Melatonin in perioperative medicine: Current perspective

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ABSTRACT

Melatonin, a new addition to the armamentarium of anesthesiologist, has some unique properties that are highly desirable in routine peri-operative care. Available clinical data show that preoperative melatonin is as effective as benzodiazepines in reducing preoperative anxiety with minimal action on psychomotor performance and sleep wake cycle. It may be considered as a safe and effective alternative of benzodiazepines as preoperative anxiolytic. It may have opioid sparing effect, may reduce intraocular pressure, and have role in prevention of postoperative delirium. The short-term administration of melatonin is free from significant adverse effects also.

Key words: *Anxiolytic, melatonin, opioid sparing, postoperative delirium*

INTRODUCTION

Preoperative anxiety and postoperative pain are the two major concerns to the anesthesiologists.[1] Preoperative anxiety may also be associated with postoperative pain. In current practice, benzodiazepines are most commonly used drugs to mitigate preoperative anxiety. However, benzodiazepines may impair psychomotor performance,[2] cause excessive sedation, and also decrease the duration of the rapid eye movement (REM) sleep.[3] There is growing interest in the peri-operative use of melatonin predominantly as anxiolytic. In the current review, we discuss perioperative use of melatonin for anxiolysis, analgesia, oxidative stress, and emergence delirium.

SYNTHESIS AND FUNCTION

Melatonin (*N*-acetyl-5-methoxytryptamine), discovered about half a century ago,[4] is a hormone produced chiefly by the pineal gland but also in much smaller amounts by the gastrointestinal tract, retina, platelets, respiratory epithelium, bone marrow, thymus, and skin.[5] Melatonin is synthesized from tryptophan by a relatively simple step-wise fashion. Tryptophan is initially converted to serotonin; then two more enzymes are involved in melatonin synthesis. Serotonin-*N*-acetyl transferase is the rate-limiting enzyme in this synthetic pathway.[6] Regulation of melatonin synthesis is controlled by the light–dark cycle, acting by activation of anterior hypothalamus via the axons of retinal ganglion cells running in the optic nerve and forming the retino-hypothalamic tract.[7] The *O*-methylation of *N*-acetyl-serotonin is a light-dependent process. Serotonin and melatonin synthesis show diurnal rhythms, so that pineal serotonin levels are markedly higher during the day than at night, while the levels of its downstream derivatives, *N*-acetyl-serotonin and melatonin, peak during the night.

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Serum melatonin reaches a peak value (80-150 pg/mL) between midnight and 3 a.m., while its concentration during the day is low (10-20 pg/mL).[8] The calculated serum half-life of melatonin is about 30-50 minutes.[9]

The principal physiological action of melatonin is the regulation of circadian rhythm, but serum melatonin level and sleep phase usually does not correlate.[10] When exogenous melatonin is administered a dose-dependent shift in the timing of sleep occurs. Sleep benefits associated with the use of melatonin are an increase in the total sleep time, sleep efficiency, and stage 2 sleep with a reduction in slow wave sleep.

However, it has also a role in modulation of immune defense responses, body weight and reproduction, tumor growth inhibition, and anti-jetlag effects.[11] Recently, its antioxidant property has also been established.[12] Animal studies show

that exogenously administered melatonin protects against anesthetic-induced apoptotic neuro-degeneration in the developing rat brain, particularly in the cerebral cortex, and anterior thalamus,[13] suggesting its neuro-protective function. Melatonin and its analog drugs have hypnotic effects mediated through MT1 and MT2 receptors, especially in the suprachiasmatic nucleus, which acts on the hypothalamic sleep switch cycle.[14]

