Original Article

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Effect of Two Doses of Oral Melatonin on Perioperative Anxiety and Postoperative Analgesia in Patients Undergoing Orthopaedic Surgeries: A Randomised Controlled Study

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ABSTRACT

Introduction: Perioperative anxiety and postoperative pain are the most common complaints associated with orthopaedic surgeries leading to increased morbidity and hospital stay. Melatonin, a recent alternative to benzodiazepines with fewer side-effects, has been shown to reduce anxiety and pain in perioperative settings.

Aim: To investigate the anxiolytic effect of melatonin perioperatively and its analgesic potency postoperatively.

Materials and Methods: The present randomised, controlled double-blinded study was conducted including 90 patients equally distributed to three groups receiving placebo (Group P), 6 mg (M6) and 12 mg oral melatonin (M12) 60-90 minutes before surgery. Primary outcome was preoperative anxiety, assessed using State Trait Anxiety Inventory (STAI) before drug administration and 60-90 minutes after it. Postoperative anxiety, assessed using STAI and and postoperative pain, assessed using Visual Analogue Score (VAS) for the next 72 hours both at rest and in movement, time of request for rescue analgesia and total analgesic requirements within 72 hours were considered as secondary outcomes. One-way Analysis of Variance (ANOVA) and Kruskal-Wallis test were used to compare the three groups regarding continuous and dichotomous variables, respectively.

Results: Ninety patients were enrolled in the study and were randomly distributed into three matched groups according to age, sex, anthropometric parameters and American Society of Anaesthesiologists (ASA) grading. Significantly reduced ($p<0.001$) STAI scoring was found in group M12, from the preoperative period to 72 hours postoperatively. A statistically significant reduction in VAS scoring for pain both at rest and movement was always observed in group M12 from six hours to 72 hours postoperatively ($p<0.001$). The time of request for first and second rescue analgesics in group M12 was significantly later than group M6 and group P. Total consumption of rescue analgesics was found to be significantly low ($p<0.001$) in group M12.

Conclusion: A 12 mg of oral melatonin premedication reduces anxiety during perioperative phase as compared to 6 mg of melatonin and placebo, with no significant difference between the latter two. It was also found that significant reduction in postoperative anxiety and pain at rest and during movement in the M12 group, but not in groups M6 and P. M12 group also required significantly less rescue analgesic than groups M6 and P. In summary, 12 mg of oral melatonin exhibited desired analgesic, sedative and anxiolytic properties to ameliorate perierioperative anxiety and postoperative pain, without any negative haemodynamic effect.

Keywords: Acute pain, Anxiolysis, Pain tolerance

INTRODUCTION

Perioperative anxiety is one of the pernicious reasons causing increased morbidity among patients undergoing surgery. Excessive perioperative anxiety can lower pain tolerance and aggravate haemodynamic as well as sleep disturbances, cognitive dysfunction and postoperative pain, increasing the analgesics requirement and hospital stay [1].

Various strategies have been employed to alleviate this issue. Non pharmacological techniques included acupressure [2], music therapy [3], aromatherapy skin patch [4], or hydration with carbohydrate drinks up until two hours before surgery [5]. Pharmacological approaches included midazolam [6], dexmedetomidine [7], and gabapentin [8]. With the varying degrees of success of different techniques and looking for safer alternative pharmacological approaches, melatonin has recently created a new stir.

Melatonin (N Acetyl-5-methoxy tryptamine), a neuro-hormone, is mainly produced in the pineal gland from tryptophan as a precursor that plays an intricate role in circadian rhythm. The novelty of action lies in the potency of the melatonin molecules to alter the redox status attenuating tissue injuries in both receptor-dependent and independent fashion [9]. It also decreases the expression of proinflammatory regulators such as nuclear factor-κ beta, c-Fos and matrix metalloproteinases-3 [10]. It is shown to possess intrinsic chronobiotic, antioxidant, anxiolytic, analgesic and sedative properties with an excellent safety profile with rare occurrences of nausea, dizziness, and daytime sleepiness [11]. As compared to undesired sedation and the negative influence on REM sleep quality by benzodiazepines, melatonin produces no hangover or dependence. The circadian secretion of melatonin matches pain perception, which is essential for analgesia [12]. A possible clinical effect with an appealing safety profile makes melatonin an interesting new drug for the perioperative setting.

Melatonin has been used in varying doses (3-15 mg) to relieve preoperative anxiety with mixed results: sublingually or orally administered melatonin proved to be an effective premedication in adults and children [13-19] but not in elderly patients [20]. These inconsistent results could have stemmed from difference in demographics of the patients recruited, the surgeries they underwent and/or anaesthesia techniques and usage of subjective

VAS as anxiety assessment tool. In the present study, the authors compared 6 mg and 12 mg of oral melatonin in patients undergoing lower limb orthopaedic surgeries, with a more specific and reliable STAI scoring as an anxiety assessment tool [21]. The authors also consider secondary objectives to evaluate the anxiolytic effect along with analgesic effect in postoperative period, time of first analgesic request, total analgesic consumption within 72 hours postoperatively, perioperative quality of sleep and any side-effects.

