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Original Article

Anaesthesia Section

Effect of Preoperative Oral Melatonin on Postoperative Sedation and Analgesia among Patients undergoing Elective Surgery under General Anaesthesia: A Randomised Controlled Study

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ABSTRACT

Introduction: Postoperative pain is one of the major causes of dissatisfaction and prolonged hospital stay in patients undergoing surgery under general anaesthesia. Melatonin has been used for sleep regulation and Intensive Care Unit (ICU) sedation but there is limited knowledge regarding its effect postoperative analgesia and sedation.

Aim: To evaluate the effects of preoperative melatonin on postoperative sedation and analgesia.

Materials and Methods: This randomised controlled study was conducted from June 2020 to June 2021, at Mahatma Gandhi Memorial Medical College and M.Y. Hospital, Indore, Madhya Pradesh, India. Total 100 patients belonging to American Society of Anaesthesiologists (ASA) grade I and II of either gender, of age 18-60 years who were planned for elective surgery under general anaesthesia were randomly divided into two groups. Group M (n=50) was given 6 mg oral melatonin (two capsules of 3 mg each), and group C (n=50) was given multivitamin capsules, 90 minutes before induction of anaesthesia. General anaesthesia was induced using standard method for both the groups. Sedation score was assessed in preoperative period as well as after giving drugs and till four hours postoperatively by using Ramsay Sedation score. Pain was evaluated by Visual Analogue Scale (VAS) score till 8 hours postoperatively. Time of request of first rescue analgesia was noted and compared to that of control group.

Results: At preoperative time sedation score was comparable between both the groups. At postoperative time, sedation score 4 was seen in significantly higher number of patients of group M in comparison to group C, while at all the other time intervals, sedation scores were comparable between the two groups. Mean VAS score was found to be significantly higher in group C (3.2±0.4) in comparison to group M (3.02±0.14), four hours postoperatively. The mean time to request for first rescue analgesia in group M was 7.27±1.01 hours and in group C was 5.40±0.78 hour (p-value=0.001).

Conclusion: Preoperative oral melatonin can be used to effectively reduce the postoperative pain without producing undue sedation.

Keywords: Postoperative pain, Ramsay sedation score, Rescue analgesia

INTRODUCTION

General anaesthesia is the preferred mode of anaesthesia for many elective and emergency surgeries thus limiting the postoperative analgesic effect. Moderate to severe postoperative pain can decrease mobility in the immediate postoperative period, cause major discomfort and delay hospital discharge.

Most commonly used modality for providing postoperative pain relief is through opioid analgesics. However, opioids have several side effects such as sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance and respiratory depression. These clinical concerns may thus prevent proper prescribing and in turn lead to inadequate pain management.

Pre-emptive analgesia is a treatment modality which is initiated before the surgery in order to prevent the establishment of central sensitisation evoked by the incisional and inflammatory injuries occurring during the surgery and in the early postoperative period [1]. Pre-emptive analgesia can be used effectively to mitigate pain in postoperative period rather than treating it after the surgery.

Melatonin is an endogenous hormone secreted by pineal gland, primarily associated with regulation of sleep-wake cycle which is its chrono biotic action. It is known for its hypnotic actions as well as potent analgesic properties in a dose dependent manner [2,3]. Exogenously administered melatonin helps to synchronise the sleep cycle in certain sleep disorders as jet lag and insomnia [4]. It has got anti-inflammatory, antioxidant and antihypertensive effects [5]. It produces no hangover effect and lacks negative effects like addiction, dependence and does not produce any cognitive impairment [6].

Melatonin currently is being used primarily for sleep regulation and has been evaluated for sedation in Intensive Care Unit (ICU) and as preoperative anxiolytic agent [7]. The literature currently available, provides varied conclusions for its us as well as doses. It has been studied in reducing blood pressure and heart rate in different doses of 6 mg and 9 mg was found to be equally efficacious [8]. Very few studies have been conducted to evaluate and explore its potential to reduce postoperative pain.

In the light of effects of melatonin in hypnosis, anxiolysis, antihypertensive and sympatholytic actions and unique mechanism with high margin of safety [9-12]. The primary aim of this study was to evaluate if melatonin can be effectively used preoperatively to reduce postoperative pain and evaluate its sedative effect in preoperatively as well as postoperative period. The secondary aim was to evaluate any adverse effects of melatonin.

