COMPARATIVE STUDY BETWEEN ORAL MELATONIN AND ORAL PREGABALIN ON PREOPERATIVE ANXIETY, PERIOPERATIVE SEDATION AND POST-OPERATIVE ANALGESIA IN SURGERIES DONE UNDER REGIONAL ANAESTHESIA: A RANDOMIZED CONTROL STUDY

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ABSTRACT

Preoperative anxiety in patients is a major concern for any anesthetist, more so in patients undergoing regional anaesthesia. The aim of this study was to compare the efficacy of oral Melatonin (6mg) with oral Pregabalin (300mg) as preoperative anxiolytic, preoperative sedative and for post-operative analgesia in patients undergoing surgery under regional anaesthesia.

The study is a randomised controlled trial which included 64 patients under ASA I-II, scheduled for surgery under spinal anesthesia, in the age group of 18-60. Patients were randomized into two groups of 32 patients each with Group 1- receiving oral Melatonin 6mg and Group 2- oral Pregabalin 300mg. The study drug was given 60 minutes prior to taking up for surgery. VAS anxiety score, orientation score, Ramsay sedation score, TMT A and TMT B test were assessed in the study groups before and after giving the study drug.

Change in VAS score is significant for both melatonin and pregabalin (p=0.000, p=0.001 respectively).Comparison of TMT-A values were not significant for either melatonin or pregabalin (p=0.4116, p=0.0723), similarly TMT-B value comparisons were not significant (p=0.1333, p=0.1499 respectively). There was no significant difference between both groups in time taken to first analgesia demand(p=0.410). Both melatonin and pregabalin have similar preoperative sedation trends.
Melatonin is a better pre medicant as compared to pregabalin to lower preoperative anxiety. There is no significant loss of psychomotor and cognitive functions in either group. There is no significant post-operative analgesic effect in either pregabalin or melatonin.

**KEYWORD:** Preoperative anxiety, Postoperative analgesia, Sedation, Melatonin, Pregabalin, TMT A and B, VAS anxiety score, Ramsay Sedation score.


**INTRODUCTION**

Preoperative anxiety and post-operative pain are two main concerns for any anesthesiologist. Preoperative anxiety is described as an unpleasant state of uneasiness or tension that is secondary to a patient being concerned about a disease, hospitalization, anaesthesia and surgery or the unknown\(^1\). It has been found to correlate with increased post-operative pain, analgesic requirement prolonged hospital stay\(^2,3\). For this benzodiazepines(mainly midazolam) are made use of. But as with any drug, there are certain drawbacks. This makes us venture out for alternative measures.

Melatonin is an endogenous sleep hormone produced by the pineal gland with the primary role of regulating the circadian rhythm. Melatonin mediates its hypnotic effects via the MT-1 and MT-2 receptors which act on the hypothalamic sleep switch cycle. It has similar anxiolytic effects as benzodiazepines but with less psychomotor impairment \(^4\). Melatonin is different from benzodiazepines and their derivatives in that it exerts a promoting effect on sleep by amplifying day/night differences in alertness and sleep quality and displaying a modest sleep-inducing effect, quite mild as compared to that seen with benzodiazepines \(^5\).

Pregabalin is a synthetic molecule and a structural derivative of the inhibitory neurotransmitter \(\gamma\)-amino butyric acid. It is an \(\alpha_2-\delta\) ligand that has analgesic, anticonvulsant, anxiolytic, anxiolytic and sleep modulating activities. Pregabalin binds potently to the \(\alpha_2-\delta\) subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine and substance p. It is effective in treatment of generalized anxiety disorders and is also a sleep modulating drug. Pregabalin is well tolerated and associated with dose dependent adverse effects that are mild to moderate and usually transient \(^6\).
Regional anesthesia is a group of techniques which render a part of the body anaesthetised while the patient is essentially awake as opposed to general anesthesia where the entire body is anaesthetised and patient is unconscious. Spinal anesthesia was the technique chosen for this study. It is otherwise known as sub arachnoid block (SAB), a regional anaesthetic technique where a small volume of local anaesthetic is injected directly into the sub arachnoid space. It is indicated for lower abdominal, pelvic organ, lower limb and caesarean surgeries.