MATERIALS AND METHODS

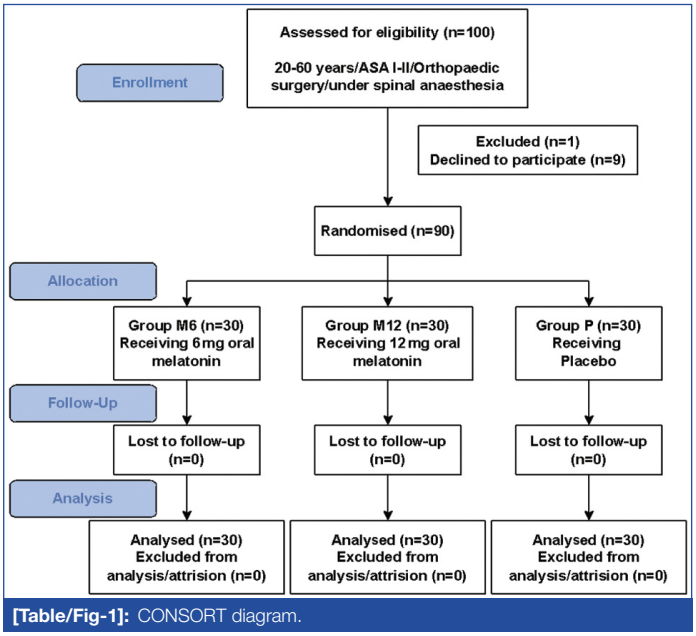
The present double-blinded, randomised controlled study was conducted at Pandit Bhagwat Dayal Sharma Postgraduate Institute of Medical Sciences, a tertiary care hospital in India, from May to December 2022. The study was registered under the Clinical Trial Registry-India (CTRI/2022/05/042801) and approved by the Institutional Ethics Committee (BREC/Th/20/Anaesth/027). All participants signed an informed consent form before taking part in study.

Sample size calculation: With the reference study of Ionescu D et al., the authors took mean (s.d.) preoperative anxiety score (STAI) across three different groups 11.6 (3.2), 10.5 (2), 13.5 (3.4) and took p-value of <0.005 [22], they calculated the sample size to be 23 per group in three groups, with 90% confidence interval and power of the study being 0.9 using G*Power software (A priori power analysis) [23]. Further they adjusted the sample size according to the variables of the age group and type of surgery by applying a variance inflation factor (chosen conservatively) which resulted in the sample size to be 30 in each group among three groups to ensure a robust result in the present study.

Inclusion and Exclusion criteria: Ninety adult patients of either sex aged between 18-65 years included in the study, belonging to American Society of Anaesthesiologists (ASA) physical status 1-2, who were undergoing lower limb orthopaedic surgeries under spinal anaesthesia and able to understand State-Trait Anxiety Inventory (STAI). Patients with contraindications to regional anaesthesia, significant renal, hepatic or cardiovascular dysfunction, psychiatric disorders like depression, known allergy to melatonin, pregnancy, psychotropic therapy, and language or communication difficulties were excluded.

Study Procedure

Patients were enrolled and followed in the postoperative period by the primary and secondary investigators. They were allocated to three groups of 30 each randomly by a computer-generated sequence using a sealed coded envelope [Table/Fig-1] by a fellow resident who is not primarily involved in the research. Groups M6, M12 and P received 6 mg, 12 mg melatonin and placebo resembling melatonin tablets orally 60-90 minutes before surgery respectively. The study drug was administered by a fellow Anaesthesiologist with no further involvement in drug administration or data handling as per code number. A register having records of code numbers assigned to drug groups was maintained. The Anaesthesiologist administering the study drug as well as patients was blinded to the group allocation. The blinding process was rigorously ensured throughout the study. The patients, staff providing postoperative care and data collectors were blinded to group assignments.



[Table/Fig-1]: CONSORT diagram.

On the day of surgery, no other premedication was given to the patients enrolled except for melatonin/placebo. All the patients were given injection paracetamol intravenously one hour after melatonin/placebo administration. Patients were assessed before and after giving premedication, also in the recovery using following tools-

1. Baseline values of Pulse Rate (PR), Non-Invasive Blood Pressure (NIBP), Mean Arterial Pressure (MAP), pulse oximetry (SpO_2) were obtained as a part of haemodynamic variable monitoring.
2. Anxiety assessment was done using STAI (with permission from Mind Garden), which is based on a 4-point Likert scale [24]. Score ranging from 20 to 80 with higher scores correlating with more significant anxiety; 20-37 as no/low anxiety, 38-44 as moderate anxiety and 45-80 as high anxiety.
3. For pain assessment, a VAS was used in the postoperative period, where 0 and 100 will denote no pain and worst pain, respectively.
4. Insomnia was assessed using VAS, where quality of sleep was rated by patients (0=no insomnia/excellent quality of sleep to 100=absolute insomnia) [25,26]. Sedation score was noted using a sedation scale (awake and alert=0; quietly awake=1; asleep but easily roused=2; difficult to arouse=3; asleep but unarousable=4) at 60 minutes after study drug administration, then postoperatively at 6, 12, 24, 36, 48 and 72 hours [13].

Standard ASA monitors {NIBP, Electrocardiogram (ECG) and SpO_2} were attached after patients reached the operating room. All the patients were given a subarachnoid block with 2.5 mL hyperbaric bupivacaine 0.5% with fentanyl 25 µg in L3-4 or L4-5 interspace. Pinprick test and modified Bromage scale were used every two minutes to assess the sensory and motor blocks, respectively, until the patient exhibited complete unresponsiveness up to the level of T-10. Intraoperative variables and anaesthetic complications were noted. We recorded the HR, NIBP, MAP and SpO_2 values before and immediately after the subarachnoid block, at five minutes and every 15 minutes until the end of surgery or two hours, whichever is maximum. The duration of surgery was noted.

