.

Recommendations

We recommend use of oral melatonin or pregabalin to attenuate hemodynamic response to laryngoscopy and intubation if it is not contraindicated as it simple, cheap and effective method to attenuate stress response. Our study performed in normotensive females undergoing elective laparoscopic surgery, not cardiac and with easy airway. Our finding cannot be extrapolated in genders, different types of surgery, patients with hypertension, IHD or difficult

airway, so we encourage further studies involving these categories.

Also, we recommend trying other adjuvant to improve the blunting of stress response to endotracheal intubation.

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