Original Article

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The effects of premedication melatonin on anxiety and hemodynamic stability for patients undergoing cesarean section: A randomized controlled study

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Abstract

Background: Premedication carries some significant goals during general anesthesia, it regulates the hemodynamic, relieve anxiety, induces sedation, offers proper analgesia and reduces the need for anesthetic drugs. Study objectives: The aim of this study was to evaluate the efficiency of Melatonin as a premedication agent for patients undergoing elective cesarean section on anxiety and blood pressure. Methods: The study included 80 individuals who were scheduled for elective spinal anesthesia-based cesarean sections. We assigned them at random. every group has 40 patients, melatonin group (M) and placebo group (P). The dose was given to patient at two separated times; at night and 90 minutes before the operation (10 mg) sublingually per each dose. Anxiety was evaluated for three times; pre the administration of the second dose (premedication) of melatonin, before the insertion of spinal needle and after 1 hour postoperatively by using Visual Analogue Scale. Hemodynamics were monitored) SBP, DBP and MAP) using a Nihon Kohden patient monitor during preoperative, after 5 min, 10 min, 20 min, 15 min, 60 min and 120 min. Result: This study included 80 patients, divided into two groups, including 40 patients, the melatonin group) M), as well as the placebo group (P) 40 patients. The results showed a decrease in the level of anxiety in the melatonin group before and after surgery p value (<0.001). as well as mean value was lower in melatonin group at min 120 postoperative, and this difference was statistically significant (p<0.05). Conclusions: The results of the present study showed that the use of 10 mg of melatonin at night and 90 min before cesarean section with spinal anesthesia is not only safe, but also reduces level of anxiety of patients', regulate blood pressure pre and post-operative.

Keywords:

Melatonin, Spinal anesthesia, Hemodynamic, Blood pressure, Anxiety, Pre-operative, Postoperative, Premedication.

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Introduction

A feeling of fear, tension, and nervousness can arise by increasing the level of anxiety as well as discomfort [1]. Caesarean section patients feel anxious as a result of the surgery or feel afraid of the operating room and due to autonomic response to surgical environments. This stress response can induce vasoconstriction in the uterine blood vessels and may cause fetal distress [2]. In addition to anxiety Spinal anesthesia usually induces autonomic sympathetic block which inhibits the systemic vascular resistance and leads to hypotension, that can be minimized or managed by different pharmacological and non-pharmacological ways such as left uterine displacement, crystalloids or colloids fluids preloading or co-loading, application of vasopressors like ephedrine and phenylephrine [3] [4]. Premedication refers to medications that used before surgery to attenuate or decrease the Patient anxiety before, during and after surgery [5]. Many medicines are used to reduce anxiety before surgery [6-8]. Midazolam administration preoperatively to cesarean section showed reduced anxiety, also anxiety scale was lower with patient after mirtazapine administration [9].

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Some previous studies suggested that melatonin has the ability to reduce oxidative stress in human newborns with septicemia, improve clinical outcomes and decrease products associated with oxidative stress and damage in the blood of asphyxiated newborns[10] [11]. The purpose of this randomized trial was to search and evaluate the effects of melatonin as a premedicant on patient's anxiety and blood pressure stability for those who are undergoing elective cesarean section with spinal anesthesia.

Methods

A randomized double-blind study was conducted after ethical committee approval and patients' informed consent signed, the study carried out through the operating room of caesarean sections in obstetric department of Bint Al-Huda Teaching Hospital in Nasiriyah/Iraq from August 2022 to January 2023. The determination of sample size is predicated on the alteration in hemodynamic. with a consideration of the distinctions metrics the effect size was determined to be 0.45 with a standard deviation of 0.71. The minimum sample size was calculated to be 80 patients divided into two groups, each group consisting of 40 patients, in order to maintain a minimum power of 80% and a maximum type I error of 0.05. sample calculation was performed online at: http://marne.u707.jussieu.fr/biostatgv/). All caesarean section patients who agreed to take part in the experiment were enclosed by fulfilled the subsequent requirements: age more than 18 years, categorized as ASA I or ASA II, pregnancy at a gestational age surpassing 37 weeks, unbroken membranes, scheduled surgical procedures, patient agreement by a written consent for study participation, and women with a solitary pregnancy.