After completion of the surgical procedure, patients were transferred to Post-Anaesthesia Care Unit (PACU). Postoperative HR, NIBP, SpO_2, and respiratory rate were monitored at 0, 30, and 60 min. The primary outcome measure in this study was STAI score for anxiety, noted preoperatively, 60 minutes after study drug administration. Secondary outcome measure was STAI score for anxiety 6, 12, 24, 36, 48 and 72 hours postoperatively, VAS score for postoperative pain, time to first request for analgesic, paracetamol and diclofenac sodium consumptions at blocks of 0-6, 6-12, 12-24, 24-48 and 48-72 hours. All patients were asked to score their pain at rest and on movement at the time of first analgesic requirements, 6, 12, 24, 36, 48 and 72 hours after surgery. When VAS score for pain was ≥4, an injection of paracetamol 1 g was administered intravenously as the first rescue analgesic and time was noted. If pain was not relieved and VAS score remained ≥4, an injection of diclofenac sodium 75 mg was administered intramuscularly as a second rescue analgesic. We also evaluated the occurrences of insomnia, sedation, nausea and side-effects.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 28.0 (SPSS, Chicago, Illinoias). Continuous variables are presented as mean±SD or median (IQR) and categorical variables were analysed using the chi-square or Fisher's-exact tests. One-way Analysis of Variance (ANOVA) was used to evaluate the differences among the three Groups. If the p-value was significant and the variance was homogeneous, Tukey's multiple comparison test was used to assess the differences between the individual groups; otherwise, Tamhane's T2 test was used. The Kruskal-Wallis test compared the three groups regarding dichotomous variables or non-normally distributed data. The p-value less than 0.05 was used to indicate a significant difference.

RESULTS

The distribution of the study population (n=90) according to age, sex, anthropometric parameters, ASA grading and duration of surgery is shown in [Table/Fig-2]. No significant difference was found in STAI scoring between groups P and M6 at any point in time. Anxiety score was found to be the lowest in group M12. A significant difference in STAI scoring was found from the preoperative period to 72 hours postoperatively while comparing group P and M12 (p<0.001, respectively) as well as group M6 and M12 (p<0.001, respectively) at all the time points [Table/Fig-3].

A statistically significant reduction in VAS scoring for pain at rest as well as at movement was observed in group M12 in comparison to group P and group M6 at all the time points from six hours to 72 hours, postoperatively (p<0.001) [Table/Fig-4,5].

The time of request of the first rescue analgesic and second rescue analgesic were compared among the three groups. Group M12 took significantly (p<0.001) longer time requesting both analgesics (Mean±SD 475.8±44.4, 976.2±87.66 min) as compared to group M6 (222.12±51.0, 488.4±82.14 min) and P (210.04±49.2, 481.8±82.62 min), respectively [Table/Fig-6]. Total consumption of rescue analgesic drugs was found to be significantly low (p<0.001) in group M12 as compared to M6 and P separately. Differences in analgesic consumption among these three groups were observed only in the first 24 hours postoperatively for paracetamol [Table/Fig-7], whereas differences in diclofenac consumption were seen up to 72 hours postsurgery [Table/Fig-8].

Melatonin was not found to affect haemodynamics intraoperatively and postoperatively on either dosage. BP was slightly less in patients of group M12, though no hypotension was noted [Table/Fig-9-11]. Oxygen saturation measures did not show any significant difference across groups [Table/Fig-12]. Insomnia score was comparable in three groups and statistically insignificant [Table/Fig-13]. No patient complained of side-effects like nausea, vomiting, headache, or dizziness.

Variables	Group P (n=30)	Group M6 (n=30)	Group M12 (n=30)	ANOVA test results	p-values		
					P vs M6	P vs M12	M6 vs M12
Age (years)	42.73±11.68	42.53±11.56	47.27±9.41	p=0.17	0.997#	0.249#	0.220#
Sex (male/female) (%)	16/14 (53/47)	16/14 (53/47)	14/16 (47/53)		1.000#^	0.605#^	0.605#^
Weight (kg)	68.43±10.34	67.27±10.78	70.23±7.47	p=0.49	0.886#	0.751#	0.461#
Height (cm)	156.7±6.31	156.87±6.54	154.27±5.15	p=0.18	0.994#	0.267#	0.223#
Body mass index (kg/m^2)	27.99±4.79	27.49±4.99	29.56±3.40	p=0.18	0.902#	0.362#	0.176#
ASA grading (n=I/II) (%)	21/9 (70/30)	22/8 (73/27)	18/12 (60/40)		0.774#^	0.417#^	0.237#^
Duration of surgery (min)	119.17±17.67	119.67±18.19	116.03±14.28	p=0.66	0.993#	0.751#	0.681#
Types of surgery (n) (%) (both bone leg/feet/femur/tibia)	5/5/17/3 (17/17/56/10)	6/4/17/3 (20/13/57/10)	2/1/21/6 (7/3/70/20)		0.978#^	0.431#^	0.456#^

[Table/Fig-2]: Comparison of demographic parameters of study groups.
*All parameters are expressed as Mean±SD (standard deviation) or percentage (%), #statistically insignificant, ^-Chi-square test

