

Efficacy of preoperative oral melatonin on post operative pain in patients undergoing infraumbilical surgeries under subarachnoid block: A double blind randomized control study

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Abstract

Introduction: Melatonin, naturally occurring sleep hormone secreted by pineal gland has sedative, hypnotic, analgesic, anti-inflammatory, antioxidant and chronobiotic properties that distinguishes it as an attractive premedicant. Our aim was to assess the effectiveness of preoperative oral melatonin on post operative pain and perioperative anxiety in patients undergoing infraumbilical surgical procedures under subarachnoid block (SAB).

Materials and Methods: After institutional ethical committee clearance and patients informed written consent, 70 ASA I and II patients aged between 18 to 60 years posted for infraumbilical surgery under SAB were randomized into M and P groups with 35 in each. All patients received either 3mg oral melatonin or placebo one hour before spinal. Post operative pain was assessed using Visual analogue Scale (VAS) and time required for first rescue analgesia was noted. Perioperative anxiety and sedation levels were assessed using Hamilton anxiety rating scale (HAM-A) and Ramsay Sedation Scores (RSS) respectively and monitored for any adverse effects. Data was analyzed using SPSS version 22 with appropriate statistical tests.

Results: The demographic characteristics and duration of surgery were comparable between the groups. The time required for rescue analgesia was significantly longer in M group (311.8±39min) than P group (189.6±22.2min) with P value <0.001 and VAS was significantly less in M group during first 6 hours post surgery with P <0.05. The anxiety scores decreased significantly after Melatonin premedication during perioperative period with P<0.001. RSS was higher in M group up to 2hrs after surgery with P<0.001. There were no adverse events in either group.

Conclusion: Preoperative oral melatonin 3mg provided analgesia beyond first 6hrs of post operative period, reduced the requirement of analgesics in the first 24 hrs and provided perioperative anxiolysis and sedation without any adverse events in patients undergoing surgical procedures under subarachnoid block.

Introduction

Pain is a part of any surgical intervention which is associated with anxiety and apprehension in majority of the patients. Post operative pain has a major impact on recovery of the patient¹ and preoperative anxiety serves a critical role in the chain of events that control the post operative responses.^{2,3} As pain is a sensory and emotional experience studies have demonstrated that less anxious patients experienced less post operative pain.⁴

Many drugs like Benzodiazepines, Opioids, Pregabalin, Gabapentine, Alpha 2 agonists etc have been used as premedicants to provide post operative analgesia and to decrease perioperative anxiety with their own benefits and risks. Melatonin or N-acetyl-methoxy tryptamine, a naturally occurring sleep inducing hormone secreted by pineal gland, also available commercially has got sedative,

hypnotic, analgesic, anti-inflammatory, antioxidant, regulation of circadian rhythm and chronobiotic properties that distinguishes it as an attractive alternative premedicant.⁵ By virtue of its multiple function, Melatonin has the potential to be used as an alternative premedicant, as an anxiolytic, sedative and analgesic without significant hemodynamic alterations in patients undergoing surgical procedures under general or regional anaesthesia. It also helps in restoring sleep rhythm in post operative period. It has no hangover effects on the day following its intake and has no negative effects like addiction, dependence as compared to benzodiazepines.⁶

Not many studies have been done using melatonin premedication for post operative analgesia under subarachnoid block (SAB). We decided to take up this prospective randomized double blind controlled study using

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Melatonin as premedication in patients undergoing infra umbilical surgeries under subarachnoid block to assess its efficacy in providing post operative analgesia and in decreasing perioperative anxiety levels.

Materials and Methods

After ethical committee clearance and informed written consent 70 patients aged between 18 to 60 years with ASA grade I and II posted for elective infra umbilical surgeries like inguinal hernia repair, appendectomy under SAB at our Institute and attached hospitals during March to July 2018 were enrolled in the study.

Patients refusing to get enrolled in the study, history of psychiatric disorders on antipsychotic drugs, sleep disorders, on anticoagulants, patients with uncontrolled hypertension and type II diabetes mellitus, ischaemic heart disease, pregnant women, patients with contraindications for spinal anaesthesia, significant hepatic and renal disorders, chronic pain on long term analgesic drug use, H/o chronic headache were excluded from the study.

