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Effects of Melatonin Premedication on the Hemodynamic Responses and Perfusion Index During Laryngoscopy and Endotracheal Intubation

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Abstract

Context Rational: Several techniques have been proposed to prevent or attenuate the hemodynamic responses following laryngoscopy and intubation, preoperative melatonin has a significant analgesic and anxiolytic effect for patients undergoing surgery. Melatonin may play an important role in controlling hypertension also in humans. The current study aimed at assessing the usefulness of melatonin in attenuating the pressor response to direct laryngoscopy and tracheal intubation.

Methods: After approval of the ethics committee and informed written patients consent the study was carried out at rotine surgical theatre of the Suez Canal University Hospital, during the peroid from 2011 – 2012 on 90 patients with ASA physical status I, II scheduled for any elective surgery under general anesthesia with endotracheal intubation. Patients were randomly allocated according to computer-generated randomization into three groups: Group I (control group); Group II (melatonin 6mg tablet group) and Group III (melatonin 9mg tablet group). Primary outcome measures include; Heart rate (HR, Systolic blood pressure (SBP), diastolic blood: pressure (DBP), mean arterial pressure (MBP) and perfusion index were recorded before drug premedication, pre-induction, pre-intubation, 1, 2, 3, 5 and 10 minutes after laryngoscopy and intubation. Moreover perioperative anxiety was evaluated by recording the preoperative and postoperative verbal anxiety score (VAS) of the sample patients.

Results: Significant decrease in blood pressure in group II and group III receiving 6mg and 9mg of oral Melatonin 1 hour preoperative at 1, 2, 3, 5 and 10 minutes after intubation as regard SBP, DBP and MBP compared to group I. As regards to heart rate, no significant difference was found between the three groups throughout different time of measurement except for a significant difference at 1 minute after intubation measures for group II and group III compared to the control group. Moreover postoperative verbal anxiety score (VAS) was decreased significantly group II and group III compared to the control group.

Conclusion: Preoperative administration of melatonin one hour before surgery provided a significant decrease hemodynamic response of direct laryngoscopy and tracheal intubation as regard hemodynamic parameters and perfusion index.

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Key Words: *Oral melatonin premedication – Tracheal intubation– PI – Hemodynamic responses.*

Introduction

ENDOTRACHEAL intubation is one of the most invasive stimuli in anesthesia particularly during induction and after tracheal intubation **[1]**. It is usually well tolerated by normotensive patients, but even short-lasting stimulation has been associated with increased morbidity and mortality in patients with recent myocardial infarction, hypertension, pre-eclampsia, and cerebro-vascular pathology such as tumors, aneurysms or increased intracranial pressure **[1, 2]**. Stress response increases both SABP and DABP measurements increase by 36-40% in contrast to control levels. Heart rate levels increase more than 20% with tracheal intubation in contrast to laryngoscopy **[3,4]**. The pressor (stress) response reaches a peak 1-2min after laryngoscopy and tracheal intubation, and usually subsides within 5-6min, although tachycardia may persist for 10min **[5,6]**. Studies in humans indicate that 1mg of melatonin decreases arterial pressure and the plasma levels of noradrenaline during standing **[7]**. Several studies reported that melatonin has analgesic potential in addition to anxiolytic and sedative effects without disturbances of the cognitive and psychomotor skills, and thus improves the quality of recovery **[8]**. The pineal

hormone melatonin (N-acetyl-5-methoxytryptamine) has several putative functions that may make it an attractive option for premedication, including the regulation of circadian rhythms and sedative, analgesic, anti-inflammatory, and antioxidative effects [9]. Moreover, administration of 1 mg of melatonin during the daytime to healthy young women decreased systolic, diastolic and mean arterial pressure along with the reduction of norepinephrine concentration [9] the same depressant effect on BP and noradrenergic activation was observed in healthy men treated with melatonin [10].

Material and Methods

After approval of the ethics committee an informed written patient consent was taken. On arrival in the operating room following one hour of premedication, crystalloid infusion was started through a 20-gauge intravenous canula inserted in an appropriate vein and the SBP, DBP, MAP and HR was monitored.