State anxiety (STAI SCORING)	Group P	Group M6	Group M12	ANOVA test results	p-values		
	Mean±SD	Mean±SD	Mean±SD		Group P vs M6	Group P vs M12	Group M6 vs M12
STAI T0	50.4±5.661	50.27±5.777	51.07±6.236	F(2, 87)=0.16, p=0.85	0.996#	0.900#	0.859#
STAI Tp	44.7±4.458	44.47±4.501	26.47±2.209	F(2, 87)=218.73, p<0.001	0.970#	<0.001*	<0.001*
STAI T6	43.83±4.564	43.73±4.556	25.57±1.736	F(2, 87)=223.05, p<0.001	0.994#	<0.001*	<0.001*
STAI T12	42.9±4.773	42.93±4.806	24.83±1.704	F(2, 87)=201.14, p<0.001	0.999#	<0.001*	<0.001*
STAI T24	41.8±4.597	41.8±4.597	24.27±1.639	F(2, 87)=205.09, p<0.001	1.000#	<0.001*	<0.001*
STAI T36	40.93±4.705	40.91±4.712	23.5±1.834	F(2, 87)=190.84, p<0.001	1.000#	<0.001*	<0.001*
STAI T48	39.67±4.559	39.68±4.499	22.97±1.45	F(2, 87)=194.11, p<0.001	1.000#	<0.001*	<0.001*
STAI T72	39.1±4.544	39.2±4.483	22.63±1.377	F(2, 87)=192.01, p<0.001	0.994#	<0.001*	<0.001*

[Table/Fig-3]: Comparison of State Anxiety (STAI SCORING) at various time intervals between the three groups.
#p-value statistically insignificant *p-value statistically significant
T0- preoperatively before giving premedication, baseline, Tp- preoperatively 60 minute after Study drug administration, T6, T12, T24, T36, T48, T72 - 6, 12, 24, 36, 48 and 72 hours after surgery

VAS scoring for pain at rest	Group P	Group M6	Group M12	ANOVA test results	p-values		
	Mean±SD	Mean±SD	Mean±SD		Group P vs M6	Group P vs M12	Group M6 vs M12
VAS T0	2.87±0.346	2.79±0.342	2.77±0.43	F(2, 87)=0.60, p=0.55	0.185#	0.321#	0.421#
VAS Tp	2.87±0.346	2.78±0.342	2.7±0.596	F(2, 87)=1.10, p=0.34	0.157#	0.281#	0.263#
VAS T 1st pain	4±0	4±0	4±0	-	1.000#	1.000#	1.000#
VAS T6	3.07±0.254	3.02±0.232	2.07±0.254	F(2, 87)=156.27, p<0.001	0.214#	<0.001*	<0.001*
VAS T12	3±0	2.97±0.132	2.07±0.254	F(2, 87)=306.77, p<0.001	0.109#	<0.001*	<0.001*
VAS T24	2.87±0.346	2.85±0.342	2.1±0.305	F(2, 87)=52.58, p<0.001	0.411#	<0.001*	<0.001*
VAS T36	2.33±0.479	2.27±0.474	1.43±0.504	F(2, 87)=32.18, p<0.001	0.313#	<0.001*	<0.001*

VAS T48	2.1±0.305	2.05±0.301	1±0	F(2, 87)=189.11, p<0.001	0.262#	<0.001*	<0.001*
VAS T72	2±0	1.97±0.342	1±0	F(2, 87)=249.03, p<0.001	0.316#	<0.001*	<0.001*

[Table/Fig-4]: Comparison of VAS scoring for pain assessment (at rest) among groups receiving placebo (Group P), 6 mg of melatonin (Group M6) and 12 mg of melatonin (M12).
All parameters are expressed as mean±standard deviation
*statistically significant, #statistically insignificant

VAS scoring for pain at movement	Group P	Group M6	Group M12	ANOVA test results	p-values		
	Mean±SD	Mean±SD	Mean±SD		Group P vs M6	Group P vs M12	Group M6 vs M12
VAS T0	4.6±0.675	4.67±0.670	4.73±0.45	F(2, 87)=0.34, p=0.71	0.344#	0.528#	0.343#
VAS Tp	5.17±0.592	5.12±0.567	5.17±0.379	F(2, 87)=0.09, p=0.91	0.369#	0.886#	0.344#
VAS T 1st pain	6.43±0.568	6.41±0.579	6.40±0.621	F(2, 87)=0.02, p=0.98	0.446#	0.894#	0.474#
VAS T6	5.97±0.669	5.92±0.660	4.47±0.507	F(2, 87)=57.29, p<0.001	0.385#	<0.001*	<0.001*
VAS T12	5.53±0.507	5.51±0.501	4.27±0.45	F(2, 87)=65.98, p<0.001	0.439#	<0.001*	<0.001*
VAS T24	5.03±0.49	4.97±0.51	3.6±0.675	F(2, 87)=61.60, p<0.001	0.321#	<0.001*	<0.001*
sVAS T36	4.67±0.479	4.61±0.469	3.4±0.498	F(2, 87)=66.26, p<0.001	0.321#	<0.001*	<0.001*
VAS T48	4.33±0.479	4.29±0.477	3.17±0.379	F(2, 87)=64.97, p<0.001	0.373#	<0.001*	<0.001*
VAS T72	4.03±0.615	4.01±0.609	2.87±0.571	F(2, 87)=36.91, p<0.001	0.449#	<0.001*	<0.001*

[Table/Fig-5]: Comparison of VAS scoring for pain assessment (at movement) among groups receiving placebo (Group P), 6 mg of melatonin (Group M6) and 12 mg of melatonin (M12).
All parameters are expressed as mean±standard deviation
*statistically significant, #statistically insignificant