This study was registered in Indian Clinical Trials Registry site with the registration number CTRI/2018/08/015192.

The study population was randomly divided into 2 groups as group M (Melatonin) and group P (Placebo) with 35 in each.

Randomization was done by means of computer-generated random numbers using www.randomizer.org. Allocation of patients to study group was done by an anaesthetist not involved in the study and study drugs were given by a nurse not involved in the study. The anaesthetist conducting the case and spinal anaesthesia was blinded to the patient's group assignment and the study data was recorded by a blinded observer. All patients were kept fasted overnight and were given tab. Alprazolam 0.5mg and tab. Ranitidine 150mg on the previous night of surgery.

No premedications were given on the day of surgery except for the drugs predetermined by the study protocol. In the preoperative room study drug was given orally 60min before SAB. After establishing an intravenous access all patients were preloaded with 5ml/kg iv fluid. Heart Rate (HR), Non-invasive Blood Pressure (NIBP), Ramsay Sedation Score⁷ (RSS), Haemoglobin Saturation (SPO₂) were recorded at the baseline before premedication and again at 10, 20, 40 and 60 minutes after premedication. Questions related to Hamilton anxiety scale (HAM-A)⁸ were asked before and one hour after premedication and the patients were shifted to OT. In the OT all standard monitors like NIBP, ECG, SPO₂ and RR were connected. Under aseptic precautions subarachnoid block was given at L3/4 or L4/5 interspace using 25G Quincke's spinal needle with 2.5ml of 0.5% Bupivacaine through midline approach in patient being in lateral position. Immediately after intrathecal injection patient was placed in supine position and oxygen at 5L/min was given via face mask during the surgery.

Onset of sensory blockade at T12 and maximum level of sensory blockade were assessed using cold swab along

the mid clavicular line. Onset of motor blockade and degree of motor blockade were assessed using modified Bromage score.⁹ Intraoperative NIBP, SPO₂, HR, sedation scores were recorded after shifting to OT, every 3min for first 15min after spinal anaesthesia, at 5min intervals for next 15min, at 10min interval for next 30min and at 30min interval till the completion of the surgery. The above said parameters along with Visual Analog Score¹⁰ (VAS) for pain were recorded at 1hr, 2hrs, 6, 12 and 24hrs post operatively. HAM-A score was assessed at 4hrs interval postoperatively. Hypotension was defined as fall in MAP by 20% from the baseline and was treated with inj. Mephentermine iv in 6mg increments. Bradycardia was defined as heart rate <50/min and was treated with inj. Atropine 0.6mg iv. Time for first request for analgesic supplementation was recorded. The patients were instructed about the VAS during preoperative visit and to score pain from 0 to 10 (0=no pain, 10=maximum imaginable pain) during postoperative period. If the VAS was >4 and the patients request for supplemental analgesia, inj. Paracetamol 15mg/kg was given to relieve the pain and the timing was noted. Duration of post op analgesia was defined as the time from injection of spinal drug to first requirement of analgesics by the patient. Adverse effects like nausea, vomiting, hypotension, bradycardia and headache were noted if any and treated accordingly.

Statistical Analysis

Based on the previous study by Marzich Beigom Khezri et al,¹¹ the time to first analgesic request was 208.19 ±122.66min in study group (3mg melatonin) and 152.13±79.4min in control group. Keeping the power at 80% and alpha error at 5%, a sample size of 32.6 per group was required. To compensate for drop outs we decided to take 35 patients in each group and hence the sample size of 70 was taken. The statistical evaluation was done using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test and Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. P value <0.05 was considered significant statistically.

Results

70 patients participated in the study were divided into 2 groups of 35 each and randomly assigned to either group. All of them completed the study.

Table 1: Demographic Data

Demographic data	Group M (Mean ±SD)	Group P (Mean ±SD)
Age (years)	39.5± 11.5	40±12.6
Gender (M:F)	26:9	26:9
Duration of surgery in minutes	45.3±15.6	48.6±21.1

Mean age, gender distribution and duration and nature of surgery were comparable between the groups.

