Adequate postoperative pain control is an important aspect for successful outcome of orthopedic surgeries in trauma patients. Considerable pain is expected in the early recovery phase that can impair early mobilization. Melatonin is a naturally occurring hormone produced naturally in the body. Nowadays, synthetic melatonin is a OTC drug for management of sleep disorders.

**Background:** Data regarding the analgesic effects of melatonin after the surgery is scare. **Objective:** The present study was performed to investigate the effect of preoperative oral melatonin on pain intensity after orthopedic surgeries after spinal anesthesia. **Methods:** In a double-blind randomized controlled clinical trial study, 108 patients undergoing orthopedics surgery of ASA class 1 and 2 were enrolled. Patients were randomly divided into 3 groups of 36 patients. Patients in group A were given 5 mg melatonin tablets, patients in group B were given 10 mg melatonin tablets, and group C was given placebo. All patients were administered spinal anesthesia. Pain intensity and side effects viz. nausea, vomiting, pruritus and headache were assessed and recorded 2, 6, 12 and 24 h after surgery. The time of first dose of analgesia, the amount of opioid consumed within 24 h, and adverse effects if any were also recorded. Statistical analysis of data was performed using SPSS 20 software. **Results:** Repeated measurements of pain intensity during the study showed that in group B pain intensity was significantly reduced (p < 0.001). The pain reduction was greatest in group B, followed by group A and group C, respectively. The time interval between the end of surgery and the patient’s need for analgesia was significant in group B compared to group A (P = 0.035) and C (P < 0.001) and also in group A compared to group C (P = 0.011). The mean dose of opioid was significantly least in group B, (p < 0.001). Headache and nausea/vomiting were observed in 4 patients in group A and in 3 patients (10.7%) in group C. None of the patients in group B developed complications. **Conclusion:** The results of the present study showed that the use of 10 mg of melatonin in orthopedic surgeries with spinal anesthesia is not only safe, but also reduces the severity of patients’ pain, increases the duration of postoperative analgesia, reduces the need for analgesics after surgery.

**Keywords:** Melatonin, postoperative pain, orthopaedic surgery, mean pain intensity, early mobilization

**Corresponding Author:** Dr Chavi Sehgal, Associate Prof, Anesthesia department, MLB Medical College, Jhansi
INTRODUCTION:
Postoperative pain has been a major concern after orthopedic surgery that impairs patient’s early mobilization to resume back to daily-life activity, imposes psychological effects and increases the requirement of analgesic like opioids, that can have side-effects and can lead to addition\(^1\). It is reported that approximately 75–80\% of patients suffer from moderate to severe postoperative pain even after receiving analgesic treatment\(^2\)\(^-\)\(^3\). Lower limb orthopedic surgery is the most common orthopedic procedure performed in trauma patients where its incidence is reported to be 40–50\%\(^4\)\(^,\)\(^6\). On the other hand, pain relief after orthopedic surgery is very important due to the increased risk of thromboembolic episodes that may be exacerbated by inactivity due to postoperative pain\(^7\). The consequences of these complications includes various medical problems such as increasing the length of hospital stay, the need for readmission, and finally patients’ increasing unnecessary economic burden\(^8\)\(^,\)\(^9\).

Conventionally, for the management of acute postoperative pain, mainly oral or injectable (intramuscular and intravenous) analgesics are used. Injectable narcotics are beneficial in relieving acute pain but associated with dose-dependent complications such as respiratory depression, nausea, vomiting, urinary retention, pruritus, drowsiness, or postoperative ileus\(^13\)\(^,\)\(^14\). Hence, it seems logical to use compounds that can intensify the analgesic effects of narcotics and thus create better analgesic effects with less opioid use\(^15\)\(^,\)\(^16\). Melatonin(\(\text{N-acetyl-5-methoxytryptamine}\)) is an endogenously produced neurohormone by the pineal gland in brain following a circardial rhythm, with plasma concentration maximum in the night and minimum in day time. Melatonin has important biological effects on the body and plays an important role in regulating the sleep-wake cycle. Recently its role is highlighted as an analgesic, antioxidant and neuroprotective role in a few human trials.

