SRHU JOURNAL OF ADVANCED RESEARCH

# Evaluation of cognitive & psychomotor skills perioperatively after administration of melatonin, clonidine and pregabalin as premedicant in laparoscopic cholecystectomy

[1]**Anu Goel,** [2]***Parul Jindal,** [3]**Sanjay Agrawal**

[1,23,]*Department of Anesthesiology & Pain Management, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Jolly Grant, Dehradun, Uttarakhand, India*

**Keywords**

Cognitive function, clonidine, melatonin, pregabalin, psychomotor skills

**Abstract**

The addition of premedicative to the anesthesiologist armamentarium improves the anesthetic management and benefits the patients perioperatively. This prospective randomized double-blind placebo-controlled study included 160 patients aged 18-65 undergoing laparoscopic cholecystectomy under general anesthesia. Patients were randomly assigned to following groups (n= 40 each) Group D: Placebo (sugar pill) Group A: Melatonin (6mg) Group B: Clonidine (100mcg) and Group C Pregabalin (75mg) the night before and 60 minutes prior to surgery as oral premedicants. The following data was recorded; anxiety score, quality of sleep preoperatively and Trieger dot test (TDT) and digit symbol substitution test (DSST) preoperatively and then at 0, 30,60,90,6,12,24 h post operatively. The TDT and DSST score and time taken to complete DSST test was significantly less ($p<0.05$) in group A as compared to other groups at all time intervals. None of the subjects belonging to group B, C, D were able to perform cognitive and psychomotor test up to 60 min. This study reports melatonin as a premedicant has improved postoperative cognitive function and psychomotor skills as compared to pregabalin and clonidine in patients undergoing elective surgery.

***Corresponding Author:** paruljindal@srhu.edu.in

**Article Info**

Received: 17 April 2026, received in revised form: 25 May 2026, accepted: 21 June 2026, available online: 28 June 2026; Volume: 1; Issue: 2; Pages: 64-72.

**Citation:** Goel, A., Jindal, P., Agrawal, S., 2026. Evaluation of cognitive & psychomotor skills perioperatively after administration of melatonin, clonidine and pregabalin as premedicant in laparoscopic cholecystectomy. SRHU J Adv Res. 1(2): 64-72.

DOI:



## 1. Introduction

Individuals perceive stressful situation differently and in doing so, may have different levels of anxiety. These anxious moments may be the result of past experiences, beliefs, methods of reasoning, perceptions and state of mind (Caumo et al. 2001). These fearful experiences have long term postoperative implications in form of postoperative stress disorders and present as flashback, nightmares or repetitive and distressing images or sensation, pain sweating and trembling.

Useful and detailed information about surgical procedure, mode and type of anesthesia provides

the patients with psychological support that is believed to reduce their anxiety. Currently most commonly used premedicants in the preoperative area is midazolam (85%) followed by ketamine (4%), fentanyl (3%) and meperidine (2%) with oral route most commonly used (Mc Can metal 2001). Each of these drugs has its own limitations leading to impairment of patient's co-operation, over sedation, impairing fine motor skills and cognitive functions in post operative period. Thus, potential clinical advantages of new drugs in this setting remains to be evaluated.

Melatonin is a naturally occurring hormone secreted from the pineal gland in the brain and to a lesser extent by the gastrointestinal tract and retina (Darrow and Goldman, 1985). In humans' pineal melatonin regulates neuroendocrine function as sleep, thyroid gland secretion and growth hormone release. In preliminary reports, it has been suggested that circadian disturbances in the synthesis of melatonin have been correlated with sleep disturbances. Under normal physiological conditions, melatonin regulates circadian rhythmicity and the sleep-wake cycle. This makes it an attractive alternative premedication for control of anxiety, pain and has minimal action on psychomotor performance and sleep wake cycle (Arendt et al. 1986). Anesthetic uses of melatonin are described by different authors for premedication, analgesic effect and anti-inflammatory and immunological effects.