MATERIALS AND METHODS

This randomised controlled study was conducted from June 2020 to June 2021, at Mahatma Gandhi Memorial Medical College and M.Y. Hospital, Indore, Madhya Pradesh, India. The approval from Institutional

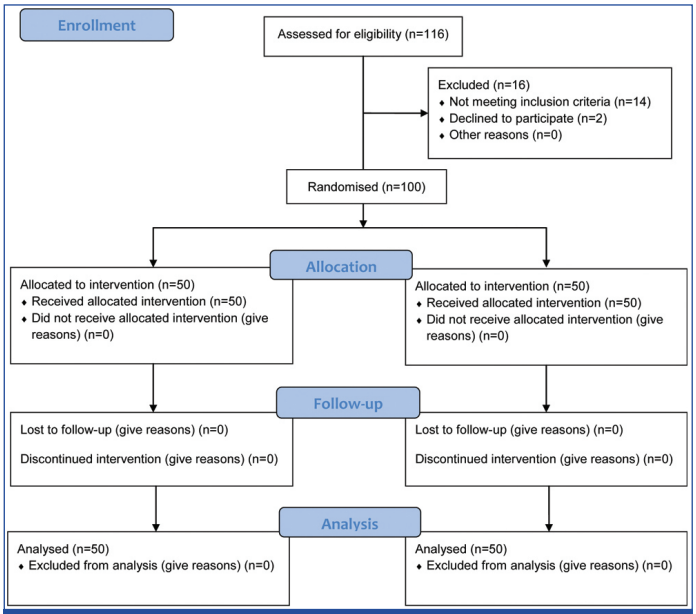
Ethics and Scientific Review Committee was obtained (IEC/MGM/feb/37). Written informed consent was taken from all patients.

Sample size calculation: Sample size was calculated based on comparison of means of two independent groups available in MedCalc version 19. Considering the mean±SD of Systolic Blood Pressure (SBP) of both the groups based on the study done by Gupta P et al., in which the mean SBP at two hours in group M was 119.10±8.36 mmHg and group C was 124.80±6.30 mmHg [13]. Putting these values in the MedCalc software, a sample size of 28 was obtained for each group, at a confidence interval of 95%, and power of study at 80%. However, the sample size of 50 each was considered for each groups.

Inclusion criteria: Total 100 patients belonging to American Society of Anaesthesiologists (ASA) grade I and II of either gender, of age 18-60 years, Mallampati class I and II, planned for elective surgery under general anaesthesia of duration one to two hours were included in the study.

Exclusion criteria: Patients with known hypersensitivity to melatonin, surgery of time duration of <1 hour and >2 hours, pregnancy and lactation and patients on chronic neuroleptic medications, tricyclic antidepressants, serotonin and nor epinephrine reuptake inhibitors, alcohol abuse, immunosuppressants, oral contraceptives, anticoagulants, antidiabetic medications and antihypertensives were excluded from the study.

On the morning of surgery, the patients were assigned into either group randomly, by chit method [Table/Fig-1]. Before administration of drugs sedation score was noted for both the groups, by using Ramsay Sedation score [14].



[Table/Fig-1]: CONSORT chart.

- Group M (study group, n=50): All patients were given oral melatonin capsules 6 mg (two capsules of 3 mg each)
- Group C (control group, n=50): All patients were given two oral multivitamin capsules with a sip of water, 90 minutes before surgery by the nurse.

Study Procedure

At 90 minutes after the administration of drugs, preoperative sedation score was noted and then shifted to operation theatre. Multipara monitor was connected after preoxygenation with 100% oxygen, intravenous inj. midazolam 0.05 mg/kg and inj. fentanyl 2 mcg/kg was given and induction was done with propofol 2 mg/kg. Laryngoscopy and intubation was facilitated with intravenous inj. succinylcholine 1.5 mg/kg.

Anaesthesia was maintained with 60% nitrous oxide in oxygen along with isoflurane and muscle relaxation was maintained with intravenous inj. atracurium loading dose 0.5 mg/kg and maintenance dose 0.1 mg/kg. Inj. paracetamol was given one hour after induction of anaesthesia to all the patients. At the end of the surgery, residual blockade was reversed with inj. neostigmine 0.05 mg/kg and inj. glycopyrrolate 0.01 mg/kg and estuation was done after return of reflexes. Patient was monitored for 10 minutes in the operation theatre before shifting to Postanaesthesia Care Unit (PACU). In the postoperative period, if there was vomiting, Inj. ondansetron was given and Inj. paracetamol was given for treatment of headache. VAS score is a numeric score of assessing subjective pain on a scale of 0 to 10 as no pain and worst pain experienced.

STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package of Social Science (SPSS) version 20.0, Chicago Inc. USA. Minitab version 17.0 was used for calculating the p-values. To test the normality Kolmogorov-Smirnov test was applied. Comparison of means between the two groups was done using unpaired t-test. Descriptive statistics was presented in the form of numbers and percentages. The p-value <0.05 was taken as statistically significant.