The exact cellular mechanism is still not clear but perioperative administration of melatonin yielded significant positive effects. Findings of studies have shown that anesthesia and surgery impair the secretion of melatonin from the pineal gland\(^21\). Another study of patients undergoing orthopedic surgery showed that anesthesia with surgery significantly reduced the amount of melatonin sulfatoxy (one of the most important metabolites of melatonin) in the evening of the first day after surgery and anesthesia\(^22\). So Melatonin supplementation has been advised in patients undergoing surgery. In different doses of melatonin (including\(3, 5, 6 \) and \(10 \) mg)\(^24\)\(^-\)\(^27\).

We designed a randomized double blinded clinical study to evaluate the analgesic effects of preoperative 5 mg and 10 mg melatonin tablets in orthopedic surgeries in trauma patients referred to MLB Medical College Jhansi.

METHODS
In this double blinded clinical trial, trauma patients posted for lower limb orthopedic surgeries from January 2021 to February 2022 of ASA I and II were included. Inclusion criteria was the patient’s consent, insensitivity to melatonin, age between 40 and 20 years, no history of tuberculosis, diabetes, seizures, hypertension and organ transplantation, no use of narcotic painkillers for 24 h before the intervention, no abuse alcohol.

The exclusion criteria of the study included: the patient’s refusal to participate in the study. The patients were randomly allocated in three groups using codes with Random Allocation Software. Prior to surgery, patients were provided with adequate information and training on how to determine the severity of postoperative pain, nausea, vomiting, pruritus, and headache using the VAS criteria. Written consent was obtained from all the patients for the participation in the study.

Since the studies have already reported the
insignificance of 3 mg dose of melatonin, the dose of the drug used in the study was 5 mg and 10 mg, respectively. The patients were divided in the three groups, patients in group A received a 5 mg melatonin tablet, patients in group B received a 10 mg melatonin tablet., and patients in group C received the placebo vitamin C tablet 1 h before surgery. Patients and researchers were unaware of group placements, and drugs were coded in a white envelope by the resident.

**Group A** – Oral melatonin 5mg at night time 1 day before surgery and 1 hour before on surgical day, continued 24 hrs post operatively.

**Group B** - Oral melatonin 10mg at night time 1 day before surgery and 1 hour before on surgical day, continued 24 hrs post operatively.

**Group C** - Oral melatonin placebo vit C at night time 1 day before surgery and 1 hour before on surgical day, continued 24 hrs post operatively.

In the operating room, all patients underwent spinal anesthesia with the same anesthesia protocol, which included spinal anesthesia using needle 25G and 3cc of 0.5% Bupivacaine hyperbaric solution. After surgery patients entering the ward were administered intravenously 1gm of paracetamol by infusion. Pain intensity, nausea, vomiting, pruritus and headache in the study groups were evaluated and recorded 2, 6, 12 and 24 h after surgery. In addition, the patient's first request for postoperative analgesia and the patient's opioid intake in the 24 h after surgery. The primary outcomes of the study were the severity of pain and the amount of dose of drugs used and the secondary outcomes were the rate of nausea, vomiting, pruritus and headache. The evaluation was performed by the anesthesiologist. The placebo required for the study was Vit-C tablets.

Inj. fentanyl 0.5 mg was used as a rescue analgesic. All patients entered the study with full knowledge and informed consent. The study was performed after the approval of the ethical committee. In addition, patients were assured that all the information in the study would be kept confidential and that researchers would only use it to provide a final report.

Statistical analysis of the data was performed using SPSS v20 software. Chi-square, T-test, analysis of variance with repeated measures and generalized estimation equations were used for analysis. Also, before examining the primary and secondary outcomes, demographic and clinical features were compared between the three groups. P-value less than 0.05 was considered as the significance of the relationship.

