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Effect of Melatonin Premedication on Postoperative Analgesic Requirement in Laparoscopic Cholecystectomy Surgery

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Abstract: *The pineal hormone, melatonin (N-acetyl-5-methoxytryptamine), has several recognized functions that can make it an attractive option for premedication, including the regulation of circadian rhythms, and sedative, analgesic, anti-inflammatory, antioxidative, and chronobiotic effects. The present study was designed to determine the effect of oral melatonin premedication on sedation, analgesia, and postoperative analgesic requirement in patients undergoing laparoscopic cholecystectomy. This randomized, double-blind, placebo-controlled study included 100 patients of either sex, ASA physical status I–II, scheduled for laparoscopic cholecystectomy. Patients were randomly assigned to receive either oral melatonin 3 mg (Group: M; n = 50) or placebo (Group P; n = 50) the night before and 1 h before surgery. The melatonin group patients required less fentanyl by patient-controlled analgesia. Mean dose requirement was 2500µg and 3439µg in groups M and P respectively (p<.001). There was significant difference in sedation scoring between M and P group. There was higher sedation scores in M group compared to P group. It can be concluded from the present study that melatonin is an effective and safe premedication as it provided mild sedation in the preoperative period and significantly reduced fentanyl requirement in the postoperative period without any untoward effect in patients undergoing laparoscopic cholecystectomy.*

Keywords: *Melatonin, Premedication, Postoperative pain, Sedation*

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I. INTRODUCTION

Millions of patients receive sedatives to reduce anxiety before surgery, but the choice of premedication is often determined by habit and tradition, rather than by any scientific evidence. [1] A study revealed that usually more than 75% of the healthy patients admitted for surgery administered sedative premedication. [2] Although the use of preoperative benzodiazepines is the most common practice, the potential clinical benefits of new therapeutic options in this setting remain to be investigated. The pineal hormone, melatonin (*N*-acetyl-5-methoxytryptamine), has several putative functions that make it an attractive option for premedication, including the regulation of circadian rhythms, and sedative, analgesic, anti-inflammatory and anti-oxidative effects. [3]

Melatonin is a methoxyindole synthesized from tryptophan and secreted principally by the pineal gland. It has an endogenous circadian rhythm of secretion induced by the suprachiasmatic nuclei of the hypothalamus that is entrained to the light/dark cycle. [4] In mammals, melatonin is present in almost all tissues, with or without the melatonin receptors, because it acts both as a hormone and an antioxidant. [5] Considering the time-dependent action of melatonin, it can be better classified as a chronohypnotic. [6,7] Five milligrams of oral melatonin per day has been used to alleviate jet lag and as a preoperative sedative agent. [8,9,10] Also melatonin has been related with the relief of pain in patients with extensive tissue injuries. [3] Considering the potential pharmacological benefits of melatonin, this study was designed to determine the effect of oral melatonin premedication on sedation, intraoperative analgesia and postoperative analgesic requirement.

II. MATERIAL AND METHODS

A prospective, randomized placebo controlled comparative study was undertaken in 100 patients, aged 25–55 years, of either gender and belonging to ASA physical status grade I–II, scheduled for laparoscopic cholecystectomies. Patients with hypersensitivity to any drug, history of congestive heart failure, valvular heart disease, renal or hepatic disease, neuropsychiatric disorders and pregnancy, and patients on steroids, beta blockers analgesics or any psychotropic drugs in the present or in the past were excluded from the study. After approval from the Institutional Ethics Committee, 100 patients were recruited for the study and an informed written consent was obtained from each participant. They were randomly allocated into either of the two groups with the help of a computer-generated random number table. Group M (melatonin group): received 3mg oral

melatonin the night before (10 pm) and 1 hour before surgery and Group P (Placebo group): received a placebo the night before (10 pm) and 1 hour before surgery.

No other sedative preoperative medication was given. Distribution of the study drugs was performed by an anaesthesia technician who was not involved in the further evaluations of the patients. Other individuals involved in the care of the patients were unaware of type of group allocation. The primary outcomes were postoperative pain, as assessed by pain scores and analgesic consumption. Secondary outcomes were sedation level in the patients.

All the patients were assessed the day before surgery. The staff who provided instructions on the use of patient-controlled analgesia (PCA) pumps and Visual Analog Scale (VAS**)** was unaware of group assignment. A 100 mm VAS, that ranged from 0 (no pain) to 100 (worst pain imaginable), was used to assess the post-operative pain, and was explained to the patient. A record of preoperative sedation as well as intraoperative and postoperative hemodynamics (systolic, diastolic and mean arterial blood pressure, and heart rate) for initial 2 hours were made. Preoperative sedation was assessed at 30 min and 1 hr after administration of morning dose of melatonin. Sedation was assessed by a five-point scale: 1-alert and wide awake, 2-arousable to verbal command, 3-arousable with gentle tactile stimulation, 4-arousable with vigorous shaking, 5-unarousable.

