Original Article

A Comparative Study of Effect of Oral Melatonin Versus Oral Midazolam as Premedicant in Children Undergoing Surgery Under General Anesthesia

Sunanda Gooty[1*], Devi Sai R Priyanka[2], Ravikanth Pula[1], Vandana Pakhare[1*], Gopinath Ramachandran[1]

Abstract

Background: Preoperative anxiety in children is associated with multiple post-operative outcomes like post-operative regressive behavioral disturbances, prolonged distress in the recovery phase, eating disorders, and bedwetting. The present study was designed to use low-dose oral melatonin versus oral midazolam in relieving pre-operative anxiety in children in the Indian population.

Materials and Methods: A prospective randomized comparative study was conducted on children aged between 2 to 10 years of age scheduled for elective surgeries under general anesthesia are included in the study. This study was conducted with a sample size of 70. Patients were randomly distributed into two groups of 35 content. Group A (received 0.2mg/kg melatonin as premedical) and group B (received 0.5mg/kg midazolam as premedical).

Results: Mean induction dose of propofol in the melatonin group was 52.143± 18.36 mg and in the midazolam, the group was 48.714 ± 16.6 mg. In our study, 90 minutes after premedication, the anxiety score was less in the midazolam group. There was no statistically significant difference between the sedation scores in melatonin and midazolam.

Conclusion: Low-dose melatonin (0.2mg/kg) is not an effective alternative premedicant in children to alleviate preoperative anxiety compared to midazolam.

Keywords: Melatonin, Midazolam, Pre-operative anxiety, Anesthesia, Propofol

1. Department of Anesthesiology, ESIC Medical College and Hospital, Sanath Nahar, Hyderabad, India
2. Post graduate, Department of Anesthesiology, ESIC Medical College and Hospital, Sanath Nahar, Hyderabad, India

***Corresponding Author:** Dr Vandana Pakhare, Assistant Professor, ESIC Medical College, Sanath Nahar, Hyderabad, 500080 India
Email: Vandana.Pakhare@gmail.com

Please cite this article as: Gooty S, Priyanka DSR, Ravikanth P, Pakhare V, Ramachandran G. A Comparative Study of Effect of Oral Melatonin Versus Oral Midazolam as Premedicant in Children Undergoing Surgery Under General Anesthesia. J Cell Mol Anesth. 2022;7(3):160-7. DOI: https://doi.org/10.22037/jcma.v7i3.37594

Introduction

In children, pre-operative anxiety is most familiar with adverse postoperative outcomes, like the emergence of delirium in the recovery phase and postoperative regressive behavioral disturbances, such as nightmares, bedwetting, separation anxiety from parents, and eating disorders (1). Relieving this anxiety is of the most significant importance for providing a calm and pleasant anesthetic experience and preventing an adverse impact on the psychological background of the child in the future (2).

Benzodiazepines (midazolam), chloral hydrate, and Triclofos are the most commonly used premedicants to reduce anxiety (3). Triclofos is excluded from the FDA drug list because of the same

reason we have chosen melatonin and midazolam in this study.

Melatonin is a ubiquitous molecule and hormone naturally produced by the pineal gland at night in humans (4). Melatonin has been proposed as an alternative premedicant to midazolam before anesthesia induction (5).

The literature review demonstrated that premedication with melatonin reduces anxiety and pain in neonates and children undergoing painful procedures (6). Also, premedication of melatonin compared with midazolam significantly reduced the induction dose of propofol for anesthesia for pediatric patients (7).

The study aims to compare the efficacy of oral Melatonin versus oral Midazolam as a premedicant in children undergoing elective surgeries under general anesthesia.

The primary objective of this study is to evaluate oral melatonin's efficacy on pre-operative anxiety and sedation in children undergoing surgery.

The secondary objective is to investigate the possible effect of melatonin premedication on the required induction dose of propofol in comparison to midazolam and to assess sedation scores in both groups after ten minutes from the conclusion of anesthesia.