Clonidine is a centrally acting alpha 2 receptor agonist which acts by its action on spinal and supraspinal receptors (De Vos et al. 1994). Locus coeruleus noradrenaline system has been proposed as mechanism of mediating anxiety symptoms. Clonidine decreases locus coeruleus firing and norepinephrine release and has shown efficacy in treatment of anxiety and in both spontaneous & induced panic disorder (Davis et al.. 1982).

Pregabalin is a structural analogue of gabapentin. Gabapentenoids are group of drugs which act primarily as anticonvulsants by their action of reduction of calcium entry to the nerve terminals of the central nervous system via their action on voltage gated calcium channel receptors in over excited presynaptic neurons reducing release of excitatory neurotransmitters, leading to a reduction in levels of anxiety (Lesser et al.. 2004; Rose and Kam, 2002).

We designed this study to assess postoperative cognitive function and psychomotor skills after administration of premedicants melatonin, clonidine, pregabalin and placebo in patients undergoing laparoscopic cholecystectomy under general anesthesia.

1. **Material and Methods**:

After obtaining Institutional Ethical Committee approval and informed consent, 160 patients aged 18-65 yrs (American society of anesthesiologist physical status ASA grade I, II) of either sex who were about to undergo elective laparoscopic cholecystectomy under general anesthesia were included in the study. Fig 1 shows the process of patient selection.

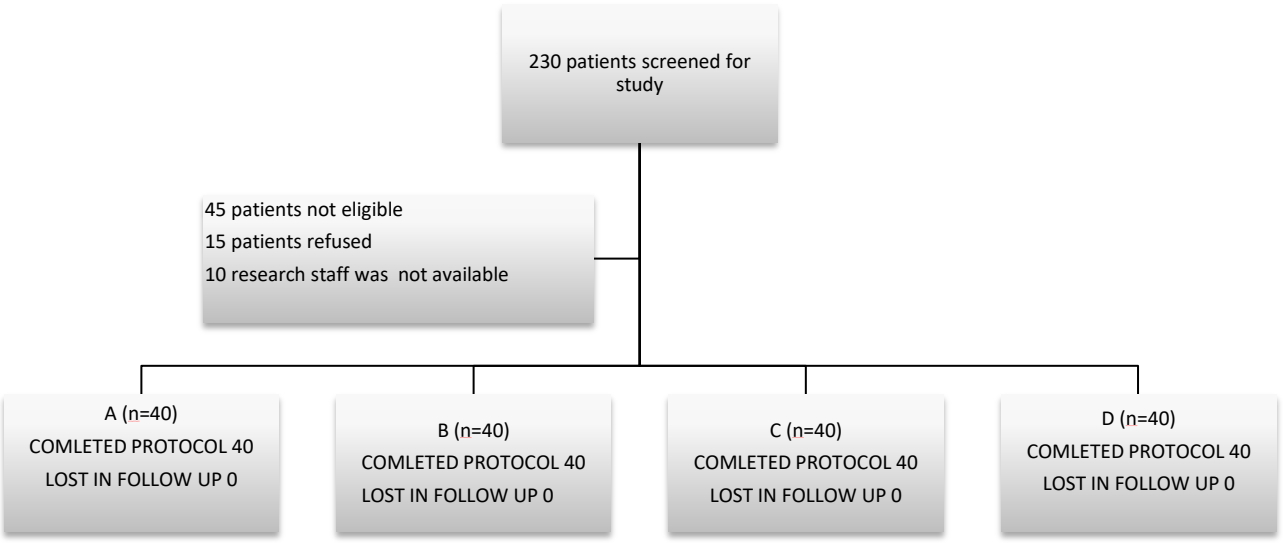


**Fig 1. CONSORT flow diagram**

Exclusion criteria: American society of Anesthesiologist (ASA) grade III and IV, patients' refusal for participation, age less than 18 or more than 65 years, Body mass index (BMI) greater than 35 kg/$m^2$, Pregnant or breast-feeding females, at risk for aspiration, allergy to the study drugs and pre-operative intake of hypnotics/ psychotropic drugs/ substance abuse, use of monoamine oxidase inhibitors. Chronic intakes of beta-blocker, analgesic, and coumadin derivative were also excluded from the study.