Melatonin homeostasis in the perioperative period

Surgery and anesthesia are known to alter the normal circadian pattern of melatonin production from the pineal gland. But available clinical studies on this issue fail to come to a conclusion. Gogenur *et al.* concluded that patients have significantly increased REM sleep, light sleep, and reduced awake time during the daytime period after surgery compared with before surgery.[15] They also concluded that disturbances in the circadian regulation of the sleep – wake cycle may be involved in the development of postoperative sleep disturbances. Kärkelä *et al.* found that anesthesia in conjunction with surgery acutely disturbed the normal circadian rhythm of melatonin by delaying the onset of nocturnal melatonin secretion.[16] Vician *et al.*[17] observed higher postoperative nocturnal melatonin levels in patients with colorectal carcinoma undergoing surgery. They suggested that the higher levels were a stress response to the major abdominal surgery due to either the release of gut melatonin into the circulation or to stimulation of pineal melatonin production. However, Nishimura *et al.*[18] were not able to demonstrate any significant changes in melatonin secretion in patients who underwent major surgery. Various drugs commonly used in anesthesia are also reported to alter melatonin secretion; benzodiazepines,[19] non-steroidal anti-inflammatory drugs (NSAIDs),[20] clonidine,[21] corticosteroids,[22] and beta-blockers[23] decrease plasma levels of melatonin. However, opioids may increase plasma melatonin by stimulating serotonin-*N*-acetyl transferase.[24] Clinical studies are not unanimous on melatonin secretion in the perioperative period which may be due to different methods of melatonin estimation, variety of surgical procedures and their complexity, premedications used, differences in anesthetic techniques, and other drugs administered during the perioperative period.

Elliot[25] found that basal secretion level of melatonin in the day-time period was reduced immediately after surgery and normalized on the second day after surgery. Positive correlation was found between the duration of surgery and the onset of the night-time melatonin peak on the first night following major surgery, suggesting that either the surgical stress or the time in "lights off" in the day-time may have an impact.

Pharmacology of melatonin

Melatonin undergoes extensive first pass metabolism with varying bioavailability.[26] Melatonin is a highly lipophilic substance with a consequent high volume of distribution[27] and 70% of plasma melatonin is albumin bound.[28] Ninety-nine percent is metabolized in the liver to 6-hydroxymelatonin by cytochrome enzymes CYP1A2, conjugated to form sulfates and glucuronides and then, along with the other 1% unchanged, excreted in the urine.[29] The elimination half-life in humans is approximately 45 minutes.[30]

Adverse effects of melatonin

Buscemi *et al.*[31] in 2006 in a meta-analysis concluded that melatonin is safe for short-term use. They found that most common side-effects of melatonin used in this setting were headache, dizziness, nausea, and drowsiness. Adverse effects of melatonin premedication have been evaluated in detail in a systematic review by Yousaf *et al.*[32] Adverse events were evaluated in terms of psychomotor impairment, sedation, disorientation, and amnesia. It was shown that even large dosage of melatonin in healthy volunteers do not cause impairment of fine motor skill, memory, or visual sensitivity.[33] However, melatonin lacks amnestic effects. Memory recalls both immediately after surgery and 24 hrs postoperative period remain unaffected in patients receiving melatonin. Though melatonin causes more sedation than placebo, the sedation is significantly less than midazolam. They concluded that in comparison with midazolam, melatonin has similar anxiolytic efficacy but less psychomotor impairment and fewer side effects.

Melatonin and preoperative anxiolysis

Anto' n-Tay *et al.* first demonstrated that exogenously administered melatonin has hypnotic properties in human and it is similar to that seen during intravenous and volatile anesthetic-induced loss of consciousness in terms of electroencephalographic appearance.[34] Most of the clinical studies which addressed the issue of preoperative anxiolytic effects of melatonin found a significant reduction in anxiety in comparison to placebo. Ionescu *et al.*[35] concluded that Melatonin 3 mg can be successfully used as a premedication because of its anxiolytic, analgesic property, and a better recovery profile. Acil *et al.*[36] reported that melatonin premedication was associated with preoperative anxiolysis and sedation without postoperative impairment of psychomotor performance. Caumo *et al.*[37] found that melatonin and clonidine are comparable in terms of anxiolysis and postoperative morphine consumption and more effective than placebo. They compared 5 mg melatonin and 100 μg clonidine with placebo administered in the night before surgery and 1 hour before surgery. However, Capuzzo