Methods

The study was a prospective randomized comparative performed in the Department of Anesthesiology, ESIC Medical College and Super Specialty Hospital, Sanath Nagar, Hyderabad. The study population included children aged between 2 to 10 years of either sex, belonging to ASA grades I and II, scheduled for elective surgeries under general anesthesia are included in the study. The study was conducted for six months, from October 2019 to March 2020, after obtaining approval from the institutional ethical committee. The sample size included a Total of 70. It is based on the results of previous studies. The sample size required to get a 0.5 mg reduction of propofol dose is 35 in each group with alpha 0.01, power (1-beta) = 95, and enrollment ratio 1.

The inclusion criteria included ASA physical status I and II, Age between 2-10 years scheduled for elective surgery, and Patients coming for elective surgery. However, the Exclusion criteria included: Patient refusal, Patients who had taken benzodiazepines, opioid drugs, or other sedatives in the previous month, Patients who had sedation previously, and Patients undergoing emergency surgery.

Patients were randomly assigned to 2 groups based on computer-generated random number sequence whether they will receive 0.2 mg/kg (max 5 mg) oral melatonin premedication (group A) or 0.5 mg/kg (max 20 mg) oral midazolam premedication (group B).

Study procedure: A pre-anesthetic evaluation of previous medical and surgical illnesses, previous anesthesia exposures, drug allergies, clinical examination, airway examination, and baseline investigation of complete blood picture and blood sugar are done. These findings are recorded on a predesigned proforma. In their native language, the child's parents explained the nature of the study, and their signatures were obtained on the Informed Consent Form.

Annex 1- University of Michigan Sedation Scale (UMSS)

0	Awake and alert
1	Minimally sedated: tired or sleepy, appropriate response to verbal conversation, and/or sound.
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep aroused only with significant physical stimulation
4	Unarousable

