The use of melatonin to attenuate the hemodynamic response to endotracheal intubation under general anesthesia

Talal Abdulrazaq Shaker Shnayien*, Jaafar Hameed Mahboba**
*M.B.Ch.B**Professor, M.B.Ch.B., DA, FICMS A&IC, Consultant Anesthetist, Medical Collage/Kufa University

Abstract
Background: Laryngoscopy and endotracheal intubation are an integral part of general anesthesia for surgerical procedures. The hemodynamic response to the stress of laryngoscopy and endotracheal intubation does not present a problem for most patients. However, cardiac patients are more prone to develop hemodynamic instability on induction of anesthesia and endotracheal intubation and frequently respond to stress with an increase of blood pressure and heart rate. Melatonin has been suggested to attenuate such hemodynamic response.
Objective: The objective was to study the changes in blood pressure and heart rate during endotracheal intubation in patients undergoing general anesthesia in two groups (melatonin versus control).
Patients and Methods: Sixty patients were randomly assigned to two equal groups (n = 30). Group C (control group) received two placebo tablets 120 min before surgery. Group M (melatonin group) received oral melatonin tablets 6 mg (two tablets of 3 mg each), administered 120 min before surgery.
Results: Regarding systolic blood pressure ,diastolic blood pressure and heart rate there was no significant difference at baseline reading ($P > 0.05$); however, it was significantly lower in study group than in control group before and after induction of anesthesia and also at time of endotracheal intubation and 5 and 10 minutes after intubation ($P < 0.001$).
Conclusion: Melatonin is an effective drug to attenuate hemodynamic response to endotracheal intubation in patients undergoing general anesthesia.
Key words: Melatonin, general anesthesia, hemodynamic status

Introduction

Laryngoscopy and endotracheal intubation are an integral part of general anesthesia for surgical procedures [(1)]. The hemodynamic response to the stress of laryngoscopy and endotracheal intubation does not present a problem for most patients [(2)]. The major stimuli to cardiovascular change during laryngoscopy and tracheal intubation are the forces exerted by the laryngoscope blade on the base of the tongue while lifting the epiglottis [(3)]. These hemodynamic changes can be detrimental in vulnerable patients, e.g., those with ischemic heart disease, cerebrovascular disease, etc., and need to be prevented. Anesthetic literature has focused more on the pharmacological methods for attenuation of the response, and literature related to non-pharmacological methods, specifically laryngoscopy blade design, is limited [(4, 5)]. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous sleep-regulating hormone secreted by pineal gland. Exogenous administration of melatonin facilitates sleep onset and improves the quality of sleep. It is different from benzodiazepines and their

derivatives in that it produces natural sleep pattern and does not lead to impairment of cognitive functions [6]. Various researchers have used this drug in different dose patterns as premedication in both adults as well as children. It has been mainly studied in view of pre-operative anxiolysis, sedation in Intensive Care Unit, pre-operative cognitive and psychomotor functions [7]. We assumed that its inhibitory actions on central nervous system responsible for sedation and anxiolysis may have role in attenuating hemodynamic responses to laryngoscopy and intubation. Based on this, we made a hypothesis that melatonin can provide hemodynamic stability during laryngoscopy and intubation when given 120 min before the procedure [8]. Melatonin is used in a number of therapeutic indications such as sleep disorders, circadian rhythm, in jet lag management, as an antioxidant, in prevention and treatment of some malignant disorders, as an immune modulator in rheumatoid arthritis and in management of neurodegenerative disorders [9-11]. Melatonin is contraindicated in those with immune and lymphoproliferative disorders, as well as in those taking immunosuppressants [12]. In general, animal and human studies documented that short-term use of melatonin is safe, even in extreme doses. Only mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported [13].