Table 2: Time distribution for various parameters of outcome between two groups

	Group				P value
	Melatonin		Placebo		
	Mean	SD	Mean	SD	
Onset of motor blockade in minutes	1.8	0.4	2.0	0.2	0.001*
Onset of sensory blockade (T12) in minutes	2.1	0.5	2.2	0.4	0.310
2 segment regression time in minutes	96.5	9.7	55.6	4.6	<0.001*
Time to rescue analgesia in minutes	311.8	39.0	189.6	22.2	<0.001*

* = P<0.05

There was no significant difference in mean onset of motor blockade and sensory blockade between the groups clinically, though present statistically.

Time to rescue analgesia was on an average 100 plus minutes longer in M group which was statistically significant and 2 segment regression times between the groups was also longer by 40 minutes in M group.

Table 3: Post-operative VAS score comparison between two groups at various intervals

VAS scores	Group M Median (IQR)	Group P Median (IQR)	P value
Immediate	0 (0-0)	0 (0-0)	0.003*
1 hour	1 (0-1)	1 (1-1)	0.001*
2 hours	1 (1-2)	2 (2-2)	<0.001*
6 hours	5 (5-5)	6 (6-7)	<0.001*
12 hours	5 (5-5)	5 (5-5)	0.590
24 hours	5 (5-6)	6 (5-6)	0.287

Median VAS score in our study was lesser in M group compared to P group and was statistically significant in the first 6 hours of post operative period.

Table 4: Paracetamol doses administered between two groups

Paracetamol doses in 24 hours	Group M No of Patients	Group P No of Patients
2	23 (65.7%)	0 (0.0%)
3	12 (34.3%)	25 (71.4%)
4	0 (0.0%)	10 (28.6%)

The average consumption of paracetamol over 24hrs in group M was 2.34±0.48g and in P group was 3.28±0.45g which was significant statistically with P <0.001.

Table 5: HAM-A score comparison between two groups at various intervals

HAM-A	Group M		Group P		P value
	Mean	SD	Mean	SD	
Baseline	7.2	0.8	7.5	0.9	0.145
Before shifting to OT	2.2	0.7	6.7	0.9	<0.001
Immediate post op	2.2	0.8	6.8	0.9	<0.001
4 hours	2.3	0.7	5.9	0.9	<0.001
8 hours	2.5	0.7	5.8	0.9	<0.001
12 hours	2.4	0.6	5.9	0.8	<0.001
16 hours	2.6	0.5	5.8	0.9	<0.001
20 hours	2.5	0.5	5.9	0.9	<0.001
24 hours	2.5	0.5	5.9	0.8	<0.001

There was statistically significant difference in mean HAM-A score and it was lower in M group at all observed time intervals after premedication.