**RESULT:**

The number of patients in the study was 108 with 36 patients in each group. The mean pain intensity of patients 2 h after the start of the study in group A patients (group receiving 5 mg oral melatonin before surgery) was 7.25 ± 1.35 cm (between 4 and 10, Median = 8 cm), in group B patients (group receiving 10 mg oral melatonin before surgery) was 4.50 ± 1.54 cm (between 2 and 10, Median = 5 cm) and in placebo group (group C) was 7.84 ± 1.58 cm (between 2 and 10, Median =8 cm) (Fig. 1). There was a statistically significant difference between pain intensity in group A and B patients and pain intensity in group B patients was significantly lower than group A patients (P < 0.001). Also, the mean pain intensity of group B patients was significantly lower than group C patients (P < 0.001). Fig.-1.
In the study of pain intensity of patients 6 h after surgery, the mean pain intensity in group A was 4.51 ± 1.01 cm (between 3 and 8, Median = 5 cm), in group B was 3.47 ± 1.47 cm (between 1 and 6, Median = 3 cm) and in group C was 5.74 ± 1.41 cm (between 2 and 8, Median = 6 cm) (Fig. 2). Pain intensity in group B patients was significantly lower than group A patients ($P < 0.001$) and group C patients ($P < 0.001$). There was a statistically significant difference between the pain intensity in group A and group C and the pain intensity of group A patients was significantly lower ($P = 0.013$) (Fig.-2).

The mean pain intensity of patients 12 h after surgery in group A, B and C patients was 3.74 ± 1.71 cm (between 1 and 8, Median = 4 cm), 2.71 ± 1.34 cm (between 1 and 7, Median = 2 cm) and it was 5.64 ± 1.40 cm (between 2 and 8, Median = 5 cm) (Fig. 3). The mean pain intensity of group B patients was significantly lower than group A patients ($P < 0.001$) and group C patients ($P < 0.001$). In addition, pain intensity in group A patients was also significantly lower than group C patients ($P < 0.001$) (Fig.-3).
The mean pain intensity 24 h after surgery in group A was 2.59 ± 1.25 cm (between 1 and 6, Median = 2 cm), in group B was 1.50 ± 0.63 cm (between 1 and 3, Median = 1 cm) and in group C was 2.51 ± 1.04 cm (between 1 and 4, Median = 2 cm). Pain intensity of patients in group B, 24 h after surgery was significantly lower than patients in group A (P < 0.001) and group C (P < 0.001). However, there was no statistically significant difference between pain intensity in group A patients and group C patients (P = 0.710) (Fig.-4).

Need of rescue analgesic in post operative period.
We evaluated the need of analgesics at different time intervals after the surgery. The time interval after surgery to the onset of the need for opioid analgesia in group A was 2.67 ± 2.14 h after surgery (between 1 and 12 h, Median = 2 h), group B was 3.54 ± 1.44 h after surgery (between 1 and 6 h, Median = 3 h) and in group C was 2.40 ± 1.34 h after surgery (between 1 and 12 h, Median = 1 h). The time interval between the end of surgery and the patient's need for analgesia was significantly longer in group B patients than in group A patients (P = 0.035) and C patients (P < 0.001). Also, this time interval was significantly longer in group A patients than in group C patients (P = 0.011) (Fig.-5).
The mean dose of opioid analgesic in patients in group A was 60.37 ± 10.09 \( \mu g \) (between 50 and 90 \( \mu g \), Median = 60 \( \mu g \)), in group B was 49.12 ± 9.22 \( \mu g \) (between 50 and 75 \( \mu g \), Median = 50 \( \mu g \)) and in patients in Group C was 74.34 ± 9.88 \( \mu g \) (between 70 and 100 \( \mu g \), Median = 70 \( \mu g \)).

The mean dose in group B was significantly lower than patients in group A (P < 0.001) and C (P < 0.001). The mean dose in group A and group C (P < 0.001) (Fig. 6).
SIDE EFFECTS OF MELATONIN

A total of 7 patients were presented with headache and nausea/vomiting. 4 patients were in group A and 3 patients were in group C. None of the patients in group B reported such side effects. The incidence of complications was significantly lesser in group B patients from group C patients (P = 0.007) and group A (P = 0.007). However, there was no statistically significant difference in the incidence of complications between groups A and C (P = 1).