Patients and methods

The current prospective randomized double-blind clinical study was conducted after obtaining permission from the scientific council of Iraqi board of anesthesia and intensive care and informed patient consent. Sixty patients were randomly assigned to two equal groups (n = 30). Group C (control group) received two placebo tablets 120 min before surgery. Group M (melatonin group) received oral melatonin tablets 6 mg (two tablets of 3 mg each), administered 120 min before surgery. Each patient received either drug in a thick opaque, similar looking envelope by the pre-operative nurse. Both patient and investigator were unaware of the type of drug. Vitamin D3 tablets were used as placebo and looked similar to melatonin tablets. Moreover, the study drugs were administered by nurse in the pre-operative area, and he was unaware of the study. Hemodynamic parameters such as heart rate: systolic, diastolic and mean blood pressures were recorded before the administration of drug (baseline), 120 min after administration of study drug (just before induction), immediately after induction, at laryngoscopy and intubation, and intubation and at 5 and 10 min thereafter. For within-group comparison of ratio and interval scale data, repeated-measures ANOVA and *post hoc* LSD *t*-tests were used. $P < 0.05$ was considered statistically significant. As the LSD test is very conservative *post hoc* test, the conventional $P < 0.05$ was selected even for multiple comparisons. SPSS version 23 was used.

Results

General characteristics of the study and control groups, including age, gender, ASA grade, type of operation and duration of anesthesia, are demonstrated in table 1. This table showed statistical match (no significance difference) between the two groups, control and study groups, regarding all parameters ($P > 0.05$). Regarding systolic blood pressure, there was no significant difference in mean systolic blood pressure at baseline reading ($P > 0.05$); however, it was significantly

lower in study group than in control group before and after induction of anesthesia and also at time of endotracheal intubation and 5 and 10 minutes after intubation (P < 0.001), as shown in table 2. Regarding diastolic blood pressure, there was no significant difference in mean diastolic blood pressure at baseline reading (*P* > 0.05); however, it was significantly lower in study group than in control group before and after induction of anesthesia and also at time of endotracheal intubation and 5 and 10 minutes after intubation (P < 0.001), as shown in table 3. Regarding heart rate, there was no significant difference in mean heart rate at baseline reading (*P* > 0.05); however, it was significantly lower in study group than in control group before and after induction of anesthesia and also at time of endotracheal intubation and 5 and 10 minutes after intubation (P < 0.001), as shown in table 4.

Table 1: Demographic characteristics of control and study groups

Characteristic	Control group n = 30	Melatonin group n = 30	*P*
Age			
Range	20-43	20-45	
Mean ±SD	33.19 ±4.71	32.81 ±5.01	> 0.05
Gender			
Male	17	15	> 0.05
Female	13	15	
Duration of anesthesia			
Range	30-95	35-100	
Mean ±SD	47.81 ±12.73	48.01 ±10.95	> 0.05
ASA grade			
I	18	16	> 0.05
II	12	14	
Type of surgery			
Open	23	25	> 0.05
Laparoscopic	7	5	

Table 2: Systolic blood pressure throughout the period of operation

Time	Control group n = 30	Melatonin group n = 30	*P*
Base line	128.56 ±7.51	127.91 ± 6.09	> 0.05
before induction	129.19 ± 8.17	119.03 ±7.01	<0.001
After induction	123.31 ± 7.14	118.38 ±6.92	<0.001
At intubation	141.01 ± 5.27	121.09 ± 7.01	<0.001
5 minutes	137.04 ± 6.91	118.03± 6.04	<0.001
10 minutes	130.39 ± 7.01	115.48 ± 7.03	<0.001