Anesthesia was induced with thiopental sodium (5mg/kg), fentanyl 1ug/kg and cisatracurium (0.1mg/kg), and maintained with 1.2 MAC isoflurane with a fresh gas flow of 100% O_2. Neuromuscular block was confirmed with a nerve stimulator .Laryngoscopy and tracheal intubation was then performed 3min after loss of verbal contact by the same experienced anesthesiologist using a suitable Macintosh Laryngoscope blade and 7.0-8.0mm endotracheal tube (for women and men, respectively). Melatonin 6mg, 9mg or placebo tablets were administrated 1 hour before surgery. Patients were randomly allocated according to computer-generated randomization. The patients and investigator were not aware about the type of drug used (double-blinded pattern). All patients received their drug one hour pre induction of anesthesia in the pre-anesthestic area. Baseline Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were evaluated in the pre-anesthetic visit. Patients were not premedicated by other drugs. The study drugs were prepared by the pharmacy, and an appropriate code number was assigned. Airway assessment: The patient was assessed preoperatively according to a multivariate risk index (MVRI), [11] in which the total score was determined by the sum of the values of the 7 parameters, score ≤ 3 predicts easy intubation and score ≥ 4 predicts difficulty (Table 1).

Table (1): Prediction of difficult intubation (DI) using a multivariate risk index [11].

Variable	0 points	1 points	2 points
Inter-incisor gap (cm)	>4	2-4	<2
Mallampati score	Class I	Class II	Class III
Head/Neck movement	>90°	80-90°	<80°
Ability to prognath	Can prognath or edentulous	Can approximate teeth	Can't approximate teeth
Thyromental distance (cm)	>6.5	6-6.5	<6
Body weight (Kg)	<90	90-110	>110
History of DI	Non	Questionable	Definite

Primary outcome measures include; HR, SBP, DBP and MAP measured using Datex Ohmeda S/S monitor® were recorded before drug premedication, pre-induction, pre-intubation, 1, 2, 3, 5 and 10 minutes after laryngoscopy and intubation.

Secondary outcome measures included; anxiety using verbal anxiety score (12) before and after premedication by asking the patient how they would rank their anxiety on a score from 1-10. Other outcomes included the occurrence of any side-effects, such as nausea and vomiting, respiratory depression, dizziness, somnolence, headache and emergence agitation was recorded.

Data management and statistical analysis: Power calculations suggested that a minimum of 30 patients per group would detect a 15% difference in SAP or HR between the groups after intubation (a=0.05, b=0. 2). Data collected was coded, entered and analyzed using Microsoft Excel software. The data was then imported into the Statistical Package for the Social Sciences (SPSS version 11.0) software for analysis. According to the type of data, the following tests were used to test differences for significance; Chi square, paired *t*-test, and analysis of variance (ANOVA) with at least significance difference. Parametric data were analyzed by multivariate analysis of variance (MANOVA). Differences in hemodynamic data among groups were analyzed with Bonferroni's test correction for multiple comparisons. Differences from baseline within groups were evaluated using paired-sample *t*-test. The assessment of Odds ratio and multiple logistic regression analysis was used to test the relationship between different dependent and independent variables. $p<0.05$ was considered as significant.

Results

There was no significant difference between the three groups as regard age, gender, height and weight. In our study there was highly significant decrease in blood pressure in group II and group III receiving 6mg and 9mg of oral Melatonin consecutively 1 hour preoperative and at 1, 2, 3, 5 and 10 minutes after intubation as regard to the SBP, DBP and MBP compared to group I (p<0.001). (Table 2 & Fig. 1) Moreover there was a significant decrease in blood pressure recorded in group III at 1 minute after intubation as regard to the SBP, DBP and MBP compared to group II (p<0.001). While the group I which received the placebo showed a significant increase in blood pressure after induction of anesthesia at 1, 2 and 3 minutes after intubation as regard to the SBP, DBP and MBP. Group III which received 9 mg of oral melatonin 1 hour prior the operation, showed significant decrease in SBP and MBP at 1, 2, 3, 5 and 10 minutes after intubation compared to premedication measures (p<0.001). Moreover it showed a significant decrease in DBP at 2, 3, 5 and 10 minutes after intubation compared to premedication measures (p<0.001) (Fig. 2). However no significant difference was found between Group II and Group III as regard to SBP, DBP and MBP at pre-intubation, 5 and 10 minutes after intubation except at 1 minute after intubation was significant (p 0.002). In our study there was a significant difference between both groups II and III perfusion index measures before induction and at 1, 2 and 3 minutes after intubation compared to group I measures (p 0.044-0.001). Moreover there was a significant difference in perfusion index measures for group II before induction and at 1, 2, 3, 5 and 10 minutes after intubation compared to group I (p 0.015-0.001). (Table 3 & Fig. 3).