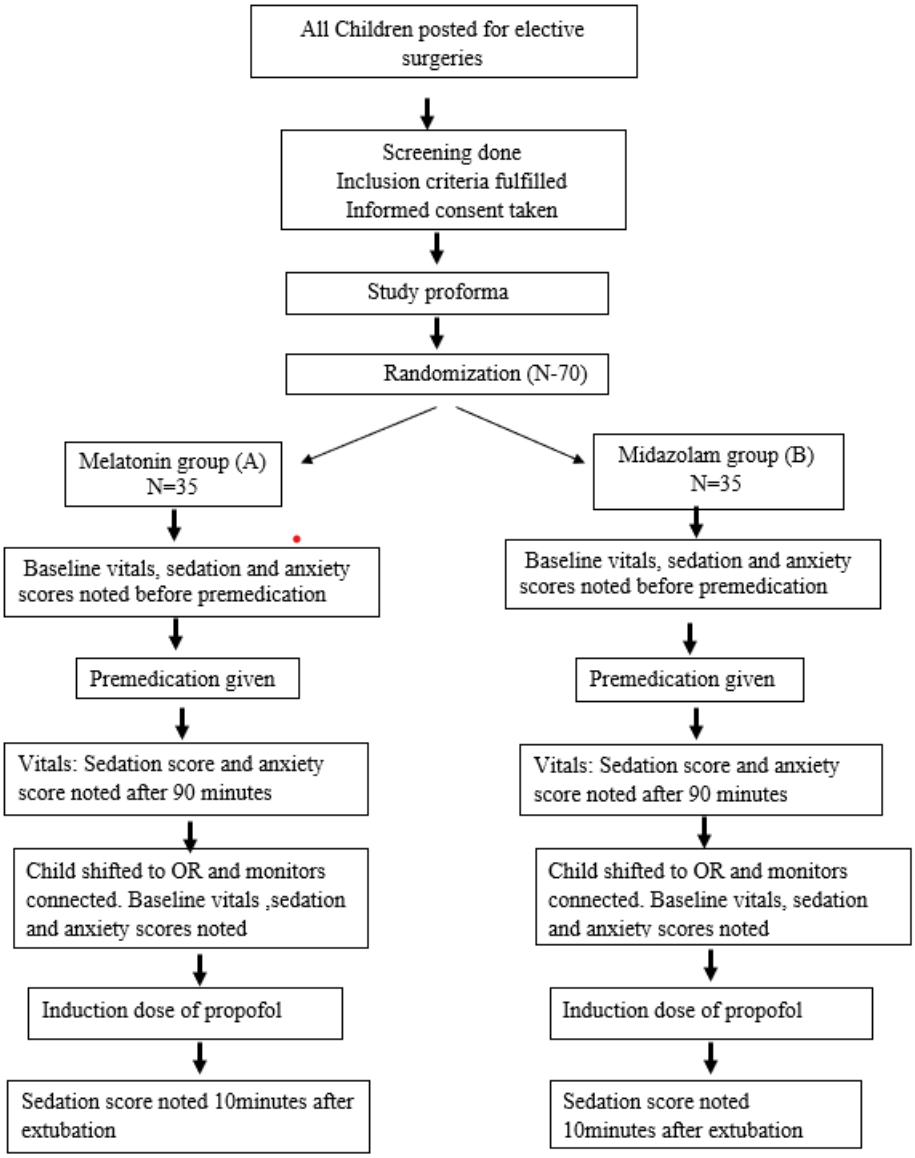

Figure 1. Study flow chart.

- The child was kept nil by mouth per pediatric fasting guidelines before surgery.
- Children between the age of 2 and 10 years scheduled for elective surgery were enrolled in the study.
- Children were randomly assigned to 2 groups based on a computer-generated random number sequence whether they would receive 0.2 mg/kg (max 5 mg) oral melatonin premedication (group A) or 0.5 mg/kg (max 20 mg) oral midazolam premedication (group B) before induction of anesthesia with propofol.
- Approximately90 minutes before the induction of general anesthesia, patients were transported to a quiet room where they received melatonin or midazolam syrup orally by a resident not involved in the study.
- The child's level of sedation and anxiety were assessed and recorded before the premedication and 90 minutes after the administration of melatonin or midazolam using the University of Michigan Sedation Scale (UMSS) (8), which has a score of 0-4 (**Annex** 1), and the modified Visual Analogue Scale (VAS) which has a score of 0-10 respectively.

Preparation of operation room: The Anesthesia machine was checked. Appropriately sized endotracheal tubes, working laryngoscope with medium and large-sized blades, stylet, drugs required for maintaining general anesthesia, and working suction apparatus were kept ready before the procedure.

- In the operating room, pre-operative vitals like pulse, blood pressure, respiratory rate, and temperature were checked, and an IV line was secured with a 24G or 22G cannula after applying EMLA cream. An initial induction dose of 1 mg/kg of intravenous propofol was administered to both groups, followed by additional doses of propofol as required.
- Standard anesthesia protocol was followed. The total dose of propofol administrated was recorded.
- University of Michigan Sedation Scale was calculated after 10 min from the conclusion of anesthesia for objective information on physical condition.
- Pre-operative and post-operative sedation scores and pre-operative anxiety scores will be assessed in both groups.

Statistical analysis: The following methods of statistical analysis were used in this study.

The results were averaged (mean ±standard deviation) for continuous data, and the number and percentage for dichotomous data were presented in tables and figures.

1) Proportions were compared using the Chi-square test of significance
2) The student "t" test for quantitative variables
3) Mann-Whitney test for median comparison
4) Bar charts and box plots were used for the visual representation of the analyzed data

In the above test, the "p" value of less than 0.05 was accepted as indicating statistical significance. Data were entered into Microsoft Excel (windows 7; version 2007), and analysis was carried out using Statistical Package for Social Sciences (SPSS).

Results

The present study was carried out on 70 children undergoing elective surgeries under general anesthesia with melatonin or midazolam as premedication. Patients included in the study were divided into two groups consisting of 35 each. The data has shown in table 1

The following data were compared between the two groups:

The mean age in the melatonin group was 6.171 years, and in the midazolam group, it was 5.286 years. On performing an unpaired T-test, the difference was not found to be statistically significant (P-value >0.05). The mean weight in the melatonin group was 19.07 kgs; in the midazolam group, it was 16.66 kgs. On performing an unpaired T-test, the difference was not found to be statistically significant (p-value >0.05) (Table 1).

In the melatonin group, 40% were females, and 60% were males. In the midazolam group, 28.6% were females, and 71.4% were males. On performing the chi-square test, this difference was not found to be statistically significant (p-value >0.05) (Table 2).

In the melatonin group, 80% were ASA grade 1, and 20% were ASA grade 2. In the midazolam group, 82.9% were ASA grade 1, and 17.1% were ASA grade 2. On performing the chi-square test, this difference was not found to be statistically significant (p-value >0.05) (Table 2).