The evening before the surgery patients were randomized by computer generated tables of random numbers into four study groups: Group D (n= 40) placebo (sugar pill), Group A (n=40) melatonin 6mg (Meloset Aristo pharmaceutical), Group B: (n=40) clonidine 100mg (Arkamin, Unichem pharmaceutical) Group C: (n=40) pregabalin 75mg (Maxgalin-Exr, Sunpharma) as oral premedicant night before and 1 hour prior to surgery with sip of water.

The drug was handed over to the nurse in-charge of patient in similar looking thick opaque envelope marked A, B, C, D to be administered as per the instruction. The nature of drug was not known to the nurse. The patients were shown and explained in detail about the various parameters in questionnaires scheduled to be used during the study. A trained anesthesiologist resident blinded to the group conducted all the tests. Anxiety was evaluated by using CD Spielberger's questionnaire, STAI-S, (Inosec et al.. 2008) which is designed to assess the actual state of anxiety. This questionnaire is validated and standardized. After discussion with a qualified psychiatrist and reviewing literature, six items were chosen from this questionnaire, related to perioperative anxiety (Table 2), to produce a total score (range 6 to 24) in each patient. Higher values represent greater anxiety. Cognitive and psychomotor skills were assessed using DSST (Newman et al.. 1969) and TDT respectively (Rosano et al.. 2008).

The patients were premedicated with oral ranitidine (150 mg) and oral metoclopramide (10 mg) along with the study drug as per group allotment with sips of water, on night before and one hour prior to surgery.

Preoperative anxiety was evaluated by anaesthesia resident utilizing the Spielberger's questionnaire while the quality of sleep was assessed by questioning the patients and grading as grade 1=good sleep, grade 2=insomnia and grade 3 =nightmares. The patients were then shifted to Operation Theater.

Peripheral intravenous infusion was started with ringer lactate and baseline hemodynamic parameter monitoring was recorded using multiparameter monitor (Drager infinity vista XL model no

M514750E539U). Anaesthesia was induced with fentanyl 2µg/kg and propofol 2-2.5mg/kg in all the groups and muscle relaxation was achieved with injection vecuronium 0.1 mg/kg. After tracheal intubation anesthesia was maintained sevoflurane (end tidal level 1-1.5MAC) in 50:50 oxygen and air supplemented with intermittent top-ups of inj fentanyl (1µg/kg) and inj. Vecuronium (.05mg/kg). End tidal concentration of oxygen, sevoflurane and carbon dioxide was adjusted to maintain normocapnia ($EtCO_2$ 35-45mm Hg). Electrocardiography and saturated oxygen in arterial blood $SpO_2$ was monitored continuously and non-invasive blood pressure monitoring was recorded every 3minutes. Inj paracetamol 1.0gm iv was administered 15 minutes prior to expected completion of surgery. Neuromuscular blockade was reversed using inj. neostigmine (0.05 mg/kg) and glycopyrolate (0.01mg/kg) and patient was extubated and shifted to postanesthesia care unit (PACU).

In PACU patient was asked to complete the Trieger Dot Test (TDT) and Digit Symbol Substitution Test (DSST) at 30 min, 60 min, 90 minutes, 6 h, 12 h, and 24 h. All the patients were positioned with 45-degree head elevation and used the same writing implement (ball point pen medium point black). For the Trieger Dot Test (TDT), the subject used a pen to connect a number of dots in order to complete the shape of the figure. The extent of psychomotor impairment was assessed by analyzing number of dots missing, extraneous deviation of lines and time required to complete the test. Thus, higher the value of these factors, the greater the degree of psychomotor impairment.