Table (2): Comparison of SBP changes in mm Hg between the three studied groups.

	SBP	Control	6mg melatonin	9mg melatonin	p
Before premed.	Range	107.0-155.0	108.0- 153.0	113.0-152.0	
	Mean±SD	130.77±15.40	132.47±11.61	134.67±10.91	0.499
	Median	128.0	135.0	139.0	
	p_1		0.608	0.241	
	p_2			0.507	
Before induction	Range	105.0-185.0	100.0-147.0	100.0-139.0	
	Mean±SD	129.83±15.97	126.57±11.95	120.23±11.14	0.020*
	Median	128.0	130.0	118.50	
	p_1		0.340	0.006*	
	p_2			0.066	
Before intubation	Range	80.0-112.0	86.0-126.0	85.0-116.0	
	Mean±SD	96.77±9.09	107.47±8.79	103.70±8.86	<0.001*
	Median	97.0	107.50	105.50	
	p_1		<0.001*	0.003*	
	p_2			0.105	
1min	Range	130.0-169.0	110.0-141.0	102.0-141.0	
	Mean±SD	147.30±11.67	131.20±8.32	120.53±9.93	<0.001*
	Median	146.0	133.50	119.0	
	p_1		<0.001*	<0.001*	
	p_2			<0.001*	
2min	Range	122.0-160.0	102.0-135.0	99.0-136.0	
	Mean±SD	140.97±11.02	121.53±8.04	117.53±8.80	<0.001*
	Median	142.0	122.50	118.0	
	p_1		<0.001*	<0.001*	
	p_2			0.102	
3min	Range	117.0-153.0	98.0-130.0	96.0-131.0	
	Mean±SD	134.47±10.80	115.67±8.58	112.73±8.20	<0.001*
	Median	136.50	117.0	112.50	
	p_1		<0.001*	<0.001*	
	p_2			0.223	
5min	Range	114.0-149.0	96.0-125.0	91.0-129.0	
	Mean±SD	129.03±10.69	112.27±7.25	109.07±8.65	<0.001*
	Median	130.0	112.0	109.0	
	p_1		<0.001*	<0.001*	
	p_2			0.171	
10min	Range	100.0-129.0	90.0-121.0	84.0-121.0	
	Mean±SD	115.53±9.51	106.87±7.13	103.50±9.88	<0.001*
	Median	117.0	107.50	103.50	
	p_1		<0.001*	<0.001*	
	p_2			0.148	

p: p-value of the ANOVA test.
*: Statistically significant at $p \leq 0.05$.
p_1: p-value of Post Hoc test (LSD) between group I with other groups.
p_2: p-value of Post Hoc test (LSD) between the 6mg melatonin and 9mg melatonin.

As regards to heart rate (Table 4 & Fig. 4), no significant difference was found between the three groups throughout different time of measurement, except for a significant difference at 1 minute after intubation measured for group II & group III compared to the control group (p 0.005 and <0.001 respectively). VAS significantly lowered in group II and group III compared to the control group (Table 5).

Table (3): Comparison of PI between the three studied groups.