In the operating room, standard monitoring was used. Anaesthesia was induced with propofol 2 $\mu g.kg^{-1}$ i.v., fentanyl 2 $\mu g.kg^{-1}$ i.v., lidocaine 1.5 $\mu g.kg^{-1}$ i.v. and endotracheal intubation was facilitated with vecuronium bromide 0.1 $\mu g.Kg^{-1}$ i.v. Maintenance of anaesthesia was done with propofol infusion 50-150 $\mu g.kg^{-1}$ i.v. and 70% nitrous oxide in oxygen. Intermittent fentanyl $1\mu.kg^{-1}$ hr^{-1} for analgesia and vecuronium 0.02-0.04 $mg.kg^{-1}$ for muscular relaxation were given as and when indicated. Upon completion of surgery, the neuromuscular blockade was reversed with neostigmine 0.04 $\mu g.kg^{-1}$ i.v. and glycopyrrolate 0.01 $mg.kg^{-1}$ i.v. Patients were extubated when adequate spontaneous ventilation was achieved. Upon completion of the surgery, the patients were shifted to the post anaesthesia care unit (PACU). Pain scores were recorded upon the completion of surgery at 0 min, then every 30 min for initial 6 h and 2 hourly for next 24 hrs. Pain scores were recorded by a resident blinded to the type of medications received intraoperatively by the patients. Total fentanyl consumption during the first 24 h was noted. Any incidence of adverse event was recorded and treated according to the standard protocol in both the groups. Respiratory depression was defined as inability to maintain oxygen saturation >90% on spontaneous ventilation without supplemental oxygen, or a respiratory rate less than 8 min^{-1}. The side effects viz. nausea, vomiting, sedation, pruritus, respiratory depression, and total fentanyl requirement in the first 24 h was recorded.

After being transferred to the PACU, the patients were connected to a fentanyl PCA pump, with infusion rate of 0.4 $\mu g.k.h^{-1}$, with a delivery of 20 μg fentanyl on each demand, a 15 min lockout and a maximum dose of 80 $\mu g.h^{-1}$. The PCA was maintained during the first 24 h after the surgery. The analgesic consumption was measured by recording the amount of fentanyl used via PCA and adjusted by patient weight. Pain sense was recorded by a resident blinded to the type of medications received by the patients, and subsequently at six hour intervals until 24h on a visual analogue scale (VAS) at rest. No other pain medication was allowed. If required, 4 mg of ondansetron was administered for postoperative nausea and vomiting.

The various parameters studied during observation period were compiled. The unpaired Student's t-test was applied for comparing the parametric data of both the groups, while Chi-square test was applied for the nonparametric data. The data were analyzed by Statistical Package for Social Science (SPSS) version 16 for windows (SPSS Inc, Chicgo, Illinois, USA). P-values < 0.05 and <0.001 were considered significant and highly significant respectively.

III. RESULTS

Out of a total of 50 patients in each group there were 24 males and 26 females in group M , and 26 males and 24 females in Group P. The mean age were 41.06±4.10 in group M and 39.40±3.71 in group P. (Table 1)

Table 1: Demographic profile of the patients

Parameter	Group M	Group P	p-value
Age (Mean ± SD)	41.06±4.10	39.40±3.71	0.0363
Gender			
M	24	26	0.160
F	26	24	
Body weight (Mean ± SD)	66.08±11.56	64.20±12.69	0.4405

The statistical comparison of mean subjective pain scores (VAS) between the two groups at different time intervals is shown in Table 2. There was a significant difference between the two groups at 0, 30, 60, 75, 90,120 and 150 minutes intervals during the post-operative period. ($p<0.05$)

Table 2: Mean VAS scores between the two groups at different time intervals in the post-operative period