The DSST is a test of cognitive performance in which the subject is given a key grid of numbers and matching symbols and test section with numbers and empty boxes. The test consists of a sheet of paper, with a key numbered 1 to 9 at the top with each number being ascribed to a different symbol. Beneath the key are five rows of 25 randomly distributed numbers without their corresponding symbol. The patient was asked to substitute as many symbols as possible in 120 seconds period, starting with the first row and working from left to right. The test was scored by counting the number of correct symbols inserted. If there are psychomotor derangement and cognitive dysfunction, the DSST scores will decrease. By completing this test, the extent of cognitive impairment was assessed by comparing number of questions that the subject got correct.

The occurrence of side effects such as nausea, vomiting, respiratory depression, dizziness, nystagmus, tremor, diplopia, somnolence, edema, diarrhea, headache, and pruritis were recorded in the first 24hrs. Postoperative nausea

2. **Statistical Analysis:**

The sample size for this study was determined based on previous literature (Naguib and Samarkandi, 2000; Kurdi and Patel, 2013). The calculation assumed a repeated-measures ANOVA (RM-ANOVA) design to evaluate the main parameter, anxiety score, across 4 groups over 7 repetitions. Detecting a small effect size of 0.20 (Cohen's criteria) with 80% statistical power and a 5% significance level required a total sample size of 160 patients (40 patients per group).

Statistical analyses were performed using Microsoft Excel 2007 and IBM SPSS Statistics version 22 (SPSS South Asia Pvt. Ltd., Bengaluru, India), with statistical significance set at $p < 0.05$. Qualitative data were expressed as frequencies and percentages, while quantitative data were presented as mean ± standard deviation (SD). Group proportions for gender and ASA physical status grading were analyzed using the Chi-square test. The Kruskal-Wallis H test was utilized to evaluate analgesia. Finally, one-way ANOVA followed by Tukey's Honestly Significant Difference (HSD) post-hoc test was applied to analyze total duration of tolerance (TDT) and Digit Symbol Substitution Test (DSST) scores.

**3 Results:**

Patients in all the groups were comparable in demographic profile and operative time (Table 1). Anesthesia techniques were kept standard in all the four groups. Majority of the subjects 130 (81.2%) had good sleep on the night before surgery. None of the subjects had nightmares prior to surgery (Table 1).

**Table 1: Demographic profile and operative details of the study population (Mean ± SD)**

| | Group D (n=40) | Group A (n=40) | Group B (n=40) | Group C (n=40) | p value* |
|---|---|---|---|---|---|
| Age in years (Mean±SD) | 45.87±13.39 | 37.37±12.39 | 40.82±12.56 | 42.1±12.69 | 0.098 |
| Weight in Kgs (Mean±SD) | 60.75±13.36 | 61.87±11.30 | 61.25±15.50 | 61.32±10.65 | 0.985 |
| Sex M:F | 6:34 | 10:30 | 10:30 | 8:32 | 0.170 |
| ASA I:II | 30:10 | 32:8 | 30:10 | 33:7 | 0.804 |
| Sleep score 1:2 (mean±SD) | 32:8 1.2±0.40 | 31:9 1.1±0.3 | 33:7 1.17±0.38 | 34:6 1.15±0.36 | 0.652 |
| Duration of surgery (min) | 56.12±26.9 | 55.75±26.4 | 50.62±23.8 | 58.33±28.47 | 0.54 |
| Propofol (mg) | 130.75±37.37 | 134.75±28.64 | 143.25±39.83 | 138.5±31.90 | 0.39 |
| Fentanyl (μg) | 103.12±11.58 | 103.75±16.55 | 111.25±23.98 | 103.12±11.58 | 0.17 |
| Vecuronium (mg) | 6.55±4.68 | 5.76±0.93 | 6±1.12 | 6.02±0.80 | 0.65 |

Quality of sleep grade 1=good sleep, grade 2=insomnia and grade 3 =nightmares **(***One-way ANOVA p<0.05 was considered significant)

At the doses employed in the current study there was significant difference (p<0.05) between all the four groups in preoperative anxiety scores. There was statistically significant difference between groups in anxiety score achieved by all groups (Table 2).