RESULTS

The study included 53 male and 47 females. Mean age distribution was 36.26±12.74 years in group M and 38.28±13.47 years in group C. Most of the patients belonged to ASA grade I. The mean duration of surgery was 102.30 minutes in group M and 103.68 minutes in group C [Table/Fig-2].

Variable	Group M (Mean±SD)	Group C (Mean±SD)	p-value
ASA grade I/II	41/9	42/8	0.790*
Gender male/female	26/24	27/23	0.841*
Duration of surgery (minutes)	102.30	103.68	0.620**
Age (years)	36.26±12.74	38.28±13.47	0.443**

[Table/Fig-2]: Demographic Data.
Fischer's exact test*; Unpaired t-test**; p-value <0.05 was taken as statistically significant

Preoperatively, all the patients in both the groups had a sedation score 2. In the immediate postoperative period just after estuation, group M patients had more sedation score (p-value=0.039), while at all time intervals in postoperative period sedation score was comparable in both the groups (p-value >0.05), and there was no undue sedation noted in group M [Table/Fig-3].

The mean VAS was significantly higher at four hours of estuation in group C (3.2±0.4) in comparison to group M (3.02±0.14) (p-value=0.004). Whereas, at 6 hours and 8 hours, the mean VAS was significantly higher in group M compared to group C (p-value=0.049 and p-value=0.001, respectively), as analgesic medication was administered earlier in control group [Table/Fig-4].

The mean time to request for first rescue analgesia was significantly shorter in group C in comparison to group M (p-value=0.001) [Table/Fig-5]. Intraoperative bradycardia was seen in two patients in each group and hypotension was seen in three patients in group M and two patients in group C which was statistically not significant (p-value >0.05). Hypertension was found in four patients in group M and in 14 patients in group C which was statistically significant (p-value=0.017) [Table/Fig-6].

Vomiting was seen in three patients in each group in postoperative period, while headache was seen in three patients in group M and four in group C, which were statistically not significant [Table/Fig-7].

DISCUSSION

Melatonin has immense diversity and versatility. It is best known by medical professionals and lay persons for its hypnotic actions, and is also a potent analgesic, in a dose dependent manner. This study was aimed to evaluate the efficacy and safety of oral

Sedation score	Preoperative		Postoperative (Te)		At 30 minutes		At 1 hour		At 2 hours		At 3 hours		At 4 hours	
	Group M	Group C	Group M	Group C	Group M	Group C	Group M	Group C	Group M	Group C	Group M	Group C	Group M	Group C
1														
2	50 (100%)	50 (100%)			16 (32%)	18 (36%)	49 (98%)	48 (96%)	50 (100%)	49 (98%)	50 (100%)	50 (100%)	50 (100%)	50 (100%)
3			32 (64%)	42 (84%)	34 (68%)	32 (64%)	1 (2%)	2 (4%)		1 (2%)				
4			18 (36%)	8 (16%)										
5														
6														
Fisher's exact test p-value														
2	1													
3			0.0039		0.833		1		1		1		1	
4			0.0039		0.833		1		1					

[Table/Fig-3]: Comparison of sedation score between the two groups.
p-value <0.05 was taken as statistically significant; Te: Time just after extubation

Visual Analogue Scale (VAS) after estuation	Group M (Mean±SD)	Group C (Mean±SD)	t-value	p-value
At 0 min	3±0	3±0	-	-
At 2 hours	3±0	3±0	-	-
At 4 hours	3.02±0.14	3.2±0.4	-2.973, df=98	0.004*
At 6 hours	3.26±0.44	2.96±0.97	1.993, df=98	0.049*
At 8 hours	2.62±0.9	2±0	4.866, df=98	0.001*

[Table/Fig-4]: Comparison of mean VAS between the two groups.
*Unpaired't' test applied; p-value <0.05 was taken as statistically significant

Parameter	Group M (Mean±SD)	Group C (Mean±SD)	t-value	p-value
Time to request for first rescue analgesia	7.27±1.01 hours	5.40±0.78 hours	10.342, df=98	0.001*

[Table/Fig-5]: Comparison of mean time to request for first rescue analgesia between the two groups.
*Unpaired't' test applied; p-value <0.05 was taken as statistically significant

Intraoperative adverse events	Group M n (%)	Group C n (%)	p-value (Fisher's Exact test)
Bradycardia	2 (4%)	2 (4%)	1
Hypertension	4 (8%)	14 (28%)	**0.017**
Hypotension	3 (6%)	2 (4%)	1
Abnormal SpO_2	0	0	-

[Table/Fig-6]: Intraoperative adverse events.
p-value <0.05 was taken as statistically significant

Postoperative adverse events	Group M n (%)	Group C n (%)	p-value (Fisher's exact test)
Headache	3 (6%)	4 (8%)	1
Vomiting	3 (6%)	3 (6%)	1
Drowsiness	0	0	-

[Table/Fig-7]: Postoperative adverse events.
Fisher's Exact Test applied. P-value <0.05 was taken as statistically significant

melatonin in providing sedation and postoperative analgesia when given preoperatively in a dose of 6 mg. Authors chose the dose of 6 mg as it has been evaluated in this dose in various studies without any significant adverse effects, while higher doses may produce headache, drowsiness and nausea which is not very commonly found an it has a high safety profile as 10 mg and higher doses have been found to be safe in many studies [15,16].