Most of the previous studies regarding preoperative anxiety using melatonin or pregabalin have been attempted in patients undergoing general anaesthesia. Regional anesthesia techniques in general are associated with lower morbidity mortality rates. They are cheaper to perform, have high patient satisfaction, lesser blood loss, have selective muscle relaxation and easier recognition of neurological signs for various pathologies. But on the other hand they can be used for short procedures, the patient is awake, may be anxious and may prefer to be completely sedated. Hence, anti-anxiety measures in such situations are very significant.

Thus, the aim of this study was to compare the efficacy of melatonin with pregabalin in terms of preoperative anxiety, sedation and preoperative analgesia in patients undergoing surgery under regional anesthesia.

**METHODOLOGY**

After obtaining approval from Institutional Human Ethics Committee and written informed consent from the patient, 64 patients scheduled for surgeries under regional anesthesia in the Department of Anesthesiology, in Chettinad Hospital and Research Institute, meeting the following selection criteria were included in the study.

**STUDY DESIGN**: Prospective, Randomized, Double blinded study.

**SAMPLE SIZE**: Sample size was decided in consultation with our statistician. The primary end point for this study was a reduction in the patient’s preoperative level of anxiety as assessed using the VAS. Based on a predicted 20% reduction from the patient’s pretreatment (baseline) VAS anxiety score (mean value of 5 and SD of 3), a minimum of 32 subjects were required in each of the three study groups under the assumptions of an \( \alpha \) level of 0.05 and power of 80% assuming 95% confidence interval as follows:

The anticipated decrease in mean anxiety score for oral Melatonin= 35%\(^8\)

The anticipated decrease in mean anxiety score for oral Pregabalin= 20%\(^18\)

Using statistical software Clinical (LLC, Indiana US), the sample size calculated per group- Group1=32, and Group2=32 Selected 64 patients will be randomly divided into two groups ( 32 patients in each group) using a computer generated randomization code.
Patients in each group received regional anesthesia as follows:

Group I ~ (n=32) Tab Melatonin 6mg

Group II ~ (n=32) Tab Pregabalin 300mg

All the patients underwent pre-operative assessment in the pre-anesthetic assessment clinic. They were advised fasting of eight hours for solid diet & 2 hours for oral clear fluids prior to surgery. They were also explained about the visual analog scale (VAS)-anxiety score (i.e. 0=no anxiety, 10=worst imaginable anxiety) and objective tests like trail making test (TMT) A and B were explained to them during that time and were asked to do it in a sample test. The assessment for sedation was done using Ramsay sedation scale. Orientation was assessed using orientation score (0=none; 1=orientation in either time or space; 2=orientation in both space and time).

On the day of surgery, the patient was shifted from the ward to a room near the operation theater prior to surgery. The patient’s anxiety, orientation, and sedation levels were assessed using the VAS anxiety score, orientation score and sedation score by the investigator and psychomotor and cognitive function will be assessed using TMT-A and TMT-B. The drug was given to the patient in similar looking envelope which the patient is to take drug with a few sips of water. Psychomotor and cognitive function was assessed by TMT A and TMT B test. Patient was asked to relax and sleep following the intake of tablet. After 60min the patient was assessed again with the same parameters along with the TMT A and B tests. Occurrence of side effects to Pregabalin and Melatonin were also noted if any.