et al.[38] found that 10 mg oral melatonin is no better than placebo in reducing preoperative anxiety in elderly patients (age >65 years) undergoing elective surgery. Ismail and Mowafi[39] concluded that that 10 mg oral melatonin premedication in comparison to placebo for patients undergoing cataract surgery under topical anesthesia has anxiolytic, analgesic, and intraocular pressure reducing effects. In a recent review by Wilhelmsen *et al.*,[40] the authors also affirmed the sedative and anxiolytic properties of melatonin. But, they concluded that further studies are needed to establish its analgesic property. Naguib and Samarkandi[41] compared the perioperative effects of melatonin and midazolam. They concluded that patients who received premedication with either midazolam or melatonin had a significant decrease in anxiety levels and increase in levels of sedation before surgery compared with controls. After surgery, the patients who received midazolam were more sedated and had more psychomotor impairment. Naguib and Samarkandi[42] studied the effects of different doses of midazolam and melatonin in perioperative period. They found that premedication with 0.05 mg/kg sublingual melatonin was associated with preoperative anxiolysis and sedation without impairment of cognitive and psychomotor skills or affecting the quality of recovery. Preoperative melatonin administration was associated with a faster recovery also along with less emergence excitement than midazolam premedication. The physiologic basis of these clinical findings has also been uncovered. Benzodiazepines, when administered as single large dose or multiple small doses, decrease the duration of REM sleep and thus affecting the qualities of the sleep. In contrast, melatonin, being a natural hormone, does not have any actions on the duration of REM sleep.

Melatonin as an adjunct to anesthetic drugs

Melatonin has hypnotic and anesthetic sparing properties also. Oral premedication with 0.2 mg/kg melatonin significantly reduces the propofol and thiopental doses required for loss of responses to verbal commands and eyelash stimulation.[43] Animal studies also showed potentiation of anesthetic effects of thiopentone and ketamine.[44] Intraperitoneal injection of melatonin potentiates isoflurane by reducing its MAC value in rats.[45]

Does melatonin have analgesic property?

Antinociceptive actions of melatonin have been well demonstrated in various animal studies. Melatonin interacts with multiple receptor sites including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α_1-adrenergic, α_2-adrenergic, and most importantly MT_1/MT_2 melatonergic receptors present in the dorsal horn of the spinal cord as well in the central nervous system.[46]

Results from the various clinical studies are not unanimous about the possible analgesic action of melatonin. Caumo *et al.*[47] concluded that preoperative 5 mg oral melatonin administered in the night and 1 hour before surgery produced clinically relevant anxiolytic and analgesic effects, especially in the first 24 postoperative hours. The patients who received melatonin required less PCA morphine in the postoperative period. Caumo *et al.*[37] also found that 5 mg oral melatonin administered in the night and 1 hour before surgery reduces postoperative pain and decrease postoperative morphine consumption up to 30% in patients undergoing abdominal hysterectomy. Melatonin has also been evaluated as a premedication in reducing tourniquet-related pain and improving analgesia in patients receiving intravenous regional anesthesia (IVRA).[48] The study concluded that melatonin premedication before IVRA reduced patient anxiety, decreased tourniquet-related pain, and improved perioperative analgesia. In a recent study, Laste *et al.*, found that melatonin significantly reduces inflammatory pain in rats.[49]

In a recent review,[50] the authors found that melatonin has analgesic action in all experimental studies regardless of mode of pain induction. They also found that route of administration of melatonin is irrelevant in analgesic action and analgesia is dose dependent. The reviewers also assessed current clinical evidences about the role of melatonin in fibromyalgia and irritable bowel syndrome. They found that in majority of the studies melatonin was effective in relieving pain in the above two conditions. However, the analgesic benefit of melatonin may be due to its hypnotic and anxiolytic action also.