Sedation scores at different time intervals

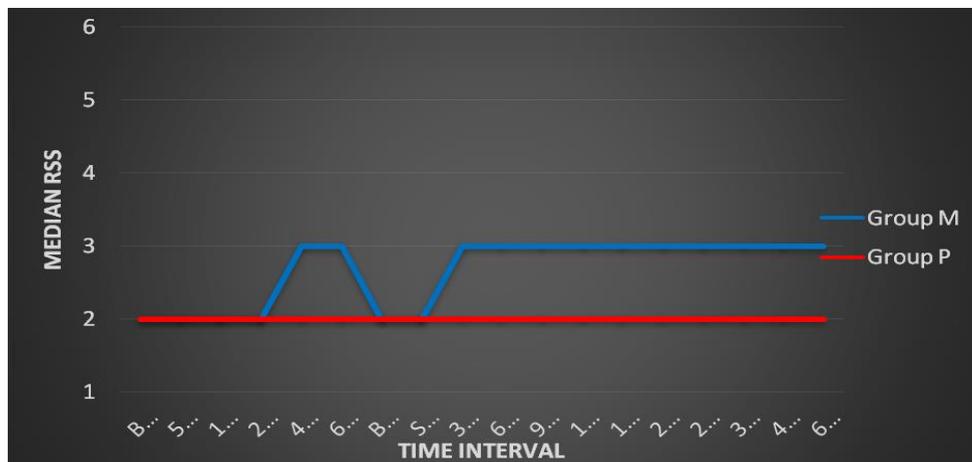


Table 6: Sedation scores at different time intervals

RSS		Group M		Group P		p value
		Median	IQR	Median	IQR	
Post Operative	Immediate	3	(2,3)	2	(2,3)	<0.001*
	1 hour	3	(3,4)	2	(2,3)	<0.001*
	2 hours	3	(3,4)	2	(2,3)	<0.001*
	6 hours	2	(2,4)	2	(2,3)	0.026
	12 hours	2	(2,3)	2	(2,3)	0.288
	24 hours	2	(2,3)	2	(2,2)	0.347

In our study RSS score was significantly high in M group with P <0.001 from 40min after oral premedication up to 2 hrs in the post op period and showed no significant difference in the scores in the later period among the two groups.

Hemodynamic Parameters

Our study showed no statistically significant difference in hemodynamic status in both the groups in terms of mean heart rate, systolic blood pressure, diastolic blood pressure, and Mean arterial pressures either in pre, intra or post operative period, though all of them were on the lower side in M group.

Discussion

While selecting a premedicant due consideration is given to its availability, dose, its action, time to onset, duration of action and its side effects. A drug that has a fast onset, long duration and minimal adverse effects could be an advantage. In that way Melatonin, a naturally occurring hormone secreted by pineal gland possesses multiple actions⁵ as mentioned in the beginning with minimal side effects that distinguish it as an attractive alternative premedicant.

Melatonin exerts hypnotic effects through activation of the MT1 and MT2 receptors.¹² It has been reported to cause preoperative anxiolysis and increase in sedation levels

without impairing orientation.¹³ Melatonin shows potent analgesic effects in experimental animals in a dose dependent manner.¹⁴ The effects may be linked to Gi-coupled melatonin and opioid μ receptors or GABA receptors.¹⁵ The peak effect of exogenous melatonin ranges from 60 to 150min.

We wanted to evaluate its effect primarily on post operative pain and secondarily on perioperative anxiety in patients undergoing infraumbilical surgeries under SAB. Considering the higher incidence of headache at 6mg dose in the study done by Marzeih Beigom Khezri and associates¹¹ in 2016 we decided to go with 3mg oral dose.

Our study population was divided into two groups of 35 each randomly but were comparable in-terms of demographic variables like age distribution, gender and duration of surgery.

In our study the mean time for rescue analgesia was 311.8±39.0 min in M group and 189.6±22.2min in P group which was statistically significant (P<0.001). There was significant difference in VAS score in the immediate post operative period and at 1, 2 and 6 hrs post surgery (P <0.001) with no significant difference at 12 and 24 hrs which was similar to the observations made by Wolnei Caumo et al^{16,17} which showed the perioperative anxiolysis with melatonin reduced post operative pain and morphine

dose in patients undergoing abdominal hysterectomy, especially in the first 24 postoperative hours.

Average dose of paracetamol as post operative analgesic over 24hrs in M group (2.34 ± 0.48 g) was less than P group (3.28 ± 0.45 g) which was statistically significant ($P < 0.001$), similar to the studies by Marzeih et al¹¹ and Hale Borazan et al¹⁸ who also reported that the total dose of analgesic request by patients during 24hrs after surgery and pain scores were significantly lower in melatonin group compared to placebo group.

Perioperative anxiety as assessed by HAM-A score at 60min after premedication and at every 4hrs post surgery up to 24hrs was significantly less in the M group with $P < 0.001$. Studies done by Acil M et al¹⁹ and Tushar Patel et al²⁰ on perioperative effects of oral melatonin and midazolam premedication showed that melatonin premedication was associated with preoperative anxiolysis and sedation. RSS score was significantly high in M group with $P < 0.001$ from 40min after oral premedication up to 2 hrs in the post op period which was comparable to our observation.