Parameters	Group P	Group M6	Group M12	ANOVA test results	p-values		
	Mean±SD	Mean±SD	Mean±SD		Group P vs M6	Group P vs M12	Group M6 vs M12
Time of 1st (PCM) analgesic requirement in hours	3.5±0.82	3.7±0.85	7.93±0.74	F(2, 87)=290.02, p<0.001	0.178#	<0.001*	<0.001*
Time of 2nd analgesic (Diclofenac 75 mg) requirement in hours	8.03±1.38	8.14±1.37	16.27±1.46	F(2, 87)=340.42, p<0.001	0.378#	<0.001*	<0.001*

[Table/Fig-6]: Comparison of time of rescue analgesic requests among groups receiving placebo (Group P), 6 mg of melatonin (Group M6) and 12 mg of melatonin (M12).

PCM consumption in ward	Group P	Group M6	Group M12	ANOVA test results	p-values		
					Group P vs M6	Group P vs M12	Group M6 vs M12
0-6 hours	1000±0	1000±0	0±0	F(2, 87)=inf, p<0.001	1.000#	<0.001*	<0.001*
6-12 hours	500±500	400±489.89	1000±0	F(2, 87)=18.98, p<0.001	0.433#	<0.001*	<0.001*
12-24 hours	1000±0	1000±0	0±0	F(2, 87)=inf, p<0.001	1.000#	<0.001*	<0.001*
24-48 hours	966.67±179.51	933.33±249.44	1000±0	F(2, 87)=1.06, p=0.35	0.552#	0.309#	0.143#
48-72 hours	900±300	900±300	933.33±249.44	F(2, 87)=0.14, p=0.87	1.000#	0.639#	0.639#

[Table/Fig-7]: Comparison of paracetamol (PCM) consumption among groups receiving placebo (Group P), 6 mg of melatonin (Group M6) and 12 mg of melatonin (M12) [Table/Fig-4].
All parameters are expressed as mean±standard deviation
*statistically significant, #statistically insignificant

Diclofenac consumption in ward	Group P	Group M6	Group M12	ANOVA test results	p-values		
					Group P vs M6	Group P vs M12	Group M6 vs M12
0-6 hours	0±0	0±0	0±0	NA	1.000#	1.000#	1.000#
6-12 hours	82.5±22.5	75±0	0±0	F(2, 87)=370.00, p<0.001	0.068#	<0.001*	<0.001*
12-24 hours	80±33.166	75±27.386	110±37.416	F(2, 87)=9.92, p<0.001	0.524#	0.001*	<0.001*
24-48 hours	132.5±31.721	127.5±34.369	75±0	F(2, 87)=41.74, p<0.001	0.558#	<0.001*	<0.001*
s48-72 hours	80±18.708	72.5±23.584	36±37.416	F(2, 87)=21.62, p<0.001	0.172#	<0.001*	<0.001*

[Table/Fig-8]: Comparison of Diclofenac consumption in ward among groups receiving placebo (Group P), 6 mg of melatonin (Group M6) and 12 mg of melatonin (M12).
All parameters are expressed as mean±standard deviation
*statistically significant, #statistically insignificant

Variables	SBP at	Group P	Group M6	Group M12	ANOVA test results	p-values		
		Mean±SD	Mean±SD	Mean±SD		Group P vs M6	Group P vs M12	Group M6 vs M12
Intra-op	0 min	129±11.823	128.47±12.042	122.93±11.468	F(2, 87)=2.44, p=0.09	0.983#	0.120#	0.169#
	5 min	126.73±12.301	126.57±12.334	119.8±10.768	F(2, 87)=3.36, p=0.04	0.998#	0.065#	0.074#
	15 min	124.33±13.015	124.53±13.161	118.2±10.496	F(2, 87)=2.57, p=0.08	0.998#	0.135#	0.119#
	30 min	123.33±12.543	123.57±12.577	115.87±10.129	F(2, 87)=4.13, p=0.02	0.997#	0.043*	0.035*
	45 min	121.2±12.201	121.2±12.201	113.73±10.058	F(2, 87)=4.20, p=0.02	1.000#	0.037*	0.037*
	60 min	120.8±11.124	120.87±11.051	114.33±9.129	F(2, 87)=3.86, p=0.02	1.000#	0.049*	0.046*
	75 min	121.07±11.138	121.07±10.989	115.8±9.789	F(2, 87)=2.45, p=0.09	1.000#	0.141#	0.141#

	90 min	123.93±10.285	124.07±10.352	118.33±8.222	F(2, 87)=3.44, p=0.04	0.998#	0.070#	0.062#
	105 min	127.5±9.027	127.5±9.236	120.88±10.101	F(2, 87)=4.89, p=0.01	1.000#	0.044*	0.044*
	120 min	128.25±8.694	128.25±8.694	122.27±10.942	F(2, 87)=3.96, p=0.02	1.000#	0.089#	0.089#
Post-op	0 min	128.27±8.69	128.33±8.664	124.53±9.202	F(2, 87)=1.81, p=0.17	1.000#	0.237#	0.226#
	30 min	129.27±8.843	129.13±8.862	125.33±9.041	F(2, 87)=1.89, p=0.16	0.998#	0.208#	0.230#
	60 min	129.73±8.674	129.8±8.652	126.2±8.763	F(2, 87)=1.68, p=0.19	1.000#	0.262#	0.250#

[Table/Fig-9]: Comparison of Systolic Blood Pressure (SBP) at various intervals among the three groups.