The exclusion criteria for the study encompass several factors, including ASA III or higher, which indicates severe systemic disease or a constant threat to life, documented drug allergy to melatonin or any other study medications, contraindications for spinal anesthesia such as spinal anesthesia or infections, inability of the patient to respond or demonstrate awareness to the questions rose, patient with chronic anemia (Hb) <8 g%, a history of mental or neurological , addiction to substances that could interfere with the study outcomes, disapproval or dissatisfaction expressed by the patient regarding their involvement in the study. congenital malformations in the fetus. Enrolled patients. we randomly allocated into 2 groups has 40 patients, melatonin group (M) and placebo group (P). the anxiety is evaluated before the administration of premedication drugs to patient and before the insertion of spinal needle and after 1 hour postoperatively by using Visual Analogue Scale (VAS) which was completely evaluated by the anesthesiologist. In VAS a 10 centimeter ruler was used for evaluating the anxiety, in which zero represents no anxiety and 10 represents a severe anxiety.blood pressure was monitored (SBP, DBP, and MAP) using a Nihon Kohden patient monitor during preoperative, after 5 min, 10 min, 20 min and 15 min, 60 min ,120 min postoperative. All patients were enrolled for standard monitoring (EKG, NIBP, and pulse oximetry). Prior to subarachnoid block administration, all subjects were administered a lactated Ringer's solution intravenous preload at a rate of 5 ml/kg. Following the implementation of an aseptic technique, a Quincke needle with a gauge of 25 was introduced intrathecal through a midline approach into the L4-5 interspace while the patient was in a seated position used Marcaine 10 mg. shortly after delivery of the neonate, oxytocin was given by I.V. infusion through a 15-minute dissolved in 500 ml of lactated Ringer's solution, the dose was determined regarding to surgeon deemed uterine tone to be insufficient. A standardized protocol was employed to administer uniform spinal anesthesia to all patients during the surgical procedures. After undergoing surgical interventions, patients were admitted to the ward and a patient-controlled analgesia pump (PCA) was employed to manage pain for all patients. The internal components of the Patient controlled analgesia pump consists of 25 mg of morphine as needed, and the remaining volume of 100 cc, which is filled with a solution of normal saline. The regulation parameters of the PCA pump comprised of a bolus size measuring 0.5 cubic centimeters and a lockout interval of 15 minutes. The collected data was revised, coded, and tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Results

The research encompassed a cohort of 80 participants who were allocated randomly to two distinct groups. No significant statistical differences were observed between the two groups with regards to their sociodemographic characteristics. There were no statistically significant differences observed in the mean age, weight, height, and BMI between the study groups, with p-values of 0.378, 0.144, 0.062, and 0.726, respectively.

Table 1: Comparison between melatonin and placebo groups regarding to demographic data.

	Melatonin n = 40	Placebo n = 40	Test (p)
Age (years)			
Mean ± SD.	28.85 ± 7.46	30.20 ± 6.08	t=0.887, p=0.378
Weight (kg)			
Mean ± SD.	77.60 ± 10.90	74.48 ± 7.76	t=1.477, p=0.144
Height (cm)			
Mean ± SD.	165.03 ± 7.91	162.30 ± 4.43	t=1.902, p=0.062
BMI (kg/m^2)			
Mean ± SD.	28.50 ± 3.37	28.27 ± 2.64	t=0.351, p=0.726

Range: Min. – Max. U: Mann-Whitney, P value comparing between melatonin and placebo, *: significant when p value<0.05. Based on our analysis of VAS score, the comparison level of anxiety between the two studied groups indicated that the P value of anxiety was higher in the placebo group premedication and after 1hour postoperative than melatonin group, and this difference was statistically significant (p<0.001). (Table 2).

Table 2: Comparison between melatonin and placebo regarding to anxiety level.