The mean induction dose of propofol in the melatonin group was 52.143 mg; in the midazolam group, it was 48.714 mg. On performing an unpaired T-test, the difference was not found to be statistically significant (p-value >0.05).

As shown in figure 2, before premedication, before induction, and 10 min after extubation, the median anxiety scores were not significantly different between the two groups (P value>0.05). Only at 90 minutes after premedication was the median anxiety score more in the melatonin group than in the midazolam group, which was found to be statistically significant (p-value <0.05).

As shown in Figure 3, at all readings before premedication, 90 minutes after premedication before induction, and 10 min after extubation, the median sedation scores were not significantly different between the two groups (p-value >0.05).

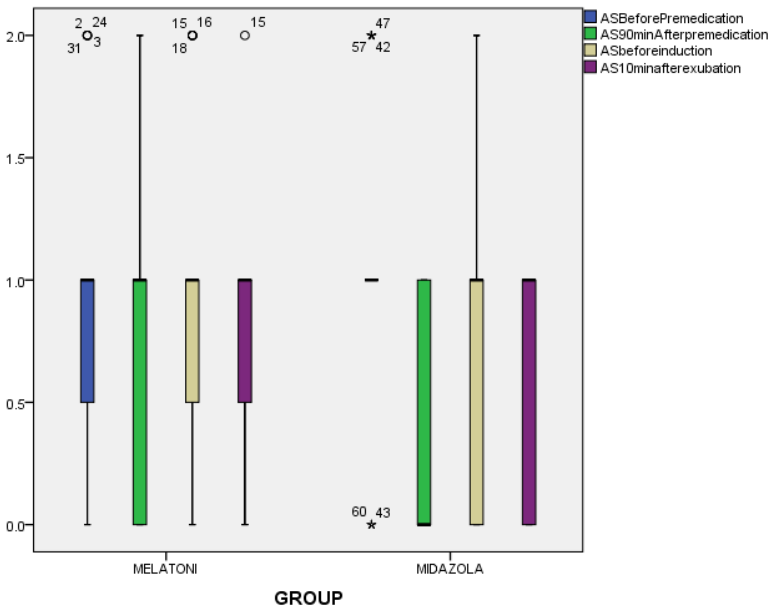

Figure 2. Comparison of anxiety scores between group A and group B.

Discussion

According to our study, results indicate that oral midazolam 0.5mg/kg caused better anxiolysis in children when compared to 0.2mg/kg of oral melatonin in children ($p<0.05$), and there is no statistically significant difference in sedation scores ($p>0.05$) in both the groups. Concerning the induction dose of propofol, there is no statistically significant difference in both groups (p-W.416).

In the study conducted by Kain ZN et al., (9) oral melatonin was compared in doses of 0.05mg/kg, 0.2mg/kg, 0.4mg/kg with oral midazolam 0.5mg/kg. They reported that oral melatonin was less effective than oral midazolam in reducing pre-operative anxiety, which is consistent with our study. In the study conducted by Samarkand et al., (10) melatonin and

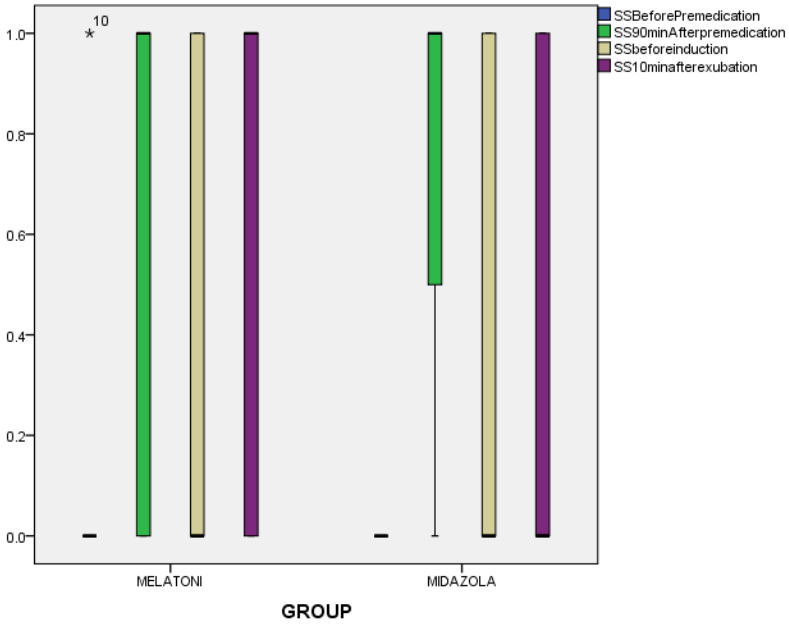

Figure 3. Comparison of sedation scores between group A and group B.