Emergence delirium in children

Samarkandi *et al.*[51] compared the perioperative effects of different doses of melatonin and midazolam in children. They found melatonin was as effective as midazolam in alleviating preoperative anxiety in children and associated with a tendency toward faster recovery, lower incidence of excitement postoperatively, and a lower incidence of sleep disturbance at second week postoperatively. Kein *et al.*[52] concluded that melatonin is more effective than midazolam in preventing emergence delirium in children and the effect is dose related. Their results showed that the incidence of emergence delirium after 0.05 mg/kg melatonin was 25.0%, incidence after 0.2 mg/kg melatonin was 8.3%, and incidence after 0.4 mg/kg melatonin was 5.4%.

Postoperative delirium: Is melatonin useful?

Derangement of circadian rhythm and increased cortisol secretion after surgery may cause disruption of REM sleep.[53] Degeneration of the suprachiasmatic nuclei in the geriatric patients may result in lower baseline serum melatonin levels and predisposes them to sleep disturbance

in the postoperative period.[54] Serum melatonin levels decrease after surgery[55] and after administration of opioids,[24] which may contribute to disruption of the sleep–wake cycle in the postoperative period.

Available data on the usefulness of melatonin in postoperative delirium is sparse. A couple of case reports[56] and a study[57] on this issue are available. In one case, melatonin was used to treat postoperative delirium in a 53-year-old male patient who underwent hip surgery. In the same report, another case was mentioned where melatonin was used to prevent postoperative delirium. A 78-year-old male patient with history of coronary artery disease and transient ischemic attack underwent hip surgery under epidural anesthesia. He had confusion, agitation, and sleep disturbance from third postoperative day onward till seventh post-operative without any concomitant medical problem that time. Three years later, he underwent knee surgery under femoral-sciatic nerve block with sedation. This time he received 2 mg melatonin for 3 days in the night starting after surgery. His postoperative course was uneventful that time.

Sultan[57] evaluated the role of preoperative sedatives in postoperative delirium. They found that midazolam and clonidine premedication is associated with statistically more postoperative delirium than placebo. However, melatonin premedication (used at a dose of 5mg orally in the night and 90 minutes before surgery) is associated with significantly less delirium than placebo (9.43% vs 32.56%, $P = 0.003$). The authors also found that melatonin was successful in treating 58% of the patients who developed postoperative delirium. Recently, melatonin has been evaluated for prophylaxis in medical patients with delirium.[58] The study concluded that low-dose melatonin (at a dose of 0.5 mg at night for 14 days) in elderly medical patients admitted in the emergency department decreases the risk of delirium (12.0% vs. 31.0%, $P = 0.014$).

Melatonin as an antioxidant

Melatonin maintains mitochondrial function in oxidative stress.[59] The mechanism of action of melatonin in reducing oxidative stress is complicated and it acts at multiple enzymatic level.[60] Melatonin scavenges nitric oxide ($NO^{\bullet}$) and suppresses the activity of its rate-limiting enzyme, nitric oxide synthase (NOS) and as an indirect antioxidant, stimulates gene expression and activity of superoxide dismutase, thereby inducing the rapid conversion of $O_2^{\bullet-}$ to the less toxic H_2O_2. Catalase and glutathione peroxidase enzymes are also stimulated by melatonin. Melatonin stimulates the γ-glutamyl cysteine synthase, thereby increasing the level of reduced glutathione (GSH).

Exogenous melatonin was found to decrease mortality in neonates from septic shock.[61] Kücükakin *et al.*[62] studied the effect of melatonin in oxidative and inflammatory stress markers and on perioperative hemodynamic parameters in patients undergoing major vascular surgery. Melatonin administration did not change hemodynamic parameters (mean arterial pressure or pulse rate) during surgery, but oxidative stress parameters (Malondialdehyde and Ascorbic acid) decreased significantly. There was a significant increase in the inflammatory parameters (IL-6 and C- reactive protein) as a consequence of surgery. These were, however, not influenced by melatonin treatment. Treatment of patients undergoing major aortic surgery with melatonin intravenously up to 60 mg in the intraoperative phase was safe and without complications. A previous study in the neonatal surgical population also demonstrated similar findings.[63]

