Original Article

Oral Melatonin Versus Placebo In Preoperative Anxiety Relief

Dr. S. Sree Ranjani[1] , Dr. D. Venkateswarlu[2] , Dr. J. Mohanasundaram[3] , Dr. N. Sudhakar[4]

[1]MBBS, DA, DNB (Anaesthesiology), FIPM, MHA Vice Principal (Admin) and Professor & Head, Dept. Of Anaesthesiology, Bhaarath Medical College & Hospital, (A unit of BIHER), Chennai, Tamil Nadu, Corresponding Author:
[2]MBBS, MD (Gen. Medicine) Professor & Head, Dept. Of General Medicine, Bhaarath Medical College & Hospital, (A unit of BIHER), Chennai, Tamil Nadu
[3]MBBS, M.D Professor, Dept. Of Pharmacology, Bhaarath Medical College & Hospital, (A unit of BIHER), Chennai, Tamil Nadu
[4]MBBS, MS (Gen. Surgery), MRCS, MCh (Urology) Professor & Head, Dept. Of General Surgery, Bhaarath Medical College & Hospital, (A unit of BIHER), Chennai, Tamil Nadu
DOI: 10.47750/pnr.2023.14.02.115

Introduction:

Before surgery and administration of anaesthesia, the patient goes through an unpleasant state which is called 'preoperative anxiety.' If left untreated, this is not only uncomfortable for the patient but is also associated with circulatory disturbances, psychological problems, infection etc.
To prevent this, some drugs such as benzodiazepines have proved themselves useful, but they have their share of adverse effects. Melatonin is a new addition in the armamentarium of the anaesthesiologist. This study will compare Melatonin with a placebo for preoperative anxiolysis.

Aim of the study:

To determine the anxiolytic effect of Melatonin compared with placebo, when administered as pre anaesthetic medication before surgery.

Objectives of the study:

- Anxiolysis
- Adverse effects

Materials and Methods:

Institutional ethical committee approval was taken.
Study design: This is a double blinded randomized controlled clinical trial.
Study Population:

- Inclusion criteria: Patients between 18 – 60 years of age, of ASA – PS classification I and II, posted for surgeries such as Hemorrhoidectomy, Lateral sphincterotomy or Herniorrphy under spinal anaesthesia.
- Exclusion criteria: patients on anti-psychotic drugs, with sleep disorders, unwilling to join, allergy to melatonin, previously on long-term melatonin

Sample size:

The sample size of the study was calculated from a previous placebo-controlled trial by Edwin Seet et al[1] on preoperative anxiety who found that a sample size of 33 patients per group was required.
Randomisation: The patients were randomized to 2 groups of 33 each using computer based randomisation. Group A – oral melatonin & Group B – placebo.

Description of the clinical intervention:

Patient's anxiety and adverse effects if any were assessed by another trained anesthesiologist who was blinded to the group that the patient belongs to. Anxiety was assessed using NRS anxiety score. The NRS is 'numerical rating scale' with score from 0 to 10. Score 0 means no anxiety, 1,2,3……9 indicates increasing levels of anxiety and a score of 10 indicates highest & worst level of anxiety.

Adverse effects noted were Excessive Sedation, changes in Orientation, nausea, vomiting, visual disturbances, changes in the vital parameters of heart rate, Blood Pressure, SPO2 and Respiratory rate. Sedation was assessed by "The Observer's Assessment of Alertness/Sedation (OAA/S) Scale Score"[2] from 5 to 0. 5 - Fully awake, 4 - Lethargic responses to name spoken in normal tone, 3 - Responds only after name is called loudly or repeatedly called, 2 - Responds only after mild prodding or shaking, 1 - Responds only after squeezing the trapezius and 0 - Does not respond after squeezing the trapezius. Orientation was scored from 3 to 0. 0 = none, 1 = orientation to either space or time or person, 2 = orientation to 2 of the 3 parameters space/time/person and 3 = orientation to space, time and person.

The drug was administered to the patient 90 min before proposed induction time. Tablet Melatonin in the dose of 0.1mg/kg body weight or the placebo 3ml sterile water given from snapoff ampoules orally, according to the group. Patient was asked to relax on the bed after taking the drug and monitored throughout. After 60min, patient was assessed again.