Table 1: Comparison of age and weight distribution in both groups.

VARIABLE	MELATONIN MEAN ± SD	MIDAZOLAM MEAN ± SD	P VALUE
AGE (YEARS)	6.171 ± 2.514	5.286 ± 2.561	0.149
WEIGHT (KGS)	19.077 ± 6.566	16.66 ± 4.84	0.085

midazolam, each in doses of 0.25 or 0.5 mg/kg respectively, were found to be equally effective as premedicant in relieving separation anxiety and anxiety associated with the introduction of the anesthesia mask and is comparable with the present study concerning anxiety scores in both the groups.

Concerning sedation scores before premedication, 90 minutes after premedication, before induction, and 90 minutes after extubation showed no statistically significant difference in both the groups. This result is consistent with the study conducted by Eloisa Gitto et al. (11). They concluded that there was no statistically significant difference in sedation scores in both melatonin and midazolam groups.

As per the presently available literature, there is no consensus on the appropriate dose of melatonin for sedation in children. In previous studies by Cauffield JS et al. and Jan JE et al., melatonin dosing for sedation in children is reported to be between 0.3mg and 20mg (12, 13) maximum doses of up to 20mg have been administered to older children without side effects apart from sedation (14). Moreover, what remains unclear is the most appropriate dose to induce sedation. Based on previous studies and the present study, higher doses of up to 20mg may be required for anxiety relief. Given patient safety, larger doses of melatonin were not used in our study even though it was indicated in previously published literature. It may be a possible reason for higher anxiety scores in the melatonin group in our study, as we used a low dose, i.e., 0.2mg/kg.

In this study, the mean induction dose of propofol in the melatonin group was52.143±18.36 mg, and midazolam group, it was 48.714 ± 16.6 mg. So, the induction dose of propofol in both groups is comparable, and there is no statistically significant difference in the dose of propofol required for induction. This result is in contrast to the study conducted by Eloisa Gitto et al. (11). where melatonin caused a significant decrease in the dose of propofol. It might be due to the higher dose of melatonin used in their study, i.e., 0.5mg/kg, whereas we used a low dose of melatonin in this study, i.e., 0.2mg/kg. Also,

Table 2: Distribution of patients based on gender, ASA status.

VARIABLE	MELATONIN N (%)	MIDAZOLAM N (%)	TOTAL N (%)
FEMALE	14 (40)	10 (28.6)	24 (34.3)
MALE	21 (60)	25 (71.4)	46 (65.7)
ASA GRADE 1	28 (80)	29 (82.9)	57 (81.4)
ASA GRADE 2	7 (20)	6 (17.1)	13 (18.6)
TOTAL	35 (100)	35 (100)	70 (100)

Table 3: Comparison of induction dose of propofol between two groups.

VARIABLE	MELATONIN MEAN ± SD	MIDAZOLAM MEAN ± SD	P VALUE
INDUCTION DOSE OF PROPOFOL (MG)	52.143 ± 18.362	48.714 ± 16.686	0.416

propofol was administered in this study in an incremental dose fashion. Bolus administration of propofol needs a significantly smaller dose to abolish the eyelash reflex than total administration of propofol. Therefore, the doses needed in our study may not represent the dose required in bolus administration used in a usual clinical setting.

The limitations of this study are that we have not used larger doses of melatonin because patient safety would have reduced anxiety scores to a greater extent. Despite that, previous studies (9-11) used similar or smaller doses than those used in our study and reported satisfactory effects of melatonin on anxiety. Secondly, to maintain similar endogenous melatonin levels, we did not recruit children who were scheduled for surgery before 9:00 AM. Theoretically, the doses used in our study could be effective for children who received melatonin very early in the morning. Another concern is the issue of the bioavailability of the melatonin that was used in our study. The bioavailability of melatonin used in our research is unknown and may vary with the individual.