**Table 2. Anxiety score (CD Speilberger's questionnaire) (Mean ± SD)**

| **PARAMETERS** | Group D (n=40) | Group A (n=40) | Group B (n=40) | Group C (n=40) | p value* |
|---|---|---|---|---|---|
| **I feel calm** | **2.90**±0.**59** | **2.25**±0.58 | **2.45+0.59** | **2.77+0.61** | **0.000*** |
| **I am worried about possible problems** | **1.45**±0.71 | **1.42**±0.54 | **1.17±44** | **1.80**±0.**82** | **0.000*** |
| **I felt rested** | **2.7**±0.72 | **2.62**±0.62 | **2.87**±0.46 | **2.62**±0.83 | **0.307** |
| **I am scared** | **1.25**±0.49 | **1.12**±0.33 | **1.1**±0.37 | **1.42**±0.71 | **0.017*** |
| **I am tense** | **1.62**±0.66 | **1.37**±0.62 | **1.15**±0.36 | **1.65**±0.76 | **0.001*** |
| **I am in good mood** | **2.75**±1 | **2.65**±0.86 | **2.8**±0.64 | **2.85**±0.97 | **0.773** |
| **Mean score** | **13.12**±3.29 | **11.45**±2.06 | **11.55±1.9** | **12.67**±2.79 | **0.007*** |

On post hoc analysis the parameter **I feel calm** of the anxiety score was significantly less in group A compared to control (p=0.000) (95% CI -0.9978 to -0.3022). Similarly, score was less in group A compared to Group C(p=0.001) (95% CI -0.8728 to -0.1772). Scores observed in group B were less compared to group D(p=0.05) (95% CI -0.7978 to -0.1022) and scores in melatonin group were less than group C (p=0.001) (95% CI -0.1772 to -0.8728). On comparing parameters, **I feel rested** and **I am in good mood** there was no statistically no significant difference among the groups. On comparing the parameters, **I am scared** and **I am tense** and **I am worried about possible problems** higher scores were observed in placebo and Pregabalin group. (Table 2)

We observed a significant impairment in performance on the DSST relative to baseline in all the group. We observed that none of the subjects belonging to group B, C, D were able to perform the TDT test at 0 min. In the present study we observed that none of the patients in group B, C and D were able to perform the tests while 8 subjects belonging to group A were able to perform the TDT test and 4 subjects were able to perform DSST at 30 min postoperatively. We observed that there was a significant difference between the four groups in TDT performance from 60 minutes till 24 hrs after operation. On comparing the number of lines deviated the results were superior in melatonin group with minimum lines deviated at all time intervals. Time taken to perform the test was significantly less in melatonin group. (Table 3) DSST score was significantly higher in melatonin group at all time intervals as compared to Clonidine, Pregabalin and placebo group ($p<0.05$). Time taken to complete DSST test was comparatively less in group A as compared to group B, C, D at all time intervals ($p<0.05$). (Table 4)

**Table 3.** Mean ± SD of Treiger dot test no. of dots missed, no of lines deviated and time taken to complete the test among different groups