Statistical analysis: The parameters were subjected to Statistical analysis using statistical software STATA 11.0. The p value of <0.05 were considered as significant. Continuous variables were represented as Mean (SD), and categorical variables were represented as Frequency (percentage). Chi-square test or Fisher's exact tests were used to assess differences in categorical data. Wilcoxon sign rank test, Mann Whitney U test and Kruskal Wallis test were also used.

Table 1: Analysis of Demographics

		Group A	Group B	P value
Gender	Female	21(63.64%)	21(63.64%)	1.000
	Male	12(36.36%)	12(36.36%)	
Age	18-40 years	16(48.48%)	23(69.70%)	0.080
	41-60 years	17(51.52%)	10(30.30%)	
ASA grade	I	14(42.42%)	16 (48.48%)	0.6237
	II	19(57.58%)	17 (51.51%)	

Table 2: Analysis of parameters after drug administration

	Group A	Group B	P-value
Anxiety	3.66±0.88	6.24±1.87	**<0.001***
Sedation Score	4.81±0.39	4.84±0.36	0.7431
Orientation	3±0	3±0	1.000
Nausea/ vomiting	1(3.03%)	0	0.314
Heart Rate	81.33±4.26	81.54±3.97	0.8519
Blood Pressure (MAP)	83.45±0.36	85.75±0.61	0.9782
SpO2	99.57±0.50	99.57±0.56	0.8868
Respiratory Rate	13.45±0.61	13.60± 0.89	0.4825

Figure 1: Analysis of parameters after drug administration

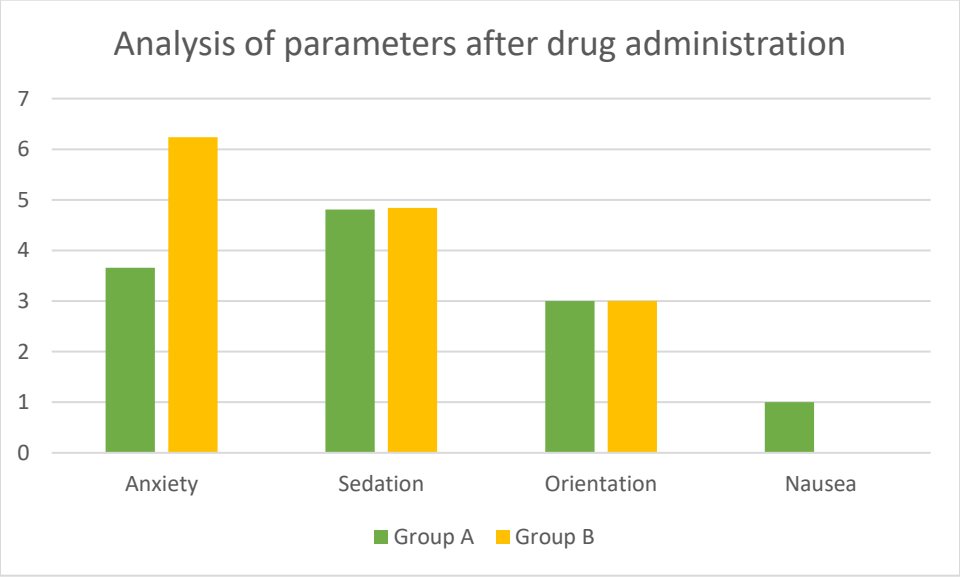
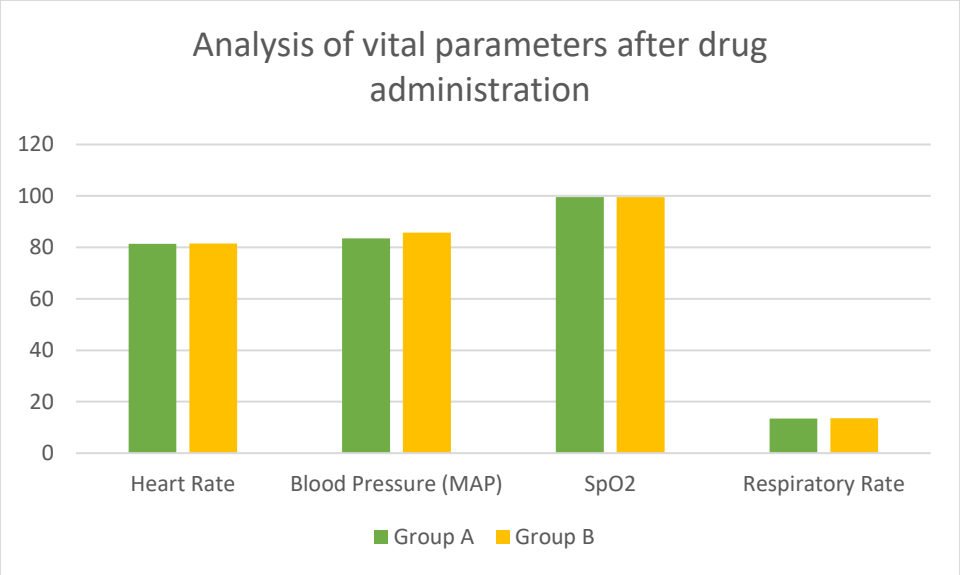