	HR	Control	6mg melatonin	9mg melatonin	p
Before premed.	Range	1.50-2.50	1.50-2.60	1.20-2.60	
	Mean±SD	2.09±0.24	2.20±0.26	2.11±0.37	0.269
	Median	2.05	2.20	2.20	
	p_1		0.131	0.794	
	p_2			0.209	
Before induction	Range	1.40-2.70	2.0-2.90	1.80-2.70	
	Mean±SD	2.10±0.33	2.35±0.25	2.29±0.24	0.002*
	Median	2.10	2.30	2.30	
	p_1		0.001*	0.009*	
	p_2			0.428	
Before intubation	Range	2.50-4.50	2.80-4.20	2.60-4.0	
	Mean±SD	3.18±0.45	3.26±0.38	3.12±0.43	0.400
	Median	3.15	3.10	3.0	
	p_1		0.426	0.581	
	p_2			0.179	
1min	Range	1.0-2.80	1.60-3.10	2.0-4.0	
	Mean±SD	2.02±0.49	2.36±0.41	2.53±0.39	<0.001*
	Median	2.0	2.50	2.45	
	p_1		0.003*	<0.001*	
	p_2			0.149	
2min	Range	2.0-2.60	2.20-3.10	2.30-4.0	
	Mean±SD	2.29±0.19	2.78±0.22	2.59±0.35	<0.001*
	Median	2.30	2.80	2.50	
	p_1		<0.001*	<0.001*	
	p_2			0.007*	
3min	Range	2.10-3.0	2.20-3.20	2.30-4.0	
	Mean±SD	2.56±0.28	2.86±0.22	2.71±0.33	<0.001*
	Median	2.55	2.85	2.60	
	p_1		<0.001*	0.044*	
	p_2			0.039*	
5min	Range	2.50-3.50	2.30-3.50	2.60-4.0	
	Mean±SD	2.97±0.30	3.18±0.26	2.92±0.27	0.001*
	Median	3.0	3.20	2.90	
	p_1		0.004*	0.544	
	p_2			0.001*	
10min	Range	2.60-3.70	2.60-4.0	2.60-4.0	
	Mean±SD	3.13±0.31	3.33±0.38	3.05±0.26	0.003*
	Median	3.15	3.30	3.0	
	p_1		0.015*	0.330	
	p_2			0.001*	

p : p-value of ANOVA test.
p_1 : p-value of Post Hoc test (LSD) between group I with each other group.
p_2 : p-value of Post Hoc test (LSD) between 6mg melatonin and 9mg melatonin.
* : Statistically significant at $p \leq 0.05$.

Table (4): Comparison of HR in beats/min between the three studied groups.

	HR	Control	6mg melatonin	9mg melatonin	*p*
Before premed.	Range	62.0-113.0	59.0-123.0	64.0-114.0	
	Mean±SD	85.47±14.83	85.33±17.61	85.53±15.19	0.999
	Median	81.50	85.0	82.0	
	p_1		0.974	0.987	
	p_2			0.961	
Before induction	Range	55.0-111.0	58.0-120.0	55.0-112.0	
	Mean±SD	84.73±15.19	81.90±17.26	80.30±15.64	0.559
	Median	83.50	80.0	78.50	
	p_1		0.496	0.288	
	p_2			0.701	
Before intubation	Range	55.0-102.0	50.0-110.0	52.0-102.0	
	Mean±SD	78.10±13.47	75.97±15.88	75.77±13.29	0.782
	Median	73.0	74.50	72.0	
	p_1		0.564	0.528	
	p_2			0.957	
1min	Range	78.0-151.0	71.0-133..0	70.0-112.0	
	Mean±SD	107.80±18.64	96.13±16.61	92.60±10.95	0.001*
	Median	102.0	93.50	90.0	
	p_1		0.005*	<0.001*	
	p_2			0.387	
2min	Range	74.0-123.0	67.0-125.0	68.0-113.0	
	Mean±SD	95.93±13.46	90.87±16.01	90.30±11.66	0.227
	Median	92.0	88.0	87.50	
	p_1		0.159	0.118	
	p_2			0.874	
3min	Range	69.0-115.0	65.0-114.0	75.0-110.0	
	Mean±SD	90.27±13.0	85.67±13.91	88.60±11.66	0.380
	Median	87.0	82.50	85.0	
	p_1		0.170	0.618	
	p_2			0.381	
5min	Range	71.0-109.0	65.0-103.0	68.0-108.0	
	Mean±SD	85.60±10.88	80.60±12.06	84.33±11.50	0.221
	Median	82.50	78.50	81.0	
	p_1		0.096	0.670	
	p_2			0.212	
10min	Range	56.0-100.0	51.0-91.0	53.0-98.0	
	Mean±SD	72.47±10.18	67.67±9.83	72.80±10.29	0.094
	Median	70.0	68.50	71.0	
	p_1		0.069	0.899	
	p_2			0.052	