We also found that there is no clinically significant difference in the onset of sensory and motor blockade among M and P group. The 2 segment regression time in M and P group was 96.5 ± 9.7 min and 55.6 ± 4.6 min respectively indicating that melatonin prolonged the duration of sensory blockade and it was statistically significant with $P < 0.001$.

There was no significant difference in the HR, SBP, DBP, MAP, SPO2 during perioperative and postoperative period up to 24hrs measured at regular intervals. None of the patients required any active intervention nor had any side effects like nausea/vomiting etc. No patients complained of headache at 3mg dosage.

The limitation of our study was that we did not assess the effect of melatonin on sleep rhythm in the post operative period.

In conclusion Melatonin is an effective alternative premedicant for providing post operative analgesia and as an anxiolytic without hemodynamic disturbances or side effects in patients undergoing surgical procedures under spinal anaesthesia.

Conflict of Interest: None.

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References

- Breivik H, Stubhaug A. Management of acute postoperative pain: still a long way to go! *Pain* 2008;137:233-4.
- Ip H Y, Abrishami A, Peng PW, Wong J, Chung F. Predictors of post operative pain and analgesic consumption: a qualitative systematic review. *Anaesthesiol* 2009;111:657-77.
- Kain ZN, Sevarino, Alexander GM, Pincus S, Mayes LC. Preoperative anxiety and postoperative pain in women undergoing hysterectomy. A repeated measures design. *J Psychosom Res* 2000;49(6):417-22.
- Wong JO, Tan TD, Cheu N W, Wang YR. Comparison of the efficacy of parecoxib versus ketorolac combined with morphine on patient controlled analgesia for post caesarean delivery pain management. *Acta Anaesthesiol Taiwan* 2010;48:174-7.
- 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 systemic review of randomized trials. *Anaesthesiol* 2010;113:968-76.
- Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. *J Pineal Res* 2011;52:365-75.
- Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol NE. *Anaesth Analog* 1993;77:919-24.
- Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959.
- EC Huskisson. Huskisson EC. Measurement of pain?. *Lancet* 1979;2(7889):1127-31.
- Ramsay MA, Savage TM, Simpson BR, Goodwin R. *Br Med J* 1974;2:656-9.
- Marzieh Beigom Khezri, Morteza Delkosh Reihany, Sonia Oveisy, Navid Mohammadi. Evaluation of the analgesic efficacy of melatonin in patients undergoing caesarean section under spinal anaesthesia: a prospective randomized double blind study. *Iran J Pharm Res* 2016;15(4):963-71.
- Kurdi MS, Patel T. The role of melatonin in anaesthesia and critical care. *Indian J Anaesth* 2013;57:137-44.
- Marseglia L, D'Angelo G, Manti S, Aversa S, Arrigo T, Reiter RJ, Gitto E. Analgesic, anxiolytic and anaesthetic effects of melatonin: New potential uses in paediatrics. *Int J Mol Sci* 2015;16:1209-20.
- Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gogenur I. Analgesic effects of melatonin: A review of current evidence from experimental and clinical studies. *J Pineal Res* 2011;51:270-7.
- Zahn PK, Lansmann T, Berger E, Speckmann E, Musshoff U. Gene expression and functional characterization of melatonin receptors in the spinal cord of the rat: implications for pain modulation. *J Pineal Res* 2003;35:24-31.
- Wolnei Caumo, Rosa Levandovski, Hidalgo MP. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double blind randomized placebo controlled study. *The J Pain* 2009;10(1):100-8.
- Wolnei Caumo, Fernanda Torres, Nivio L Moreira, Jorge A S, Cristiana A, Gustavo Londera, et al. The clinical impact of preoperative melatonin on post operative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg* 2007;105:1263-71.
- Hale Borazan, Sema Tuncer Yalcin N, Erol A, Otelcioglu S. Effects of preoperative oral melatonin medication on post operative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial. *J Anaesth* 2010;24:155-60.
- Acil M, Basgul E Celiker V, Karagon AH, Demir B, Aypar U. Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. *Eur J Anaesth* 2004;21(7):553-7.
- Tushar Patel, Madhuri S Kurdi. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive and psychomotor functions. *J Anaesthesiol Clin Pharmacol* 2015;31:37-43.

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