Figure 2: Analysis of vital parameters after drug administration



Results: Between the groups, there was no statistically significant difference in the demographics and the anxiety levels before medication. The degree of anxiolysis alone, after medication was significantly different with patients in Group A melatonin group having more anxiolysis compared to placebo group B. But comparison of the adverse effects such as excessive sedation, changes in orientation, nausea, and vital parameters, there was no statistically significant difference. No other adverse effects were seen in either group.

Discussion:

A state of anxiety is said to lower the pain threshold.[3] It also makes a person overestimate their intensity of pain.[4] An unallayed pre - operative anxiety causes a host of perioperative problems. Hence the need for pre anesthetic anxiolytic medications. In our study, melatonin was compared with a placebo.

An analysis by Sanchez – Barcelo[5] on numerous clinical trials done during the last 20 years on melatonin, have examined its therapeutic usefulness in different fields of medicine such as treatment of eye diseases, cardiovascular diseases, blood diseases, infectious diseases, sleep disturbances, hemodialysis, etc. The use of melatonin in anaesthetic procedures has been also confirmed and it was concluded that melatonin has very low toxicity over a wide range of doses.[6]
Studies by Naguib et al[7] and Yousaf et al[8] in 2010 concluded that Melatonin possesses sedative, hypnotic, analgesic, anti-inflammatory, anti-oxidative and chronobiotic properties that make it an alternative pre-medicant.

In our study, the anxiolysis produced by melatonin was higher and statistically significant as compared to the placebo group. The sedative and anxiolytic effects of melatonin are due to its action on MT (1) and MT (2) melatonin receptors present in the suprachiasmatic nucleus (SCN) of the hypothalamus.[9] A few patients responded to the placebo effect. The placebo effect is defined as a phenomenon in which some people experience a benefit after the administration of an inactive "look-alike" substance having no known medical effect. According to Brown et al,[10] if you believe that you will experience something and expect it, then even a placebo will work. Similarly, people who are highly motivated and trust the treatment to work will experience a placebo effect. Hall and Lembo[11] have found that Placebo works in people with a Gene variant that codes for higher levels of dopamine in the brain.

Contrary to our study findings, a study by Isik et al[12] with 2 doses found no significant differences in anxiolysis between melatonin and a placebo when administered to children undergoing dental treatment. Some studies[13,14] have shown that the Elderly population is resistant to the hypnotic and anxiolytic effects of melatonin.

Regarding all the other parameters, there was no significant difference between the two groups. Of the adverse effects, only nausea was observed in melatonin groups, and this was statistically insignificant. Melatonin is known to cause nausea.[15] Thus in our study, melatonin has been a very safe drug and remarkably well-tolerated. This is similar to another study by Seabra et al[16]; who have reported side effects of nausea in 3%; but with very high doses Dizziness, headache and irritability were seen. Patients on melatonin said they were feeling fresh after waking up and the reason could be because melatonin increased REM sleep which is restful sleep.[17,18] All patients in the melatonin groups stated that they were satisfied with the premedication whereas 79% (26/33) patients in the placebo group said they would prefer a different premedicant in future.