p : p-value of ANOVA test.
p_1 : p-value of Post Hoc test (LSD) between group I with each other group.
p_2 : p-value of Post Hoc test (LSD) between the 6mg melatonin and 9mg melatonin.
* : Statistically significant at $p \leq 0.05$.

Table (5): Comparison between the 3 groups as regard changes in the verbal anxiety score.

Timely points	Groups			*p*-value between I & II	*p*-value between I & III	*p*-value between II & III
	Group I (N=30)	Group II (N=30)	Group III (N=30)			
Administration	5.06±1.94	5.80±1.97	6.30±2.00	0.157	0.02*	0.33
After one hour	7.55±1.90	5.96±2.10	5.00±2.36	0.004*	0.00*	0.10

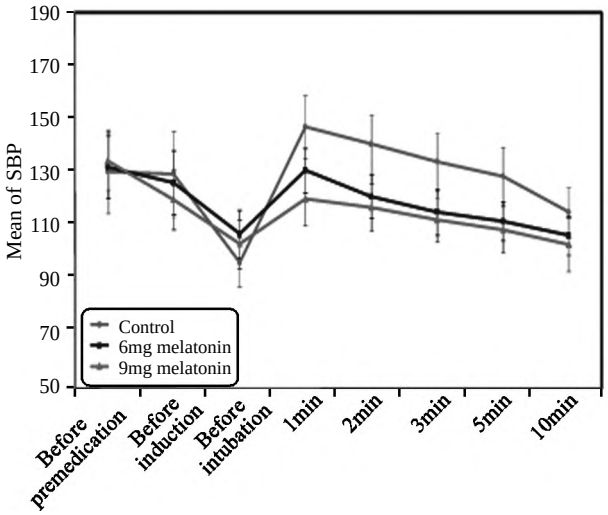

Fig. (1): Comparison of SBP changes in mm Hg between the three studied groups.

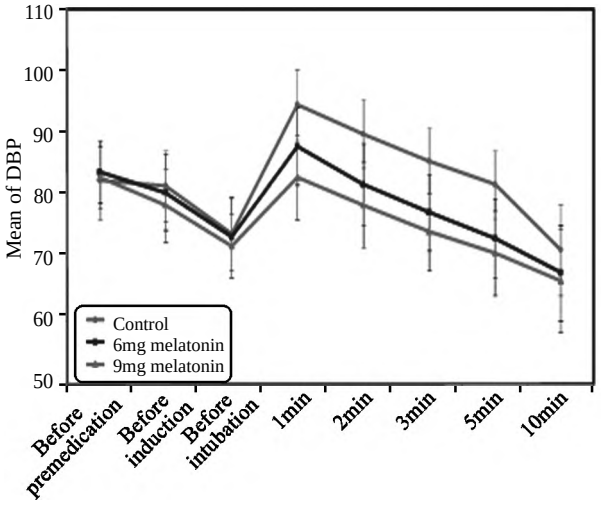

Fig. (2): Comparison of DBP in mm Hg between the different studied groups.