| | **NUMBER OF DOTS MISSED** | | | | | **NUMBER OF LINES DEVIATED** | | | | | **TIME TAKEN** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Parameters | **Group D (n=40)** | **Group A (n=40)** | **Group B (n=40)** | **Group C (n=40)** | ***P value** | Group D (n=40) | Group A (n=40) | Group B (n=40) | Group C (n=40) | *P value | Group D (n=40) | Group A (n=40) | Group B (n=40) | Group C (n=40) | *P value |
| Baseline | 1.10±0.99 | 1.17±0.98 | 1.35±1.07 | 1.2±0.96 | 0.594 | 0.27±0.45 | 0.32±0.47 | 0.27±0.45 | 0.40±0.49 | 0.594 | | | | | |
| 0 min | - | 7±7.07 | - | - | - | - | 1±1.41 | - | - | - | - | 72.5±67.17 | - | - | - |
| 30 min | - | 11.33±8.08 | - | 9.5±4.94 | 0.544 | - | 1.67±1.52 | - | 3.67±0.70 | 0.218 | - | 73.33±68.06 | - | 30±14.14 | 0.598 |
| 60 min | 16.33±7.19 | 16.33±7 | 20.36±8.31 | 18.16±8.07 | **0.040*** | 2.6±.80 | 2.46±1.06 | 3.16±.89 | 3.33±.77 | **0.022*** | 51.45±20.77 | 43.33±11.44 | 63.09±23.42 | 49.16±24.01 | **0.039*** |
| 90 min | 14.29±6.76 | 11.34±8.28 | 18.55±10.05 | 11.60±6.37 | **0.003*** | 3.08±0.82 | 2.56±1.03 | 3.06±.92 | 3.36±.71 | **0.015*** | 65.18±28.47 | 45.56±38.50 | 45.86±23.94 | 68.18±45.21 | **0.024*** |
| 6 hrs | 15.00±4.54 | 15.46±5.27 | 20.3±8.31 | 18.16±8.07 | **0.003*** | 2.69±.76 | 2.36±1.12 | 3.05±.95 | 2.52±.64 | **0.004*** | 53.36±37.87 | 34.34±29.45 | 42.8±30.63 | 61.6±50.61 | **0.011*** |
| 12 hrs | 16.58±4.9 | 13.86±11.6 | 18.55±10.05 | 13.86±6.3 | **0.000*** | 2.17±1.18 | 2.00±1.23 | 2.84±1.13 | 4.25±11.35 | **0.001*** | 41.56±33.13 | 22.84±22.11 | 31.02±29.42 | 47.7±43.59 | 0.006 |
| 24 hrs | 16.02±5.22 | 12.61±5.118 | 15.00±8.23 | 11.2712.61±5.811 | **0.000*** | 3.00±.90 | 1.82±1.51 | 2.55±1.08 | 2.22±.94 | **0.000*** | 35.34±31.78 | 15.57±14.71 | 26.13±29.06 | 35.67±35.43 | 0.008 |

*One-way ANOVA

**Table 4. Digit symbol substitution test (Time in Seconds) Mean ± SD and Score**

| **Parameters** | **Time taken** | | | | | **Score** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Group D (n=40)** | **Group A (n=40)** | **Group B (n=40)** | **Group C (n=40)** | ***P value** | **Group D (n=40)** | **Group A (n=40)** | **Group B (n=40)** | **Group C (n=40)** | ***P value** |
| **Baseline** | 118.35±1.44 | 118.35±1.44 | 118.4±1.35 | 118.9±1.17 | 0.202 | 452.6±15.94 | 452.57±17.43 | 450.57±16.53 | 452.1±16.49 | 0.941 |
| **0 min** | - | - | - | - | - | - | - | - | - | - |
| **30 min** | - | 165±63.63 | - | - | - | - | 55.5±7.77 | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **60 min** | 143.33±81.40 | 150±54.27 | 100±35.54 | 110.5±75.96 | 0.068 | 68.33±51.92 | 152±75.61 | 127.08±71.6 | 164.00±65.43 | **0.042*** |
| **90 min** | 136±76.04 | 134.77±43.65 | 105.51±70.23 | 131.5±98.74 | 0.220 | 71.4±27.58 | 152.28±80.43 | 142.23±97.01 | 186.79±108.74 | **0.013*** |
| **6 hrs** | 117.83±64.31 | 107.36±36.57 | 94.86±58.12 | 113.87±59.27 | 0.274 | 125.22±73.74 | 195.20±98.66 | 149.10±95.38 | 170.45±116.40 | **0.016*** |
| **12 hrs** | 79.73±30.35 | 75±26.78 | 103.52±60.83 | 96.75±44.05 | **0.008*** | 248.72±103.18 | 254.02±143.05 | 185.13±123.08 | 197.62±102.47 | **0.021*** |
| **24 hrs** | 71.80±27.95 | 67.81±24.23 | 93.51±59.09 | 83.25±35.69 | **0.016*** | 277.4±105.99 | 289.77±113.51 | 184.62±102.51 | 269.8±115.38 | **0.000*** |

*One-way ANOVA, Mean difference significant with p value < 0.05 * Post Hoc Test (Tukey HSD)

**4 Discussion**

Cognition is one of the four domains of assessment of neurological and behavioral functions. Cognitive subdomains include sustained attention, executive functioning including working memory, explicit and implicit memory, intelligence, time orientation, registration, attention and judgment. Cognitive impairment is a decline in function in either one or multiple domains of cognitive function (Kurdi and Patel, 2013; Han et al. 2013).