Thus, melatonin turns out to be an effective drug for anxiolysis with less side effects. Given the safety profile, melatonin can be used in Ambulatory or day care surgeries and in patients with psychiatric & neurological conditions. It can be safely advocated for use in centres with less facilities for perioperative monitoring.

Conclusion: Oral Melatonin in the dose of 0.1mg/kg body weight provided effective preoperative anxiolysis as compared to a placebo with minimal adverse effects. Hence oral melatonin is an effective drug for effective preoperative anxiolysis.

Limitation of the study: This study was not conducted in pediatric and elderly population. Only one dose was studied.

References:

1. Edwin Seet1, MBBS, MMed, Chen Mei Liaw1, MBBS, MMed, Sylvia Tay2, FDSRCS, Chang Su3, MS. Melatonin premedication versus placebo in wisdom teeth extraction: a randomised controlled trial. Singapore Med J 2015; 56(12): 666-671 doi: 10.11622/smedj.2015186
2. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol. 1990;10(4):244-251.
3. Rhudy JL, Meagher MW.Fear and anxiety: divergent effects on human pain thresholds. Pain. 2000;84:65-75.
4. Al Absi M, Rokke PD.Can anxiety help us tolerate pain?. Pain. 1991;46:43-51.
5. Sánchez-Barceló EJ, Mediavilla MD, Tan DX, Reiter RJ. Clinical uses of melatonin: evaluation of human trials. Curr Med Chem. 2010;17(19):2070-95. doi: 10.2174/092986710791233689. PMID: 20423309. (pubmed)
6. Wetterberg L.Melatonin and clinical application. Reprod Nutr Dev. 1999;39:367-82.
7. Naguib M, Gottumukkala V, Goldstein PA.Melatonin and anesthesia: a clinical perspective. J Pineal Res. 2007;42:12-21.
8. Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: A qualitative systematic review of randomized trials. Anesthesiology. 2010;113:968–76. [PubMed] [Google Scholar]
9. Rosenstein RE, Cardinali DP. Central gabaergic mechanisms as targets for melatonin activity in brain. Neurochem Int. 1990;17(3):373-9. doi: 10.1016/0197-0186(90)90019-p. PMID: 20504637.
10. Brown WA. Expectation, the placebo effect and the response to treatment. R I Med J (2013). 2015;98(5):19-21.
11. Hall KT, Lembo AJ, Kirsch I, et al. Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. PLoS One. 2012;7(10):e48135. doi:10.1371/journal.pone.0048135
12. Isik B, Baygin O, Bodur H.Premedication with melatonin vs midazolam in anxious children. Paediatr Anaesth. 2008;18:635-41.
13. Chan RC, Shum D, Toulopoulou T, Chen EY (March 2008). "Assessment of executive functions: review of instruments and identification of critical issues". Archives of Clinical Neuropsychology. 23 (2): 201–216. doi:10.1016/j.acn.2007.08.010. PMID 18096360.
14. Lee, Yong-Won & Sawaki, Yasuyo. (2009). Cognitive Diagnosis Approaches to Language Assessment: An Overview. Language Assessment Quarterly - LANG ASSESS Q. 6. 172-189. 10.1080/15434300902985108.

15. Andersen LP, Gögenur I, Rosenberg J, Reiter RJ. The Safety of Melatonin in Humans. Clin Drug Investig. 2016 Mar;36(3):169-75. doi: 10.1007/s40261-015-0368-5. PMID: 26692007.
16. Seabra ML, Bignotto M, Pinto LR, Tufik S. Randomized double blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. J Pineal Res. 2000;29:193–200. [PubMed] [Google Scholar]
17. Descamps A, Rousset C, Millan MJ, Spedding M, Delagrange P, Cespuglio R. Influence of the novel antidepressant and melatonin agonist/serotonin2C receptor antagonist, agomelatine, on the rat sleep-wake cycle architecture. Psychopharmacology. (2009) 205:93–106. 10.1007/s00213-009-1519-2 [PubMed] [CrossRef] [Google Scholar] [Ref list]
18. Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. Intensive Care Med 2004; 30:197-206.