Variables	DBP at	P	M6	M12	Anova test results	P vs M6	P vs M12	M6 vs M12
		Mean±SD	Mean±SD	Mean±SD				
Intra-op	0 min	79.8±5.997	79.67±6.239	75.07±5.552	F(2, 87)=6.18, p=0.003	0.996#	0.884#	0.921#
	5 min	76.8±6.183	76.53±6.279	73.6±4.91	F(2, 87)=2.79, p=0.07	0.983#	0.09#	0.131#
	15 min	74.67±5.101	74.6±4.959	72.47±4.447	F(2, 87)=2.00, p=0.14	0.998#	0.19#	0.209#
	30 min	73.67±6.216	73.73±6.253	70.47±3.702	F(2, 87)=3.42, p=0.04	0.999#	0.069#	0.062#
	45 min	72.4±6.112	72.47±6.163	69.6±4.825	F(2, 87)=2.45, p=0.09	0.999#	0.147#	0.135#
	60 min	72.47±4.191	72.4±4.312	69.93±3.982	F(2, 87)=3.62, p=0.03	0.998#	0.053#	0.062#
	75 min	72.87±4.569	72.8±4.597	70.53±4.265	F(2, 87)=2.65, p=0.08	0.998#	0.114#	0.128#
	90 min	74.2±4.737	74.13±4.812	72.33±2.783	F(2, 87)=1.90, p=0.16	0.998#	0.206#	0.229#
	105 min	74±3.776	74.17±3.864	72.88±2.651	F(2, 87)=1.22, p=0.30	0.985#	0.498#	0.400#
	120 min	75.5±4.222	75.58±4.252	73.36±2.985	F(2, 87)=3.18, p=0.05	0.997#	0.158#	0.137#
Postop	0 min	76.4±4.28	76.47±4.321	73.87±2.623	F(2, 87)=4.50, p=0.01	0.997#	0.032*	0.027*
	30 min	76.93±4.51	76.87±4.353	73.87±3.060	F(2, 87)=5.66, p=0.005	0.998#	0.011*	0.014*
	60 min	77.6±5.021	77.53±4.946	74.33±3.367	F(2, 87)=5.15, p=0.008s	0.998#	0.017*	0.015*

[Table/Fig-10]: Comparison of Diastolic Blood Pressure (DBP) at various intervals among groups P, M6 and M12.

Variables	MAP at	P	M6	M12	ANOVA test results	P vs M6	P vs M12	M6 vs M12
		Mean±SD	Mean±SD	Mean±SD				
Intra-op	0 min	95.67±6.9	95.6±6.976	95.2±6.472	F(2, 87)=0.04, p=0.96	0.999#	0.962#	0.972#
	5 min	93.37±7.127	93.33±7.131	89.03±6.272	F(2, 87)=3.97, p=0.02	1.000#	0.043*	0.045*
	15 min	91.37±6.825	91.43±6.852	87.67±5.616	F(2, 87)=3.34, p=0.04	0.999#	0.047*	0.045*
	30 min	89.97±6.99	90.03±7.039	85.63±4.774	F(2, 87)=4.73, p=0.01	0.999#	0.026*	0.024*
	45 min	88.77±6.981	88.8±6.97	84.33±5.744	F(2, 87)=4.57, p=0.01	1.000#	0.029*	0.027*
	60 min	88.63±5.176	88.63±5.176	84.83±4.836	F(2, 87)=5.63, p=0.01	1.000#	0.013*	0.013*
	75 min	88.8±5.156	88.77±5.151	85.57±5.263	F(2, 87)=3.84, p=0.03	1.000#	0.047*	0.049*
	90 min	100.7±56.734	100.7±56.736	87.8±3.782	F(2, 87)=0.77, p=0.46	1.000#	0.531#	0.531#
	105 min	91.75±4.366	91.79±4.354	88.96±4.158	F(2, 87)=4.28, p=0.02	0.999#	0.066#	0.061#
	120 min	92.88±4.848	92.92±4.845	89.68±5.018	F(2, 87)=4.31, p=0.02	1.000#	0.077#	0.072#
Postop	0 min	93.8±5.02	93.77±4.994	90.77±4.158	F(2, 87)=4.04, p=0.02	1.000#	0.040*	0.043*
	30 min	94.2±4.286	94.23±4.207	91±3.787	F(2, 87)=6.15, p=0.003	1.000#	0.009*	0.008*
	60 min	94.63±4.39	94.7±4.316	91.63±4.271	F(2, 87)=4.92, p=0.009	0.998#	0.023*	0.020*

[Table/Fig-11]: Comparison of Mean Arterial Pressure (MAP) at various intervals among groups P, M6 and M12.