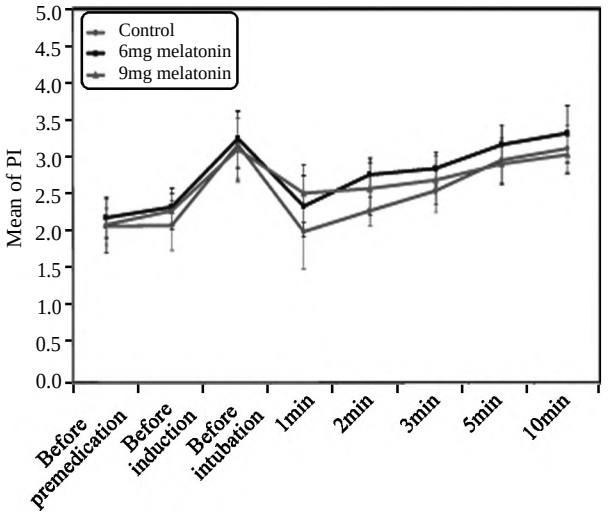

Fig. (3): Comparison of PI between the three studied groups.

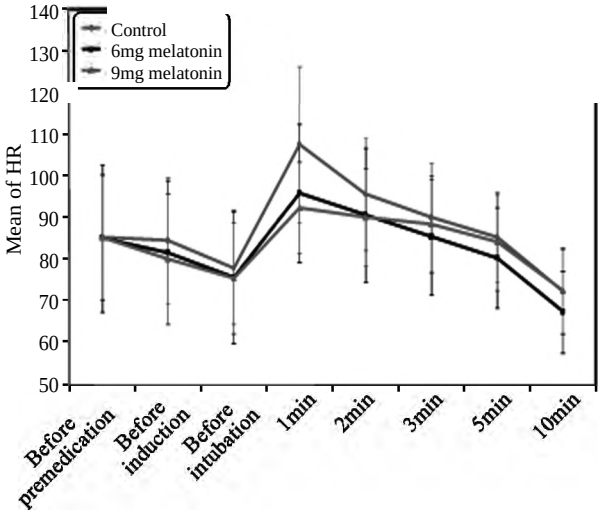

Fig. (4): Comparison of HR in beats/min between the three studied groups.

Discussion

The current study aimed at assessing the usefulness of Melatonin in attenuating the pressor response to direct laryngoscopy and tracheal intubation. Previous studies showed that melatonin could decrease MBP in healthy women [13] and men [14]. The mechanism of action of melatonin on circulation is complex and unclear. Melatonin may bind to specific melatonin receptors in the blood vessels, interfering with the vascular response to catecholamine [15]. Furthermore, melatonin may interfere with the peripheral and central autonomic system, causing a reduction in adrenergic outflow and catecholamines levels [16]. In addition, it may induce relaxation of the smooth muscle of the arterial walls via increasing nitric oxide availability [17]. Finally, melatonin may influence blood pressure also via its specific receptors MT1 (melatonin type 1) or MT2 (melatonin type 2) localized in peripheral vessels or in blood pressure modulating structures of the central nervous system [18,19].

The potential protective effect of melatonin in hypertension may go far beyond its beneficial hemodynamic actions. Due to its hypotensive, sympatholytic and oxygen load reducing action melatonin limits pathologic remodeling of the left ventricle. Melatonin reduced LVH in hyperthyroid rats [20], decreased collagenous protein and hydroxyproline level in L-NAME-induced cardiac hypertrophy [21] and, in a regression experiment with SHR, it lowered collagen content and insoluble collagen concentration in the LV [22].

Zanoboni, et al., stated that pinealectomy in rats results in melatonin deficiency, peripheral vasoconstriction and hypertension [23]. In another

study by Zeman, et al., stated that a surge in melatonin secretion reflected by the enhancement of the urinary melatonin metabolite, 6-sulfatoxymelatonin, is observed only in diapers and, similarly, the night/day ratio of melatonin is lower in nondippers compared with dippers **[24]**.

Russel, et al., stated that melatonin has a variety of actions; it may function to lower blood pressure/ hypertension. Moreover, melatonin has endothelium-relaxing effects, it is a potent scavenger of free radicals (which negatively influence blood pressure), and it may work via epigenetic mechanisms at the level of the area postrema to regulate blood pressure **[25]**.

In our study there was a significant decrease in the anxiety scores according to the verbal anxiety score in group II and group III which received 6mg and 9mg melatonin tablets relative to group I which received placebo. Moreover there was a significant decrease in the anxiety scores between group III which received 9mg melatonin tablets relative to group II which received 6mg melatonin tablets.