Psychomotor processing involves the fundamental cognitive operations that enable sensation perception and motor actions. Psychomotor impairment means a generalized slowing down of mental and physical activity. We have used the DSST and TDT which are simple and reliable tests for assessing cognitive and psychomotor function. The DSST tests a number of higher The DSST tests a number of higher mental functions including sensory perception, vigilance, visual activity, ability to alter eye fixation quickly, fine muscular coordination and mental concentration. In accordance to previous study, we noted that several of our patients belonging to clonidine and pregabalin group perceived distortion of the symbols and numbers of the DSST even after they had managed to pass the TDT. It appears that DSST is a more sensitive test than TDT for detection of residual cortical depression and can be used as an indicator of the progress of recovery (Naguib and Samarkandi, 2000).

Clonidine, the alpha 2 adrenergic agonist acts centrally through locus ceruleus where it reduces sympathetic outflow. It impairs psychomotor function (Jatti et al. 1998). On other hand, melatonin is naturally produced by the human body and plays an important role in regulation of the sleep-wake cycle (Scheer and Czeisler, 2005). It has an endogenous circadian rhythm of secretion induced by the suprachiasmatic nuclei of the hypothalamus.

Moreover, surgery induces more lowering of serum melatonin (Cronin et al. 2000) This produces a state of sleep disorders and disruption of REM sleep postoperatively. Exogenous administration of melatonin is known to facilitate sleep onset and improves quality of sleep (Claustrat et al. 2005). Clinically, it has no amnestic properties and it does not produce impairment of cognitive and psychomotor skills or tests of memory and visual sensitivity (Sultan, 2010)

The selected doses of oral melatonin (6mg), pregabalin (75mg) and clonidine (100 mg) used in our study were based on observations from previous studies which concluded that premedication with these doses had adequate anxiolytic and analgesic effects without untoward adverse effects (Goel and Sinha, 2006; Pokharel et al. 2014).

All the study drugs were administered sixty minutes before shifting to operating room. The same timing of the anxiolytic action of study drugs is related to their pharmacokinetics, where the time required reaching peak plasma concentration of melatonin ranged from 0.25h to 13 h and that of pregabalin was approximately 1h and steady state was achieved within 24-48 h and clonidine reaches peak plasma levels within 60-90 min (Singh and Arora, 2011).

The practice effect may be the limitation of the study where in after subjects have completed a certain test, usually perform better on that same test the next time around simply because of increased level of familiarity with that test.

**5 Conclusion**:

Melatonin as a premedicants has demonstrated to be efficacious in reducing perioperative anxiety as well as improvement in postoperative cognitive function and psychomotor skills in patients undergoing elective surgery.

**References**


Arendt J, Aldhous M, Marks V. 1986. Alleviation of jet lag by melatonin: preliminary results of controlled double-blind trial. Br Med J (Clin Res Ed). 292(6529):1170. doi:10.1136/bmj.292.6529.1170

Caumo W, Schmidt AP, Schneider CN, Bergmann J, Iwamoto CW, Adamatti LC, Bandeira D, Ferreira MB. 2001. Risk factors for postoperative anxiety in adults. Anaesthesia. 56(8):720-8. doi: 10.1046/j.1365-2044.2001.01842.x.