Variables	SpO_2 at	Group P	Group M6	Group M12	ANOVA test results	Group P vs M6	Group P vs M12	Group M6 vs M12
		Mean±SD	Mean±SD	Mean±SD				
Intra-op	0 min	99.5±0.509	99.43±0.504	99.4±0.563	F(2, 87)=0.29, p=0.752	0.876#	0.743#	0.967#
	5 min	99.47±0.507	99.3±0.466	99.37±0.556	F(2, 87)=0.84, p=0.436	0.420#	0.730#	0.869#
	15 min	99.57±0.568	99.27±0.583	99.17±0.461	F(2, 87)=4.46, p=0.014	0.086#	0.014#	0.754#
	30 min	99.47±0.571	99.27±0.583	99.4±0.563	F(2, 87)=0.94, p=0.393	0.370#	0.894#	0.641#
	45 min	99.43±0.504	99.4±0.563	99.5±0.509	F(2, 87)=0.29, p=0.752	0.967#	0.867#	0.743#
	60 min	99.37±0.556	99.4±0.621	99.27±0.583	F(2, 87)=0.40, p=0.670	0.974#	0.788#	0.655#
	75 min	99.47±0.507	99.3±0.466	99.43±0.626	F(2, 87)=0.82, p=0.443	0.456#	0.969#	0.604#
	90 min	99.53±0.507	99.4±0.621	99.47±0.507	F(2, 87)=0.42, p=0.656	0.615#	0.885#	0.885#
	105 min	99.54±0.509	99.42±0.584	99.4±0.5	F(2, 87)=0.61, p=0.547	0.695#	0.622#	0.993#
	120 min	99.33±0.482	99.29±0.55	99.45±0.51	F(2, 87)=0.78, p=0.459	0.958#	0.706#	0.535#
Postop	0 min	99.33±0.479	99.13±0.434	99.37±0.49	F(2, 87)=2.26, p=0.110	0.229#	0.959#	0.137#
	30 min	99.43±0.504	99.4±0.563	99.37±0.49	F(2, 87)=0.10, p=0.905	0.967#	0.873#	0.967#
	60 min	99.43±0.504	99.5±0.509	99.47±0.507	F(2, 87)=0.14, p=0.866	0.867#	0.965#	0.965#

[Table/Fig-12]: Comparison of SpO_2 at various intervals among groups P, M6 and M12.

Insomnia	Group P Mean±SD	Group M6 Mean±SD	Group M12 Mean±SD	ANOVA test results	p-value Group P vs M6	p-value Group P vs M12	p-value Group M6 vs M12
Day 0	0.64±0.40	0.57±0.77	0.57±0.73	F(2, 87)=0.11, p=0.892	0.658#	0.645#	1.0000#
Day 1	0.07±0.36	0.07±0.25	0.07±0.77	F(2, 87)=0.00, p=1.000	1.0000#	1.0000#	1.0000#
Day 2	0.07±0.36	0±0	0±0	F(2, 87)=1.13, p=0.326	0.2915#	0.2915#	1.0000#
Day 3	0.07±0.36	0±0	0±0	F(2, 87)=1.13, p=0.326	0.2915#	0.2915#	1.0000#

[Table/Fig-13]: Comparison of insomnia score among groups P, M6 and M12.

The sedation score was more significant in group M12 as compared to group P and M6 from one hour after study drug administration till 12 hours postoperatively. The difference is highly significant (p<0.001) at one hour after study drug administration and six hours postsurgery [Table/Fig-14]. However, no patient was deeply sedated.

Sedation at	Group P Mean±SD	Group M6 Mean±SD	Group M12 Mean±SD	ANOVA test results	p-values Group P vs M6	p-values Group P vs M12	p-values Group M6 vs M12
Tp	0.38±0.49	0.46±0.48	1.53±0.507	F(2, 87)=51.00, p<0.001	0.262#	<0.001*	<0.001*
T6	0.07±0.254	0.1±0.321	0.5±0.509	F(2, 87)=12.16, p<0.001	0.344#	<0.001*	<0.001*
T12	0.03±0.183	0.01±0.175	0±0	F(2, 87)=0.33, p=0.722	0.333#	0.317#	0.377#
T24	0±0	0±0	0±0	-	-	-	-
T36	0±0	0±0	0±0	-	-	-	-
T48	0±0	0±0	0±0	-	-	-	-
T72	0±0	0±0	0±0	-	-	-	-

[Table/Fig-14]: Comparison of sedation among the three groups M6, M12 and P.
***SED: Sedation; Tp- preoperatively 60 min after study drug administration, T6, T12, T24, T36, T48, T72 - 6, 12, 24, 36, 48 and 72 hours after surgery, *statistically significant, #statistically insignificant

DISCUSSION

Pharmacology of melatonin: Melatonin, being highly lipophilic with a consequent high volume of distribution and 70% albumin-binding, undergoes extensive first-pass metabolism with varying bioavailability. Oral melatonin has a peak serum concentration reported within 60-150 minutes after administration. The effect persisted for the next 10-15 hours. However, it is reported that melatonin was absorbed within 30 minutes after administration and its elimination half-life was 45-60 minutes [27]. The analgesic properties of melatonin have been attributed to the inhibition of inflammatory pathways and tissue injury by affecting COX-2 and nitric acid activity, as well as modulating glutaminergic pathways via NMDA receptors. Another recent study suggests that the analgesic property of melatonin indirectly pertains to interaction with several neurotransmitter systems, including benzodiazepine receptors, NMDA receptors, NO-cGMP-PKG pathways and directly through the MT1/MT2 pathway [1].

A wide variety of dosages (3-15 mg) and administration time for melatonin have been observed as premedication in different clinical scenarios [13-17]. A maximum safe dose of 0.4 $mg.kg^{-1}$ oral melatonin was effective in preoperative anxiolysis and has been used in adult patients undergoing surgeries under general anaesthesia [17]. The authors had opted a higher dose (12 mg) than most of the studies keeping in mind the safe range and also the intense pain experienced by patients in lower limb orthopaedic procedure.