Limitations

1. This study did not include children undergoing emergency surgeries.
2. Absence of control group.
3. The sample size in our study may be less to draw the conclusions
4. This study consisted of ASA grade 1 and 2 patients; our observations cannot be applied to ASA grade 3 and 4 patients.

Conclusion

Based on the results of our study, we concluded that melatonin had not shown a comparable effect as midazolam in relieving pre-operative anxiety in children. Still, the resulted sedation scores were similar in both groups. This study also concluded that midazolam had a more significant effect in reducing the propofol dose, whereas melatonin had a more negligible effect in reducing the propofol induction dose. Hence, low-dose melatonin (0.2mg/kg) is not an adequate premedicant for children to alleviate preoperative anxiety compared to midazolam.

Acknowledgment

I want to convey my heartfelt thanks to the Dean of the institution, Dr. M. Srinivas, ESIC Medical College, and Hospital, for permitting me to do the study. We are deeply indebted to Dr. S. Kalyani Surya Dhana Lakshmi, Associate Professor, and Dr. P. Vandana, Assistant Professor, Department of Anesthesiology, who constantly supervised my study activity, and collection of literature material, study group, and preparation of the master chart.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Perry JN, Hooper VD, Masiongale J. Reduction of preoperative anxiety in pediatric surgery patients using age-appropriate teaching interventions. J Perianesth Nurs. 2012;27(2):69-81.
2. Kain ZN, Caldwell-Andrews AA, Mayes LC, Weinberg ME, Wang SM, MacLaren JE, et al. Family-centered preparation for surgery improves perioperative outcomes in children: a randomized controlled trial. Anesthesiology. 2007;106(1):65-74.
3. Gupta A, Gunjan, Shekhar S, Gupta S, Gupta A. Comparison of

Oral Triclofos and Oral Midazolam as Premedication in Children undergoing Elective Surgery. Anesth Essays Res. 2019;13(2):366-9.
4. Amaral FGD, Cipolla-Neto J. A brief review about melatonin, a pineal hormone. Arch Endocrinol Metab. 2018;62(4):472-9.
5. Impellizzeri P, Vinci E, Gugliandolo MC, Cuzzocrea F, Larcan R, Russo T, et al. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients. Eur J Pediatr. 2017;176(7):947-53.
6. Kettle J, Deery C, Bolt R, Papaioannou D, Marshman Z. Stakeholder perspectives on barriers and enablers to recruiting anxious children undergoing day surgery under general anaesthetic: a qualitative internal pilot study of the MAGIC randomised controlled trial. Trials. 2021;22(1):458.
7. Norouzi A, Fateh S, Modir H, Kamali A, Akrami L. Premedication effect of melatonin on propofol induction dose for anesthesia, anxiety, orientation and sedation after abdominal surgery: a double-blinded randomized trial. Med Gas Res. 2019;9(2):62-7.
8. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth. 2002;88(2):241-5.
9. Kain ZN, MacLaren JE, Herrmann L, Mayes L, Rosenbaum A, Hata J, et al. Preoperative melatonin and its effects on induction and emergence in children undergoing anesthesia and surgery. Anesthesiology. 2009;111(1):44-9.
10. Samarkandi A, Naguib M, 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(3):189-96.
11. Gitto E, Marseglia L, D'Angelo G, Manti S, Crisafi C, Montalto AS, et al. Melatonin versus midazolam premedication in children undergoing surgery: A pilot study. J Paediatr Child Health. 2016;52(3):291-5.
12. Jan JE, Hamilton D, Seward N, Fast DK, Freeman RD, Laudon M. Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. J Pineal Res. 2000;29(1):34-9.
13. Cauffield JS, Forbes HJ. Dietary supplements used in the treatment of depression, anxiety, and sleep disorders. Lippincotts Prim Care Pract. 1999;3(3):290-304.
14. Gitto E, Karbownik M, Reiter RJ, Tan DX, Cuzzocrea S, Chiurazzi P, et al. Effects of melatonin treatment in septic newborns. Pediatr Res. 2001;50(6):756-60.