Claustrat B, Brun J, Chazot G. 2005. The basic physiology and pathophysiology of melatonin. Sleep Medicine Rev. 9(1):11–24. doi:10.1016/j.smrv.2004.08.001

Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO. 2000. Melatonin secretion after surgery. The Lancet. 356(9237):1244–1245. doi:10.1016/S0140-6736(00)02793-1

Darrow JM, Goldman BD. 1985. Circadian regulation of pineal melatonin and reproduction in the Djungarian hamster. J Biol Rhythms. 1(1):39–54. doi:10.1177/074873048600100104

Davis M, Gendelman DS, Tischler MD, Gendelman PM. 1982. A primary acoustic startle circuit: Lesion and stimulation studies. J Neurosci. 2(6):791–805. doi:10.1523/JNEUROSCI.02-06-00791.1982

De Vos H, Bricca G, De Keyser J, De Backer JP, Bousquet P, Vauquelin G. 1994. Imidazoline receptors, non-adrenergic idazoxan binding sites and alpha 2-adrenoceptors in the human central nervous system. Neuroscience. 59(3):589–598. doi:10.1016/0306-4522(94)90214-3

Goel S, Sinha M. 2006. Effect of oral clonidine premedication in patients undergoing laparoscopic surgery. Bombay Hospital J. 48:587–591.

Han ES, Lee Y, Kim J. 2013. Association of cognitive impairment and frailty in community dwelling older adults. Int Psychogeriatrics. 23(1):1–9. https://doi.org/10.1017/s1041610213001841

Inosec D, Badescu C, Ilie A, Miclutia I, Iancu C, Ion D, Vasian H, Bondor C, Acalovschi I, Mocan T. 2008. Melatonin as premedication for laparoscopic cholecystectomy: A double blind controlled study. Southern African J Anaest Analg. 2008;14(1):8–11. https://doi.org/10.1080/22201173.2008.10872555

Jatti K, Batra YK, Bhardwaj N. 1998. Comparison of psychomotor function and sedation following premedication with oral diazepam and clonidine in children. Int J Clinical Pharmacol Therapeut. 38:A17.

Kurdi MS, Patel T. 2013. The role of melatonin in anaesthesia and critical care. Indian J Anaesthesia. 57(2):137–144. doi:10.4103/0019-5049.111835

Lesser H, Sharma U, LaMoreaux L, Poole RM. 2004. Pregabalin relieves symptoms of painful diabetic neuropathy: A randomized controlled trial. Neurology. 63(11):2104–2110. doi:10.1212/01.WNL.0000145767.36287.A1

Naguib M, Samarkandi AH. 2000. The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: A double-blinded, placebo-controlled study. Anesthesia Analgesia. 91(2):473–479. doi:10.1097/00000539-200008000-00046

Pokharel K, Tripathi M, Gupta PK, Bhattarai B, Khatiwada S, Subedi A. 2014. Premedication with oral alprazolam and melatonin combination: A comparison with either alone-A randomized controlled factorial trial. BioMed Res Int. Article 632617. doi:10.1155/2014/632617

Rosano C, Newman AB, Kuller HL. 2008. Association between lower digit symbol substitution test score and slower gait and greater risk of mortality and of developing incident disability in well-functioning older adults. J American Geriatrics Soc. 56(9):1618–1625. doi:10.1111/j.1532-5415.2008.01854.x

Rose MA, Kam PC. 2002. Gabapentin: Pharmacology and its use in pain management. Anaesthesia. 57(5):451–462. doi:10.1046/j.1365-2044.2002.2446.x

Scheer FAJL, Czeisler CA. 2005. Melatonin, sleep and circadian rhythms. Sleep Med Rev. 9(1):59–61. doi:10.1016/j.smrv.2004.11.001

Singh S, Arora K. 2011. Clonidine effect during laparoscopies. Indian J Anaesthesia. 55(1):26–30. doi:10.4103/0019-5049.76597

Sultan SS. 2010. The role of melatonin in anesthesia and critical care. Saudi J Anaesthesia. 4(3):169–173. doi:10.4103/1658-354X.71571

Newman MG, Trieger N, Miller JC. 1969. Measuring recovery from anesthesia-A simple test. Anesthesia Analgesia. 48(1):136–140.