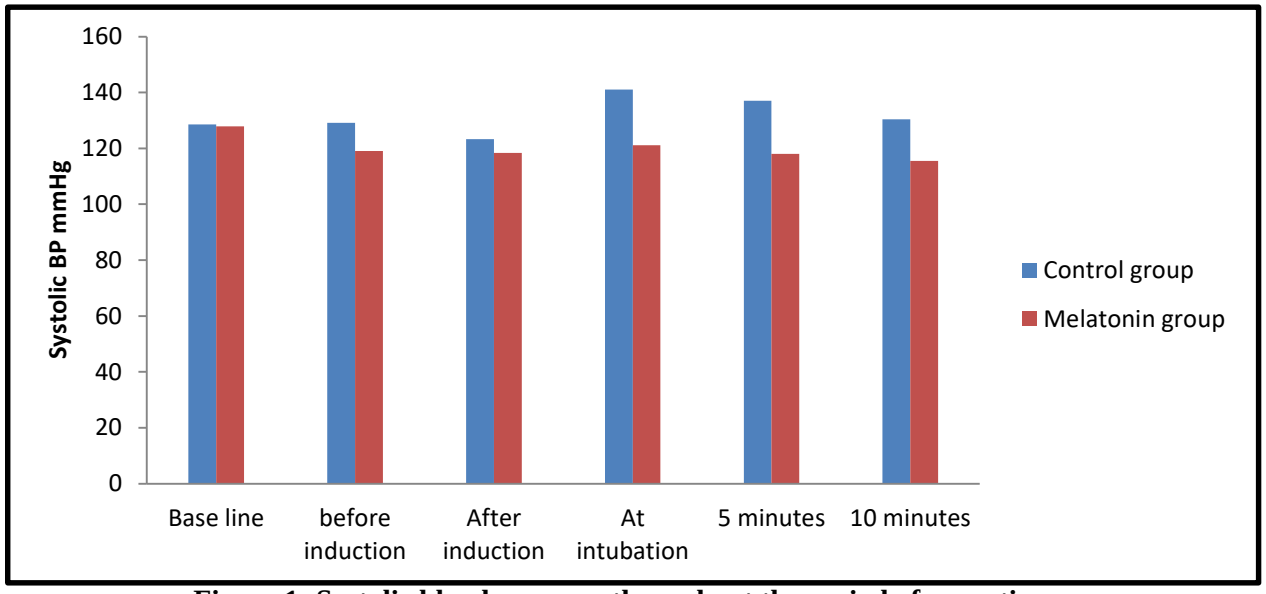

Figure 1: Systolic blood pressure throughout the period of operation

Table 3: Diastolic blood pressure throughout the period of operation

Time	Control group n = 30	Melatonin group n = 30	*P*
Base line	81.53 ± 5.52	82.72 ±5.07	> 0.05
before induction	82.29 ± 7.18	71.12 ±5.04	<0.001
After induction	81.37 ± 6.13	70.27 ±7.71	<0.001
At intubation	92.07 ± 7.22	71.14 ±6.09	<0.001
5 minutes	90.14 ± 5.97	78.12 ± 5.02	<0.001
10 minutes	89.18 ± 6.31	75.35 ± 5.07	<0.001