Mohamed Naguib, et al., stated that premedication with 0.05mg/kg melatonin was associated with preoperative anxiolysis and sedation without impairment of cognitive and psychomotor skills and without prolonging recovery **[26]**.

Ismail, et al., stated that premedication with oral melatonin provided anxiolysis, enhanced perioperative analgesia, decreased the IOP, and improved the operating conditions during cataract surgery under topical anesthesia **[8]**.

In Indian Journal of Anesthesia; the study done as evidence based data on melatonin for anxiolysis in children. Cosidering the great deal of interest in the potential uses of melatonin in perioperative setting; melatonin was preffered in pediatrics as premedicant as midazolam had multiple side effects including paradoxical reactions, interactions with opioid, variable bioavaiability and elimination half-life and delayed discharge from PACU after brief procedures **[27]**.

Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anesthesia. Melatonin is an effective premedication before IVRA since it reduced patient anxiety, decreased tourniquet-related pain, and improved perioperative analgesia **[28]**.

In another study of American Society of Anesthesiologists (ASA) I patients (mean age 33 years, n=200) having unspecified surgery, sub-lingual melatonin (0.2mg/kg) decreased preoperative anxiety and increased sedation versus placebo **[29]**.

Pediatric surgery, the first published study investigated the effects of melatonin in children (two to five years, n=105) undergoing minor general surgical procedures. It found that oral melatonin and midazolam at 0.25 and 0.5mg/kg were equally effective in decreasing separation anxiety and anxiety associated with the introduction of an anesthetic face mask at induction **[30]**.

In elderly patients, melatonin premedication for anxiolysis has also been less encouraging. In patients over 65 years of age (n=138) having a variety of surgical operations, patients who received 1 0mg melatonin orally had no significant decrease in anxiety pre- or postoperatively versus a placebo group **[31]**.

The mechanism of melatonin for anxiolysis and sedation seems to relate to both melatonin receptor activation and an effect on gamma-aminobutyric acid transmission **[32,33]** It has been reported that melatonin administration in rats increases central nervous system levels of gamma-aminobutyric acid and flumazenil also decreases the effects of melatonin **[34,35]**.

Perfusion index was measured in our study as an indicator for the analgesic effect of Melatonin premedication. Intubation is a stimulus able to increase endogenous catecholamines and thus leading to vasoconstriction possibly declining the perfusion index. Melatonin in (group II and group III) attenuated the release of norepinephrine limiting the changes in regional perfusion index **[36]**.

Patients treated with melatonin preoperatively presented a greater reduction in pain and required lower morphine consumption in the postoperative period. The benefits of these interventions were statistically and clinically significant to produce postoperative anxiolysis, which led to lower postoperative pain, as well as lower morphine consumption throughout the first 24 hours after surgery **[9]**.

Two further studies involved patients undergoing total abdominal hysterectomy under epidural anesthesia with propofol sedation (epidural catheter removed immediately postoperatively). The first of these looked at ASA I/II patients (n=33, mean age 44 years) randomized to receive oral melatonin (5mg) or placebo the night before surgery and one hour prior to the operating theatre. The treatment group reported significantly lower postoperative

pain and anxiety for the first 36 hours and also had decreased morphine consumption **[33]**. The second study investigated ASA I/II patients (n=59), who were randomized to receive either oral melatonin (5mg), oral clonidine (100 g g) or placebo both the night before and one hour prior to anesthesia. The melatonin and clonidine groups had lower anxiety scores, lower pain scores and lower morphine consumption in the first 24 hours postoperatively. However, subgroup analysis indicated that the decrease in pain scores and morphine consumption was only significant in those patients with higher preoperative anxiety scores **[37]**.

The analgesic effects of melatonin are mediated by MT1 and MT2 receptors (38) with a subsequent reduction in intracellular cAMP, and a consequent effect on potassium and calcium channels **[39]**. Other analgesic effects may relate to indirect increases in endogenous opioids **[40]**, an effect on the MRNA expression to inhibit arachidonic acid release **[41]** and a direct free radical scavenging effect **[42]**.

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