The regional anesthesia that was be given is spinal anesthesia in sitting up position, using a 26G or 27G Quincke needle to administer 3.5ml of plain 0.5% heavy bupivacaine in the L3-L4 space or the L2-L3 space. Vitals were noted for every 2 minutes for the first 15 minutes, then every 5 minutes till 20 minutes and then every 10 minutes till 90 minutes and at the end of surgery. Sensory 2 level regression time was noted. Post surgery we also noted the time when the patient first requests for analgesia. Adverse effects if any that occurred were to be reported to the Ethics Committee and appropriate treatment was given as required. After decoding of the randomized code, the collected data was presented as a mean +/- standard deviation, and percentages as appropriate. Categorical variables will be analyzed using Chi-square test and appropriate continuous variables will be tested using Student's t-test. SPSS version 25 was made use of to compute the analysis.
DISCUSSION

This study has shown that premedication with Melatonin and Pregabalin both provide good anxiolysis without loss of cognition or psychomotor function. They both provided similar preoperative sedation but did not provide any significant post operative analgesia as inferred from the time taken for first analgesia demand.

Spinal anaesthesia is a frequently used technique for many infraumbilical and lower limb surgeries of short duration. Here the patient is essentially awake. In order to keep the patient anxiety free in an environment i.e. the operation theatre absolutely alien to the patient we venture to look for anxiolytics that do not over sedate the patient and rob the patient as well as the anaesthesiologists’ of benefits of the spinal technique.

In this study it was found that the both melatonin and pregabalin were effective in reducing preoperative anxiety.

The results for first demand of analgesic did not differ in either group. These results are similar to that seen in previous study by Nasr et al on efficacy of preoperative pregabalin and melatonin on preoperative anxiety and post operative pain in laparoscopic gynecological surgeries[7].

One of the outcomes was to compare changes in cognition and psychomotor functions and on analysis it was observed that both drugs don not affect cognition after administration of one single dose. This is similar to the findings of Patel and Kurdi et al who studied the comparison of anxiety, cognition and psychomotor function in patients receiving either melatonin or midazolam[8].

Park et al studied the effects of pregabalin as premedication on post operative analgesia in patients undergoing urologic procedures. They found that even a single dose of pregabalin prior to surgery is sufficient to promote efficacy of intrathecal bupivacaine and improved postoperative analgesia. It was seen that the request for analgesics for 24 hours was lesser in the group given pregabalin as compared to the placebo group[9].

The same was also echoed by authors Bafna et al who studied the postoperative analgesia effect between pregabalin and gabapentinoid in patients undergoing spinal anaesthesia. It showed that the group receiving pregabalin had a significantly longer duration of effective analgesia[10].

This study only included 2 level regression time and demand for first analgesia as a means to gauge the analgesic effect in both group of patients. The limitation of our study included the fact that the follow up lasted only 4 hours postop whereas maximum pain occurs upto 24-48 hours post op. The total analgesic consumption for the first 24 hours should have been studied. To assess anxiety only the visual analogue scale was made use of which though simple and fast to use compromises on accuracy unlike the STAIS test.
CONCLUSION

This prospective, randomized double blinded study was conducted in 64 patients belonging to American Society of Anaesthesiologist physical status grade I and II between the age group 18-60 years. We aimed at comparing anxiolysis, sedation score, the psychomotor and cognitive function and the time taken for first demand for analgesia in both groups prior to a sub arachnoid block in patients undergoing lower abdominal and lower limb procedures.

Patients were allocated to 2 groups, each with 32 patients by a computer generated randomization code. Group 1 received oral Melatonin 6mg while group 2 received oral Pregabalin 300mg 1 hour prior to a sub arachnoid block with 3ml of 0.5 % (H) bupivacaine. The main parameters studied were, VAS-anxiety score, sedation, orientation scores along with TMT tests pre and post study drug administration, sedation was monitored throughout the procedure up to 4 hours post op, two segment regression times, the time taken to request for first analgesia after sub arachnoid block and occurrence of any side effects.

Appropriate statistical analysis of the results revealed the following conclusions: Premedication with melatonin and pregabalin are comparable in their effects on preoperative anxiety, orientation, sedation, cognition and psychomotor functions. There was no significant post operative analgesia seen in either group.

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REFERENCES