Time interval	M group	P group	t-value	p-value
0 min	1.84 ± 0.889	1.24 ± 0.822	3.504	.001*
30 min	0.88 ±1.118	1.40 ± 0.756	2.724	0.008*
1 h	1.24 ± 0.657	1.52 ± 0.580	2.260	0.026*
1.5 h	1.16±. 0548	1.60 ± 0.571	3.929	0.000*
2 h	1.40± 0.639	1.72 ± 0.536	2.713	0.008*
2.5 h	1.24± 0.431	2.16 ± 0.738	7.607	0.000*
3.0 h	1.04± 0.727	1.12 ± 0.659	0.576	0.566
3.5 h	1.72± 0.536	1.84 ± 0.681	0.979	0.330
4.0 h	1.64± 0.485	1.88 ± 0.872	1.701	0.092
4.5 h	1.56± 0.501	1.64 ± 0.631	0.702	0.484
5.0 h	1.28 ± 0.536	1.44 ± 0.501	01.541	0.126
5.5 h	2.00 ± 0. 000	2.00 ± 0.000	0.981	0.329
6.0 h	0.00 ± 0.000	1.00 ± 0.000	0.993	0.323
8 h	0.00 ± 0.000	1.00 ± 0.000	0.972	0.334
10 h	0.00 ± 0.000	1.00 ± 0.000	0.910	0.365
12 h	0.00 ± 0.000	1.00 ± 0.000	0.880	0.381
14 h	0.00 ± 0.000	1.00 ± 0.000	1.095	0.276
16 h	0.00 ± 0.000	1.00 ± 0.000	0.995	0.328
18 h	0.00 ± 0.000	1.00 ± 0.000	0.976	0.332
20 h	0.00 ± 0.000	1.00 ± 0.000	0.907	0.358
22 h	0.00 ± 0.000	1.00 ± 0.000	0.879	0.376
24 h	0.00 ± 0.000	1.00 ± 0.000	1.091	0.271

*p<0.05

The total 24-h fentanyl consumption during the post-operative period was 2500.04±238.34 µg in group M and 3439.52±453.68 µg in group P. (Table 3)

Table 3: Total fentanyl requirement (µg)

Group	Dose	t-value	p-value
Group M	2500.04 ± 238.34	12.963	<0.001
Group P	3439.52 ± 453.68		

The statistical comparison of mean sedation scores between the two treatment groups at 30 min and 1 h after administration of melatonin is shown in Tables 4 and 5 respectively.

Table 4: Sedation score at 30 min after the administration of morning dose of melatonin

Sedation	Group M		Group P		p-value
	Number of patients	%	Number of patients	%	
1	12	24	50	100	<0.001
2	33	66	0	0	
3	5	10	0	0	

Table 5: Sedation score at 1h after the administration of morning dose of melatonin

Sedation	Group M		Group P		p-value
	Number of patients	%	Number of patients	%	
1	10	20	50	6	<0.001
2	36	72	0	4	
3	4	8	0	0	

The comparison of mean pulse rate and mean arterial pressure between the two groups at different time intervals are shown in Tables 6 and 7 respectively. There was no significant difference found between both the groups.

Table 6: Mean heart rate between group M and group P at different intervals

Time interval	Group M	Group P	p-value
0 min	85.08 ± 10.488	87.14 ± 10.519	0.329
15 min	87.36 ± 10.184	89.38 ± 10.152	0.323

30 min	86.40 ± 10.186	88.38 ± 10.194	0.334
45 min	86.28 ± 9.982	88.10 ± 10.021	0.365
60 min	86.24 ± 9.938	87.98 ± 9.824	0.381
90 min	87.48 ± 9.937	89.64 ± 9.795	0.276
120 min	85.40 ± 10.371	87.24 ± 10.364	0.377

Table 7: Mean blood pressure between group M and group P at different intervals

Time interval	Group M	Group P	p-value
0 min	90.74 ± 5.034	90.80 ± 4.751	0.951
15 min	92.74 ± 5.891	92.94 ± 4.934	0.854
30 min	91.74 ± 6.121	91.96 ± 5.202	0.847
45 min	90.82 ± 5.001	90.94 ± 4.800	0.903
60 min	92.70 ± 4.850	92.98 ± 4.821	0.773
90 min	92.04 ± 4.776	92.06 ± 5.227	0.984
120 min	91.16 ± 4.821	92.02 ± 5.061	0.386

The incidence of adverse effects such as headache, nausea and vomiting, post-operative shivering, pruritus etc. in both the groups were statistically not significant. There were no incidence of hypotension or respiratory depression in either of the two groups. (Table 8)

Table 8: Incidence of post-operative adverse effects in group M and group P

Adverse effects	**Group M**	**Group P**	**p-value**
Headache	1	0	0.315
Pruritus	1	0	0315
Post-operative shivering	0	2	0.475
Nausea/ vomiting	1	4	0.359