	Group M	Group P	P value
Preoperative anxiety			<0.001**
mild	23	2	
moderate	17	36	
sever	0	2	
Very sever	0	0	
Pre spinal needle anxiety			0.004
mild	7	0	
moderate	31	29	
sever	2	10	
Very sever	0	1	
Post-operative anxiety			<0.001**
mild	36	13	
moderate	4	27	
sever	0	0	
Very sever	0	0	

The study showed that the comparison of systolic blood pressure between the two studied groups indicated that the mean value was higher in melatonin group at preoperative, but the mean value was lower in melatonin group at min 120 postoperative, and this difference was statistically significant (p<0.05).

Table 3: Comparison between melatonin and placebo regarding to systolic.

Systolic (mmHg)	Melatonin N = 40	Placebo N = 40	Test (p)
Preoperative			
Mean ± SD.	136.33 ± 13.38	126.30 ± 16.92	t=2.940, p=0.004*
5 min			
Mean ± SD.	123.35 ± 17.75	127.05 ± 15.96	t=0.980, p=0.330
10 min			
Mean ± SD.	119.23 ± 14.50	123.93 ± 13.54	t=1.498, p=0.138
20 min			
Mean ± SD.	127.03 ± 11.85	124.60 ± 18.16	t=0.707, p=0.482

SD. Standard deviation– Max.t: Student t-test, P value comparing between melatonin and placebo, *: significant when p value<0.05. Based on analyzed patient outcomes of pre, intra, and post-operative regarding diastolic blood pressure, data showed that participants who received melatonin, there were reduction at intraoperative in min 5&10, and this low was statistically significant (p<0.05), while patients who received placebo, the study showed that no change between the different times.

Table 4: Comparison between melatonin and placebo regarding to diastolic.

Diastolic (mmHg)	Melatonin N = 40	Placebo N = 40	Test (p)
Preoperative			
Mean ± SD.	81.65 ± 13.93	77.05 ± 10.35	t=1.676, p=0.098
5 min			
Mean ± SD.	70.13 ± 14.83	75.80 ± 12.14	t=1.873, p=0.065
10 min			
Mean ± SD.	68.70 ± 13.85	70.65 ± 14.95	t=0.605, p=0.547
20 min			
Mean ± SD.	74.83 ± 11.11	71.20 ± 13.12	t=1.333, p=0.186
Post 15 min			
Mean ± SD.	74.65 ± 9.02	76.03 ± 14.73	t=0.503, p=0.616
Post 60 min			
Mean ± SD.	76.48 ± 7.33	78.65 ± 9.98	t=1.111, p=0.270
Post 120 min			
Mean ± SD.	77.28 ± 5.97	79.08 ± 7.85	t=1.154, p=0.252

SD. Standard deviation – Max.t: Student t-test, P value comparing between melatonin and placebo. Regarding mean arterial blood pressure between two populations, data indicated that the mean value of MAP was lower in melatonin group at min 5 intra operative, and this low was statistically significant (p<0.05), while the other times, the study showed no difference between the two studied groups. **(Table 9) (Figure 12)**

Table 5: Comparison between melatonin and placebo regarding to MAP.

MAP (mmHg)	Melatonin N = 40	Placebo N = 40	Test (p)
Preoperative Mean ± SD.	99.87 ± 12.09	95.25 ± 14.37	t=1.558, p=0.123
5 min Mean ± SD.	87.87 ± 15.00	95.28 ± 13.07	t=2.355, p=0.021*
10 min Mean ± SD.	85.54 ± 12.92	88.41 ± 13.20	t=0.982, p=0.329
20 min Mean ± SD.	92.23 ± 9.34	89.00 ± 13.11	t=1.267, p=0.209
Post 15 min Mean ± SD.	91.27 ± 8.20	93.30 ± 14.82	t=0.759, p=0.451
Post 60 min Mean ± SD.	92.88 ± 5.68	95.19 ± 9.56	t=1.317, p=0.192
Post 120 min Mean ± SD.	92.93 ± 5.16	95.36 ± 7.30	t=1.721, p=0.090

SD. Standard deviation – Max.t: Student t-test, P value comparing between melatonin and placebo, *: significant when p value<0.05.