Figure 2: Diastolic blood pressure throughout the period of operation

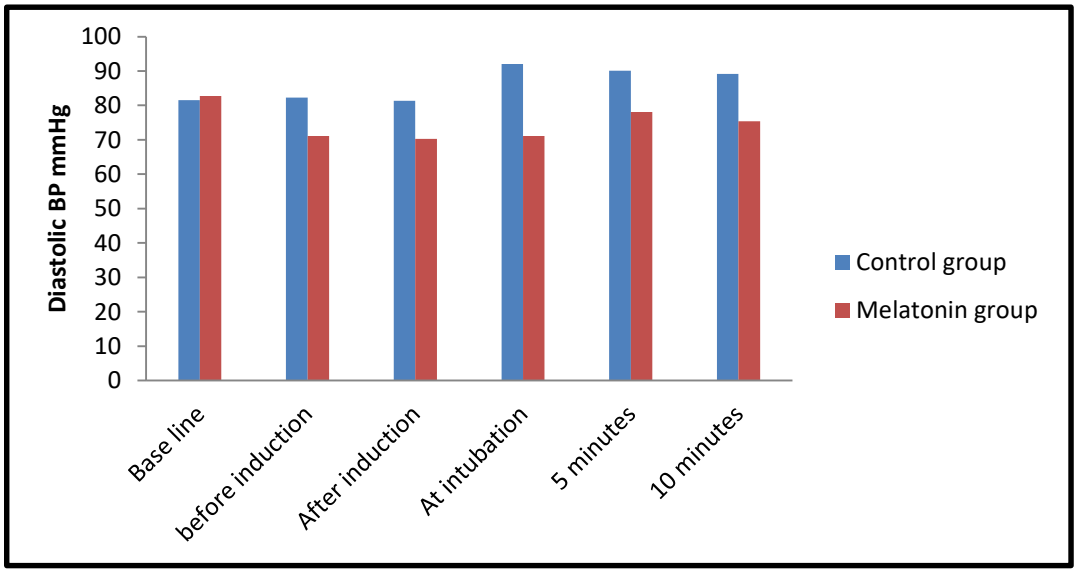

Table 4: Heart rate throughout the period of operation

Time	Control group n = 30	Melatonin group n = 30	*P*
Base line	82.42 ±8.19	83.41 ±8.18	> 0.05
before induction	83.34 ±8.25	70.24 ±6.23	<0.001
After induction	83.23 ±7.37	71.32 ±8.32	<0.001
At intubation	85.16 ±8.38	72.21 ±7.26	<0.001
5 minutes	87.21 ±7.41	79.97 ±8.17	<0.001
10 minutes	86.23 ±7.28	76.81 ±7.42	<0.001

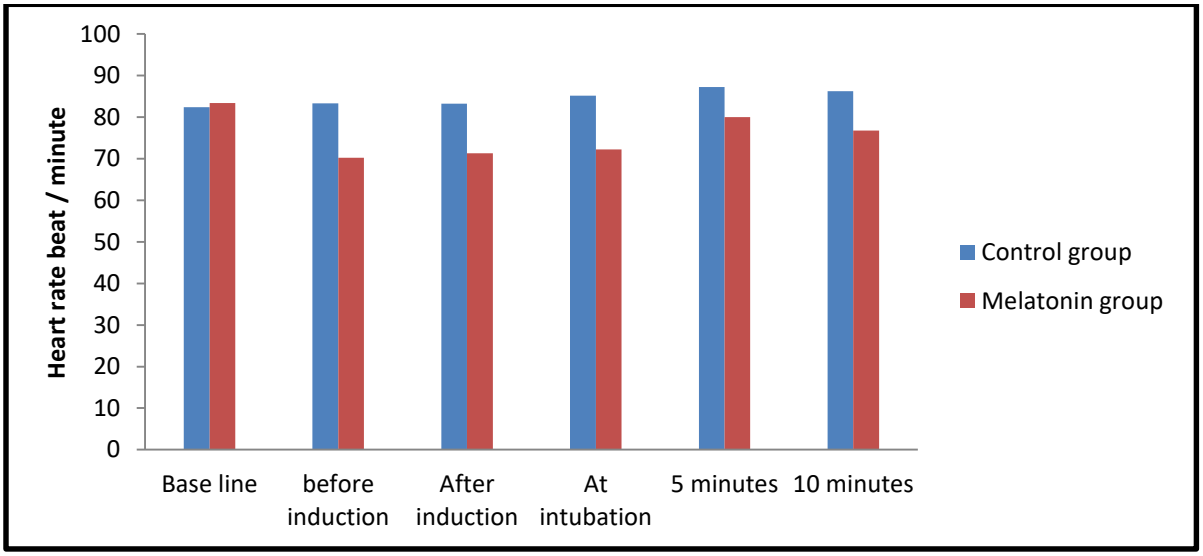

Figure 3: Heart rate throughout the period of operation

Discussion

The present study and the results shown in the previous chapter were designed for surveying the part of melatonin in constricting hemodynamic reactions to laryngoscopy and intubation. Melatonin (N-acetyl-5-methoxytryptamine) is a pineal organ hormone which controls the circadian rhythm. It has been utilized for sleep disturbances issue, perioperative anxiolysis and sedation, intellectual and psychomotor functions [14-16]. It is suggested that its inhibitory activities on focal sensory system in charge of sedation and anxiolysis may have a part in weakening hemodynamic reactions to laryngoscopy and intubation. Rosenberg et al. examined the part of perioperative melatonin in the