DISCUSSION

The mean pain intensity after surgery in patients receiving 10 mg melatonin Group B was significantly lower than in the placebo group C and in patients receiving 5 mg melatonin Group A. The mean dose of opioid required was least with 10 mg melatonin, followed by 5 mg melatonin and placebo group, showing that melatonin is likely to be associated with dose-dependent decrease in the need of opioid following orthopedic surgeries.

Melatonin is a hormone that is primarily secreted by the pineal gland and plays an important role in regulating the body's circadian rhythm. Melatonin has various effects, anti-anxiety, antioxidant, analgesic and sedative. However, data validating analgesic effects of melatonin is still not validated. In a randomized double-blind clinical study, Vidor, et al. reported that 5 mg of melatonin for four weeks is effective for treating myofascial temporomandibular disorder. These findings were significant relative to the placebo group. It improves the quality of sleep and reduces the requirement of other analgesics throughout the study period.

Caumo et al. evaluated preoperative administration of 5 mg melatonin in 33 patients undergoing abdominal hysterectomy in a double-blind placebo-controlled study. The results of the study showed that patients in melatonin group were presented with reduced need of patient-controlled analgesia and reduced postoperative pain following 24 h after the surgery. In a randomized clinical trial conducted on 52 patients, Borazan et al. reported that administration of 6 mg oral melatonin tablet overnight and 1 h before surgery is associated with reduced requirement of tramadol following and 24 after the surgery and corresponding reduced postoperative pain, compared to placebo. The sedation was higher in melatonin group at 1 and 2 postoperative hours, respectively. In a prospective randomized double-blind study by Khezri et al., 120 patients undergoing cesarean section received 3 mg, 6 mg or placebo, 20 min prior to spinal anesthesia. The study reported that the time at first dose of analgesia was required was not significantly different in the three groups following 24 h after the surgery, however, patients who revived 3 mg of melatonin required less analgesia compared to the other two groups.

The finding of our study seems more logical considering that the analgesic effect of melatonin is dose-dependent and increases with increasing dose.

However, there are other studies that have reported conflicting results, stating that melatonin cannot reduce the severity of pain and need for other analgesics. A double-blind, placebo-controlled study by Naguib and Samarkandi was conducted on 75 patients received who a single dose of 5 mg melatonin 100 min before laparoscopic gynecological surgery. Postoperative 15, 30, 60 and 90 min did not show any significant reduction in the pain and the amount of analgesia required. In the study of Khezri et al., the incidence of complications was almost the same in the three groups, and only in the group receiving 6 mg melatonin, the incidence of headache was significantly higher than the other two groups. However, in the present study, no side effects were observed in patients receiving 10 mg melatonin, while in patients receiving placebo and 5 mg melatonin were presented with headache and nausea/vomiting. Headache and nausea/vomiting do not seem to be related to melatonin and could be more related to the amount of analgesic drug received due to the severity of pain in patients.

In the present study, patients in the placebo group C and the melatonin group A received more opioid.
analgesia. Similarly, in the study of Khezri et al\textsuperscript{14}, patients receiving melatonin at a dose of 6 mg received more analgesia than patients receiving melatonin at a dose of 3 mg. On the other hand, studies have shown that the incidence of side effects of prescribed exogenous melatonin, even at high intravenous doses, is very rare\textsuperscript{39,40}. A review reported long-term side effects of melatonin like dizziness, drowsiness and somnolence in patients undergoing general anesthesia surgery\textsuperscript{41} and cognitive decline in elderly patients under general anesthesia in hip surgery\textsuperscript{42}.

Our study does not thus include comparison with other lower dose of melatonin and other preoperative analgesics. Furthermore, intraoperative parameters can act as confounding variables in determining the intensity of postoperative pain. Since, data from such studies are based on patients’ perception of pain, studies with larger sample size are required.

CONCLUSION

Results of the present study showed that the use of 10 mg of melatonin before and during orthopedic surgery with spinal anesthesia is not only safe, but also reduces the severity of patients’ pain, increases the duration of postoperative analgesia, reduces the need for opioid analgesics after surgery which will help the patient to resume physical activity and rehabilitation and reduces hospital stay.

REFERENCES:


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