IV. DISCUSSION

Recent years have witnessed an increasing interest in the postoperative pain management, as it can directly influence patient outcome. The aim of postoperative pain treatment is to provide subjective comfort in addition to inhibiting trauma-induced nociceptive impulses in order to blunt autonomic and somatic reflex responses to pain and subsequently to enhance restoration of function by allowing the patient to breathe, cough and move more easily. Unrelieved pain after surgery may have various deleterious effects. Fortunately, it is preventable or controllable in an overwhelming majority of cases. Pain control may have a further benefit of improving clinical outcome by reducing the incidence of postoperative complications such as myocardial infarction or ischemia, tachycardia and dysrhythmia, impaired wound healing, atelectasis, thromboembolic events, peripheral vasoconstriction and metabolic acidosis. With the increasing popularity of ambulatory anaesthesia, there is even more emphasis on effective postoperative analgesia. Pre-emptive analgesia can be achieved by the administration of opioids, local anaesthetic blocks and other analgesic modalities before surgery in an attempt to decrease the intensity and duration of postoperative pain. [11] However, despite high-quality anaesthetic research and advances in drugs and various other modalities for pain management, many controversies remain regarding the best clinical practice.

The present study was undertaken to determine the effect of melatonin on postoperative analgesic requirement in laparoscopic cholecystectomies. The study was performed on 100 patients of either sex, divided randomly into two groups of 50 patients each. Group M consisted of patients to whom melatonin was given, and Group P consisted of patients to whom placebo was given. A record of preoperative sedation, intraoperative and postoperative hemodynamics (systolic, diastolic and mean arterial blood pressure, and heart rate) for initial 2 hours were made. Pain scores upon completion of surgery, and total fentanyl consumption was made in both groups in first 24 hours. The side effects (nausea, vomiting, sedation, pruritus, respiratory depression) were recorded in first 24 hours.

There was no significant change in heart rate from the preoperative value, neither in Group M nor in group P. Thus the study shows that two doses of melatonin do not have any appreciable effect on the heart rate. This finding is similar to the observation of Yildiz et al who did not find significant difference in heart rate after oral administration of melatonin. [12] Mean arterial blood pressure also did not change significantly after oral administration of melatonin. This is in contradiction to the findings of Frank et al, who observed significant reduction of systolic and diastolic BP, after three weeks of 2.5 mg melatonin 1 hour before bedtime. [13] This could be due to longer duration of melatonin administration by Frank et al.

Sedation levels of the patients were assessed preoperatively at 30 min and 60 min after administration of morning dose of melatonin. Patients in the melatonin group were found to be more sedated than the placebo group. Patients who were given Melatonin tablets had higher sedation scores than those who were given placebo. Borazan et al observed that the sedation scores were significantly higher in the melatonin group than in the control group. [14] This finding is in accordance with the observation in our study. Acil et al compared melatonin with midazolam premedication, and found that melatonin leads to preoperative anxiolysis and sedation without postoperative impairment of psychomotor performance. [15] Naguib M et al also found, patients who received melatonin premedication were more sedated than those who received placebo. [16] Other authors too have observed sedative action of melatonin. [17,18]

In the present study melatonin administration resulted in significant reduction in the fentanyl consumption in the postoperative period. Similarly Borazan et al [14] and Caumo et al, [19] observed significant reduction in total tramadol and morphine consumption respectively in postoperative period in patients who had received melatonin. Ismail et al also observed analgesic role of melatonin in cataract surgeries. [20] Borazan in his study on patients undergoing prostatectomy, observed reduction in pain scores and tramadol consumption after administration of melatonin. [14]

The potential analgesic effect of melatonin that we observed is supported by previous studies in animals in which systemically administered melatonin produced dose-dependent antinociception and enhanced morphine analgesia. [21,22] Possibly, this antinociceptive effect of melatonin involves the activation of supraspinal sites. [23,24] This effect may be mediated by membrane receptors linked to G proteins, and possibly through nuclear receptors. [25] Also, experimental evidence suggests that its analgesic effect is mediated by the opioid system, because it augments γ-aminobutyric acid (GABA) systems and morphine antinociception, enhancing γ-aminobutyric acid-induced currents and inhibiting glycine effects. [26,27,28,29] It produces marked antiinflammatory effects on peripheral sites by inhibiting the release of proinflammatory cytokines, [30] and the rolling and adhesion of neutrophils to the endothelial layer. [31,32] This effect on cell defense occurs even in concentrations compatible with nocturnal secretion.

Therefore, it can be concluded from the present study that melatonin is an effective and safe preoperative medication as it provides mild sedation in the preoperative period and significantly reduces fentanyl requirement in the postoperative period without any untoward effect in patients undergoing laparoscopic cholecystectomy surgery. However, more studies are needed to further elucidate the mechanisms by which exogenous melatonin modulates nociceptive circuits.

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