alteration of blood pressure changes showing that melatonin has sympatholytic activity [17]. This is in help of our supposition. The pinnacle impact of exogenous melatonin ranges from 60 to 150 min [18]. Based on this, we made a theory that melatonin can give hemodynamic security amid laryngoscopy and intubation when given 120 min before anesthesia. It was found that in melatonin group, systolic blood pressure was lower than baseline values throughout all time intervals till 10 min after intubation in comparison with the control group in which there was a significant rise. Comparable patterns were observed for diastolic and heart rate. It has been considered that melatonin lessens mean blood pressure in volunteers [19, 20]. An investigation on rats uncovered that pinealectomy brought about serious hypertension [21]. Mohammed et al. thought about the part of oral melatonin 6 mg and 9 mg with placebo treatment directed 1 h before medical procedure in weakening blood pressure changes to laryngoscopy and intubation. They saw that there was a decrease of pulse as to systolic, diastolic and mean blood pressure; and perfusion index in study as well as control group [22]. The way of effect of melatonin on blood pressure is perplexing. The reduction in blood pressure may be attributable to binding of melatonin in the vascular walls so that catecholamins effect is obliterated [23]. It may interfere with the peripheral as well as central autonomic system, causing a reduction in adrenergic outflow and resulting catecholamine levels [24]. Furthermore, it may induce relaxation of arterial wall smooth muscle by enhancing the availability of nitric oxide [25]. What's more, it might likewise act through particular receptors melatonin receptor 1 or melatonin receptor 2 found either peripherally or centrally [26]. It additionally has free radical rummaging impact prompting dilatation of veins, and it might work by means of epigenetic component at zone postrema in the brain [27]. The pulse bringing down impact could likewise be because of the calming activity of orally managed melatonin. The sedative effect is mainly due to binding at GABA-A receptor and exerting its anaesthetic effect [23]. We saw that pulse was additionally lower than standard qualities at all purposes of time in melatonin group when contrasted with the control group. Notwithstanding, in a comparative report, no distinction was seen in the progressions of pulse in the melatonin group when contrasted with the control group [22]. The pulse bringing down impact of melatonin might be credited to its anxiolytic activities. The fundamental component is likely the cooperative energy among melatonergic and GABA ergic frameworks. It likewise has pain relieving impacts as seen by different specialists and this may likewise add to the hemodynamic stability [28]. Moreover, the size of the haemodynamic reactions is directly related to the force applied during laryngoscopy and to the duration of laryngoscopy. Therefore, those patients who were in need for more than one attempt and more than 20 s for laryngoscopy were dropped from study. Since this study is concerning haemodynamic reactions and antihypertensive drugs effects on the autonomic receptors, diabetic patients usually have some degree of autonomic

neuropathy, besides that aging may cause blood vessel wall to be harder due to atherosclerosis. All these may interfere with the study outcome; therefore, these patients were excluded from the current study. In conclusion, melatonin is a helpful medication for use in general anesthesia to ameliorate hemodynamic response to endotracheal intubation.

References

1 Kovak AL. Controlling the hemodynamic response to laryngoscopy and endotracheal intubation. J Clin Anesth. 1996 Feb;8(1):63–79.

2 Haidry MA, Khan FA. Comparison of hemodynamic response to tracheal intubation with Macintosh and McCoy laryngoscopes. *J Anaesthesiol Clin Pharmacol*. 2013;29(2):196-9.

3 McCoy EP, Mirakhur RK, McCloskey BV. A comparison of the stress response to laryngoscopy. Anaesthesia. 1995;50:943–6.

4 Tewari P, Gupta D, Kumar A, Singh U. Opioid sparing during endotracheal intubation using McCoy laryngoscope in neurosurgical patients: The comparison of haemodynamic changes with Macintosh blade in a randomized trial. J Postgrad Med. 2005;51:260–5.

5 Baandrup L, Fagerlund B, Jennum P, Lublin H, Hansen JL, Winkel P, et al. Prolonged-release melatonin versus placebo for benzodiazepine discontinuation in patients with schizophrenia: A randomized clinical trial - The SMART trial protocol. BMC Psychiatry. 2011;11:160.

6 Maitra S, Baidya DK, Khanna P. Melatonin in perioperative medicine: Current perspective. Saudi J Anaesth. 2013;7:315–21.