In this study, it was found that pre medication with oral melatonin (given 90 minutes before surgery) can provide postoperative analgesia for longer duration than controls without producing undue sedation and drowsiness. There were no significant adverse effects in intraoperative or postoperative period. Findings of this study were similar to study done by Khare A et al., [17]. While comparing the anxiolytic and sedative properties of oral melatonin and alprazolam with placebo they found that ramsay sedation score was higher in alprazolam group as compared to melatonin group and placebo group (p-value <0.05). Melatonin provided better anxiolysis along with maintenance of cognitive and psycho motor function.

The present study findings were in concordance with the finding of Borazan H et al., [18]. They administered 6 mg oral melatonin a night before and one hour before the surgery and sedation scores were found to be significantly higher in the melatonin group at one hour and two hours postoperatively than in the control group (p-value <0.05). The significant difference in sedation score till two hours after surgery could be due the fact that melatonin was administered one night before surgery as well as on the day of surgery. The observation from the index study suggests that probably one-time dose also works well.

The sedative action of melatonin is thought to be due to its dose dependent action on Gamma-aminobutyric Acid (GABA) receptors. Increased concentration of GABA in central nervous system lead to sedation and hypnosis [19].

Postoperative pain: The mean VAS score was significantly higher in group C in comparison to group M after four hours postoperatively (p-value <0.05), while it was less in group C than group M at 8 hours as analgesia was given earlier in control group. Hence, mean time to request for first rescue analgesia was significantly longer in the melatonin group than the control.

Similarly, Borazan H et al., administered 6 mg oral melatonin one night before and one hour before the surgery and concluded that postoperatively VAS score was significantly lower in melatonin group than control group at 1,2,4,6,12,18 and 24 hours after surgery [18].

Kiabi FH et al., studied 204 patients undergoing caesarean section under spinal anaesthesia. Group A, group B and group C received 5 mg melatonin, 10 mg melatonin and placebo, respectively. There was a significant pain reduction in both melatonin groups and duration of analgesia was prolonged (10 mg >6 mg) in comparison to control group [20].

Ismail SA and Mowafi HA, conducted a study in which patients received 10 mg oral melatonin 90 minutes before cataract surgery. It was found that perioperative verbal pain scores were significantly lower in the melatonin group with less intraoperative fentanyl requirement as compared with the control group [15].

Melatonin has been shown to be a good alternative as an adjunct to premedication in surgeries to provide postoperative analgesia. Melatonin exerts its antinociceptive effects through MT1 and MT2 melatonergic receptors located in the dorsal region of the spinal cord as well as in different parts of the brain involved in pain modulation [21].

In this study, the episodes of intraoperative bradycardia and hypotension were comparable in both the groups and the proportional comparison was found to be statistically not significant (p-value=1.000). Hypertension was significantly higher in patients in group C (p-value=0.010).

Choudhary S et al., also reported no significant adverse effects after using 6 mg melatonin given 120 minutes before surgery [22]. No adverse effects were found by Patel T and Kurdi MS in the melatonin group. They compared melatonin 0.4 mg/kg and midazolam 0.2 mg/kg with placebo, to study the pre operative anxiety, cognitive and psychomotor function [23].

Episodes of headache and vomiting were comparable in both the groups and statistically not significant Gupta P et al., [13]. Compared 6 mg oral melatonin to placebo in attenuation of hemodynamic response to laryngoscopy and intubation and found nausea/vomiting in one patient in each group and restlessness was found in two patients in control group.

Limitation(s)

It was a single-centre study and pregnant females were excluded. The effects of a single dose of melatonin, given 90 minutes prior to induction, was studied. It would have given more clarity regarding the dose dependent functions of melatonin if different doses given at different time intervals were also assessed.

CONCLUSION(S)

From the observations and results obtained it can be concluded that melatonin can reduce postoperative pain when given preoperatively, without producing any undue sedation and significant adverse effects. Due to high safety profile and ability to produce arousable sedation it can further be explored to be used in combination with premedication drugs and in providing postoperative pain relief and hence reducing the need of opioid analgesics thereby reducing the associated adverse effects of respiratory depression, nausea vomiting and undue sedation.

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