However, Kücükakin *et al.*[64] found that melatonin is ineffective in attenuation oxidative and inflammatory stress in vascular surgery patients. Moreover, its use is associated with more adverse effects. In this study, the patients were randomized to receive either 50 mg melatonin or placebo as infusion for 2 h, starting from the first incision. The aim of the investigators was to establish supra-physiologic levels of plasma melatonin during the surgical intervention, thereby optimizing the antioxidant capacity needed for a possible modification of the oxidative/nitrosative stress response and the degree of myocardial injury. They administered melatonin intravenously to reach higher blood levels when bypassing first-pass metabolism in the liver. However, any effect on the biochemical markers of oxidative stress and inflammation was lacking in patients who received melatonin. The authors concluded that the reason may be that the dose used was low in comparison to previous human clinical study[63] and they did not infuse melatonin for a longer duration of time.

Pharmacologic preparation and availability

Melatonin is most commonly used in per oral preparation. However, as a premedication before anesthesia and surgery, the sub-lingual route is preferred. A sublingual dose of 0.05 mg/kg body weight before surgery is found to be optimum.

In the USA, melatonin is sold as a dietary supplement but not as a drug so the Food and Drug Administration (FDA) regulations that apply to medications are not applicable to melatonin. Melatonin has been banned from over-the-counter sale in Great Britain, Canada, and many European countries.[65] However, US FDA has given melatonin an orphan drug status for circadian rhythm disturbance.

The European Medicines Agency has approved Circadin 2 mg (prolonged-release melatonin) for patients aged 55 or over, as monotherapy for the short-term treatment (up to 13 weeks) of primary insomnia characterized by poor quality of sleep.[66]

In India, melatonin is available in tablet form as a single drug (3 mg) and in a fixed dose combination with alprazolam or vit B6.

Dosing of melatonin in various conditions:
Melatonin is being used in various clinical conditions according to following dosing schedule.[67]

Benzodiazepine Withdrawal in Elderly with Insomnia: 2 mg controlled-release PO qHS for up to 6 months; taper dose over 6 weeks

- Cancer, Adjunctive Therapy: 10-50 mg PO daily
- Cluster Headache, Prevention: 10 mg PO qHS
- Migraine Headache: 3 mg PO HS
- Insomnia: 0.3-5 mg PO qHS
- Difficulty falling asleep: 5 mg PO 3-4 hour before sleep period × 4 weeks
- Difficulty maintaining sleep: Use controlled release formulation
- Thrombocytopenia, Chemotherapy-related: 20 mg PO qHS
- Jet Lag: 0.5-5 mg PO HS
- Eastbound- Preflight, early evening dose followed by HS dosing × 4 days
- Westbound- Treat HS × 4 days when in new time zone
- Chronic Fatigue Syndrome: 5 mg PO HS
- Nicotine Withdrawal: 0.3 mg PO 3.5 hours after stopping smoking
- Winter Depression: 0.125 mg PO BID
- Premedication for Surgery: 0.5 mg/kg SL
- Tardive Dyskinesia: 10 mg controlled-release PO qD
- Sleep Disorders (Orphan): Treatment of circadian rhythm sleep disorders in blind people with no light perception
- Melatonin is not recommended during pregnancy or in breast-feeding mothers because of lack of data.[68]

CONCLUSION

Available clinical data indicate that melatonin is a safe and effective anxiolytic when used as premedication. It is comparable to midazolam in terms of anxiolysis with less psychomotor impairment. It is also associated with faster recovery with less sedation in the postoperative period. However, the most important physiological benefit of melatonin may be less disruption of the sleep cycle. It may also be used to prevent emergence delirium in pediatric patients and postoperative cognitive dysfunction in elderly patients. However, further studies are required to confirm its analgesic effects.

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