7 Gupta P, Jethava D, Choudhary R, Jethava DD. Role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation. *Indian J Anaesth*. 2016;60(10):712-718.

8 Kostoglou-Athanassiou I. Therapeutic applications of melatonin. *Ther Adv Endocrinol Metab*. 2013;4(1):13-24.

9 Ochoa-Sanchez R., Comai S., Lacoste B., Bambico F., Dominguez-Lopez S., Spadoni G., et al. (2011) Promotion of non-rapid eye movement sleep and activation of reticular thalamic neurons by a novel MT2 melatonin receptor ligand. J Neurosci 31: 18439–18452

10 Forrest C., Mackay G., Stoy N., Stone T., Darlington L. (2007) Inflammatory status and kynurenine metabolism in rheumatoid arthritis treated with melatonin. Br J Clin Pharmacol 64: 517–526

11 Janjua I, Goldman RD. Sleep-related melatonin use in healthy children. *Can Fam Physician*. 2016;62(4):315-7.

12 Andersen L.P., Gögenur I., Rosenberg J., Reiter R.J. The Safety of Melatonin in Humans. Clin. Drug Investig. 2016;36:169–175.

13 Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: A randomized clinical trial. J Anesth. 2010;24:155–60.

14 Ionescu D, Badescu C, Ilie A, Mielutia I, Iancu C, Ion D, et al. Melatonin as pre medication for laparoscopic cholecystectomy: A prospective randomized placebo controlled study. S Afr J Anesth Analg. 2008;14:8–11.

15 Naguib M, Samarkandi A, Riad W, Thalaj A, Alotibi W, Aldammas F, et al. Melatonin vs. midazolam premedication in children: A double-blind, placebo-controlled study. Eur J Anaesthesiol. 2005;22:189–96.

16 Patel T, Kurdi SM. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. J Anaesthesiol Clin Pharmacol. 2015;31:37–43.

17 Rosenberg J, Gögenur I, Lykkesfeldt J. Modification of surgical stress response by perioperative melatonin administration. Dan Med Bull. 2010;57:4144.

18 Melatonin. Monograph. [Last accessed on 2016 Jan 15];Altern Med Rev. 2005 10:326–36. Available from: http://www.altmedrev.com/publications/10/4/326.pdf .

19 Arangino S, Cagnacci A, Angiolucci M, Vacca AM, Longu G, Volpe A, et al. Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men. Am J Cardiol. 1999;83:1417–9.

20 Sewerynek E. Melatonin and the cardiovascular system. Neuro Endocrinol Lett. 2002;23(Suppl 1):79–83.

21 Zanoboni A, Forni A, Zanoboni-Muciaccia W, Zanussi C. Effect of pinealectomy on arterial blood pressure and food and water intake in the rat. J Endocrinol Invest. 1978;1:125–30.

22 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;81:859–867.

23 Wan Q, Man HY, Liu F, Braunton J, Niznik HB, Pang SF, et al. Differential modulation of GABAA receptor function by Mel1a and Mel1b receptors. Nat Neurosci. 1999;2:401–3.

24 Anwar MM, Meki AR, Rahma HH. Inhibitory effects of melatonin on vascular reactivity: Possible role of vasoactive mediators. Comp Biochem Physiol C Toxicol Pharmacol. 2001;130:357–67.

25 Simko F, Paulis L. Melatonin as a potential antihypertensive treatment. J Pineal Res. 2007;42:319–22

26 Paulis L, Simko F. Blood pressure modulation and cardiovascular protection by melatonin: Potential mechanisms behind. Physiol Res. 2007;56:671–84.

27 Ghosh G, De K, Maity S, Bandyopadhyay D, Bhattacharya S, Reiter RJ, et al. Melatonin protects against oxidative damage and restores expression of GLUT4 gene in the hyperthyroid rat heart. J Pineal Res. 2007;42:71–82.

28 Srinivasan V, Pandi-Perumal SR, Spence DW, Moscovitch A, Trakht I, Brown GM, et al. Potential use of melatonergic drugs in analgesia: Mechanisms of action. Brain Res Bull. 2010;81:362–71.