Preoperative anxiolysis: The present study shows lower anxiety scores from one hour after the study drug administration up to 72 hours postoperatively with 12 mg oral melatonin premedication. Similar to our results, sublingually or orally administered melatonin proved to be an effective pre-medicant in adults and children [13-17]. Some studies reported the anxiolytic effect of preoperative melatonin at a lower dose (6 mg oral melatonin) using the VAS scale for anxiety assessment [18]. Similarly, Khare A et al., found reduction in VAS anxiety score with 6 mg of oral melatonin premedication given 120 minutes before general anaesthesia [19]. These studies had differences in methods as well as in demographics, anaesthesia techniques and anxiety assessment tools. Firstly, VAS score for anxiety is a simple and fast assessment tool, yet it lacks specificity and reliability. On the other hand, STAI can assess both trait and state anxiety, giving a better understanding of anxiety with a high internal consistency coefficient (0.86-0.95) and test-retest reliability coefficients (0.65-0.75) over two months [21]. Also, it has been found that female gender, young age, major surgery, high trait anxiety, negative future perception, history of cancer and smoking, previous psychiatric disorder and high educational level are associated with higher preoperative anxiety scores, necessitating higher dosage [28,29].

Postoperative analgesia: The present study indicates lower VAS scores for pain (both at rest and movement) from 6-72 hours postoperatively and lower analgesic consumption with 12 mg melatonin. The time of request for first and second rescue analgesia was nearly double in group M12 as compared to the other two. Similar to our study, the sparing effect of melatonin was seen in other studies [14,30,31]. Beigom Khezri M et al., found that premedicating with 3 mg sublingual melatonin 20 minutes before spinal anaesthesia prolonged the time to request for first analgesic, but the difference was not statistically significant [32]. The difference in results might be due to a shorter time gap between drug administration and anaesthesia to produce an effect. Another experimental study found that the time required for rescue analgesia was significantly longer in the melatonin group after surgery and lower VAS scores for pain in the immediate postoperative period till six hours postoperatively when 3 mg oral melatonin was administered one hour before surgery [33]. Contrary to all these, Naguib M et al., did not observe any significant difference in the intraoperative opioid use or total analgesics consumption in the melatonin or placebo group over 90 minutes after surgery in two different trials [15,34]. Similarly, Acil M et al., also failed to demonstrate any opioid-sparing effects or reduction in pain score with a single dose of sublingual 5 mg melatonin before laparoscopic surgery. They found that melatonin does not have an analgesic effect but shows an opioid-sparing effect when co-administered with other analgesic agents [13]. Yousaf F et al., also suggested in a systematic analysis of the analgesic effect of melatonin during the preoperative period is limited with controversial results [1].

Prolong analgesic action and postoperative anxiolysis: An interesting look to the prolonged postoperative analgesia in our study can be explained by decreased intraoperative nociception after administration of melatonin. It is reported that better intraoperative nociception management results in improvements in postoperative pain [35]. Pain and anxiety have a bidirectional relationship [36].

Thereby, diminished postoperative pain reduces postoperative anxiety too. As a result of better analgesia during the intraoperative period, postoperative pain perception in patients is lower than usual, thereby reducing analgesic requirements and anxiety in postoperative period, proportionately decreasing morbidity and hospital stays. So, the prolonged effect of melatonin in the present study till 72 hours is not a direct pharmacological effect as the drug is a comparatively short-acting drug and can be attributed to a more nuanced synergistic effect.

Sedation: Higher sedation was associated with group M12, which was explicitly higher one hour after the study drug administration, and difference among groups was observed up to six hours postoperatively. Melatonin exerts hypnotic effects by acting on MT1/MT2 receptors. It produces increased sedation without impairment in orientation afterwards. Similar to the present study, slight sedation without any psychomotor disturbances for the initial few hours was reported in other studies [13,15,30,33,34]. It was found that on sublingual administration, the sedative effect starts in 30 minutes and peaks at 90 minutes.

Haemodynamic changes: In addition to its analgesic, sedative and anxiolytic properties, melatonin also has haemodynamic effects. In the present study, Systolic Blood Pressure (SBP) of the patients in the M12 group was in lower range (~103-123) compared to patients in M6 (~109-133) and placebo (~109-133) groups. Similar findings were recorded in another study [31]. Melatonin binds to specific melatonin receptors inside blood vessels, causing interference in the vascular response to catecholamines. It also affects the central and peripheral autonomic nervous system, causing decreased adrenergic outflow and catecholamine release, increasing nitric oxide availability and resulting in vascular smooth muscle relaxation, ultimately leading to reduced blood pressure [37]. When melatonin was administered as premedication before general anaesthesia, laryngoscopy and intubation, increase in MAP was significantly reduced in the melatonin group compared to the control group [18].

Limitation(s)

The study only focused on lower-limb orthopaedic surgeries to limit confounders, and the results may not be applicable to other types of surgeries or patient populations. Lastly, the study used fixed dosages of melatonin (6 mg and 12 mg), without exploring the optimal dosage or individualising the dose based on patient characteristics.

CONCLUSION(S)

The present study found that 12 mg of oral melatonin premedication reduces anxiety levels preoperatively and postoperatively up to 72 hours. Additionally, the same dosage of melatonin lowers pain both at rest and movement postoperatively, reduces analgesic requirement. It does cause slight sedation and slightly lower SBP, but without any more side-effects when compared to 6 mg melatonin.

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