Discussion

The effect in regulating the circadian rhythm, for melatonin may has a sedative/hypnotic effect [12]. At the same time due to modulation of gamma-aminobutyric acid (GABAA) receptors in the brain through its effect on melatonin receptors (MT1 and MT2) [13]. Affecting the GABAA receptor through the G protein-coupled pathway. It enhances the binding of GABA to the GABAA receptor [14], so it is similar to the pathway by which other anesthetics such as propofol and benzodiazepines act as anesthetics [15].

This study showed that the level of anxiety in the melatonin group was lower one hour before and after the operation [16], while no significant effect appeared before the insertion of the spinal needle (p<0,001).

showed that the comparison of systolic blood pressure between the two studied groups that the mean value was higher in melatonin group at preoperative, but the mean value was lower in melatonin group at min 120 postoperative, and this difference was statistically significant (p<0.05). regarding diastolic blood pressure [17], the result showed that patients who received melatonin, there were reduction at intraoperative in min 5&10, and this low was statistically significant (p<0.05), while patients who received placebo, the study showed that no change between the different times.and that the mean value of MAP was lower in melatonin group at min 5 intra operative, and this low was statistically significant (p<0.05), while the other times, the study showed no difference between the two studied groups [18].

A study comparing melatonin and gabapentin showed that both are beneficial for reducing anxiety and postoperative pain in lumbar spine surgery [19]. A study conducted in Canada from 2008-2010 on adults also showed that melatonin has an effective role in reducing anxiety compared to a placebo. level of anxiety was significantly lower with melatonin than with placebo (3 [11 %] of 27 vs. 9 [45 %] of 20; relative risk 0.25 [95 % CI 0.077–0.80]) in patients undergoing breast cancer surgery [20].

Our study also showed that the mean value of anxiety was lower in the melatonin group compared to the placebo group.

The impact of melatonin on intraoperative blood pressure has been examined in several studies, yielding inconsistent findings. Several studies have demonstrated that the administration of melatonin has the potential to induce a reduction in blood pressure, particularly among individuals diagnosed with hypertension [21].

The observed decrease in blood pressure can be ascribed to the regulatory influence of melatonin on vascular tone and its interaction with the autonomic nervous system [22]. Nevertheless, alternative research endeavors have failed to detect substantial alterations in blood pressure subsequent to the administration of melatonin.

The available evidence is currently limited, but it suggests that melatonin might possess the potential to stabilize blood pressure, thereby assisting in its maintenance within the normal range [23]. However, additional investigation is necessary in order to establish a comprehensive comprehension of the effects of melatonin on postoperative blood pressure.

It is important to acknowledge that various patient-specific factors, including initial blood pressure levels, pre-existing health conditions, and concurrent medication usage, may exert an impact on the individual's reaction to melatonin [24]. Furthermore, the simultaneous administration of other medications during surgical procedures and the subsequent recovery phase may potentially interact with melatonin, leading to alterations in blood pressure [25].

Melatonin affects GABA signals by stimulating GABAergic. Therefore, the interaction between melatonin and GABAergic appears to be a cause of neuropsychological effects such as the hypnotic activity of melatonin via GABAA receptors, which is blocked by GABAergic antagonists. These melatonin-induced changes in the neuro signaling pathway may contribute to its action as an anxiolytic [26-28].

Conclusions

Anxiety and the changes that accompany it affect hemodynamics(1). The physiology of anxiety is very complex, resulting in changes in the production of stress hormones and the pathways of nerve signals. These various manifestations lie behind the search for new safe therapeutic methods or alternatives to those used to treat the manifestations of anxiety. Melatonin, which is produced in the pineal gland, has been proven by animal and clinical studies to be a good anxiolytic through a specific mechanism. The pathological mechanism behind the benefit of melatonin in anxiety may lie in its sympathomimetic effect, inhibition of the renin-angiotensin and glucocorticoid systems, modulation of serotonergic GABA signaling, and its unusual antioxidant nature, where It is released into the cerebrospinal fluid and thus its concentration increases and is higher than its concentration in the blood, which makes it an anti-oxidant and anti-inflammatory after its concentration increases in nervous tissues and thus it is likely to be an anxiolytic.

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