

## The role of melatonin in anaesthesia and critical care

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### ABSTRACT

Melatonin is a neurohormone secreted by the pineal gland. It is widely present in both plant and animal sources. In several countries, it is sold over the counter as tablets and as food supplement or additive. Currently, it is most often used to prevent jet lag and to induce sleep. It has been and is being used in several clinical trials with different therapeutic approaches. It has sedative, analgesic, anti-inflammatory, anti-oxidative and chronobiotic effects. In the present review, the potential therapeutic benefits of melatonin in anaesthesia and critical care are presented. This article aims to review the physiological properties of melatonin and how these could prove useful for several clinical applications in perioperative management, critical care and pain medicine. The topic was handsearched from textbooks and journals and electronically from PubMed, and Google scholar using text words.

**Key words:** Anaesthesia, antioxidant, chronic pain, critical care, hypnosis, melatonin, oral pre-medication, perioperative role, sepsis management

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### INTRODUCTION

Melatonin, once labelled as a master hormone, is a natural substance present in all major taxa of organisms.<sup>[1-3]</sup> It is produced mainly in the pineal gland of all mammals and vertebrates and its secretion is high during night time and low during day time.<sup>[2,4-6]</sup> Melatonin is also synthesized in a number of other organs and peripheral tissues from tryptophan.<sup>[7-9]</sup> Melatonin is a natural constituent of food. Foods rich in melatonin include cherries, rice, beet, cucumber, tomatoes, human milk, yeast, bananas, wine and beer.<sup>[10]</sup> Melatonin has a spectrum of important properties and plays several important physiological roles, many of which can have important clinical applications. Some experimental studies and clinical trials are providing the basis for future clinical applications of melatonin of use to the anaesthesiologist. Keeping this in mind, we conducted a literature search to review the various physiological roles of melatonin and explore its various potential uses in anaesthesia, critical care and pain medicine.

### PHYSIOLOGICAL ROLES OF MELATONIN USEFUL TO THE ANAESTHESIOLOGIST

#### Sleep induction and maintenance

Melatonin is best known by medical professionals and laypersons for its hypnotic actions. Several studies have showed the importance of melatonin both for the initiation and maintenance of sleep.<sup>[11]</sup> The hypnotic effects of melatonin are considered as an integral component of its physiological role.<sup>[12]</sup> It has been reported to improve sleep onset, duration and quality when administered to healthy volunteers, suggesting a pharmacological hypnotic effect.<sup>[13]</sup> Melatonin is a natural hypnotic and exerts its hypnotic effects through the activation of the MT1 and MT2 melatonin receptors.<sup>[14]</sup> The suppression of neuronal activity by melatonin is one of the possible mechanisms by which it contributes to the regulation of sleep.<sup>[15]</sup> There is evidence to suggest that the central effects of melatonin involve, at least in part, facilitation of GABAergic transmission by modulating the GABA receptor.<sup>[16]</sup> In human beings,

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peak values of melatonin concentration seen in the evening are associated with the lowest point in rhythms of core body temperature, alertness, mental performance and many metabolic functions and with maximum sleep propensity.<sup>[17]</sup> Melatonin and its analogs are different from benzodiazepines and their derivatives in that they exert 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.<sup>[18]</sup> Moreover, melatonin produces no hangover effects on the day following its intake. Melatonin and its analogs lack negative effects like addiction, dependence as compared to benzodiazepines.<sup>[11]</sup>

#### **Analgesic effects**

In experimental studies, melatonin shows potent analgesic effects in a dose-dependent manner.<sup>[19]</sup> The physiological mechanism underlying the analgesic effect of melatonin has not been clarified.<sup>[20,21]</sup> The effects may be linked to Gi-coupled melatonin receptors, to Gi-coupled opioid  $\mu$  receptors or GABA-B receptors. The exact site of action of melatonin to induce anti-nociception is not clear.<sup>[22]</sup> Possibly, it augments GABA-ergic systems and morphine anti-nociception, enhancing GABA-induced currents and inhibiting glycine effects.<sup>[23]</sup> Melatonin may enhance the levels of  $\beta$ -endorphins and the anti-nociception induced by delta opioid receptor agonists and could activate  $MT_2$  melatonin receptors in the dorsal horn of the spinal cord.<sup>[24,25]</sup> Melatonin is involved in the modulation of nociceptive transmission. Intrathecally administered melatonin is active against the formalin and thermal-induced nociception at the spinal level in rats.<sup>[26]</sup>

#### **Anti-inflammatory and immunological effects**

Melatonin has immune-enhancing and anti-corticoid function. It modulates the activity of the pineal and pituitary/adrenal axis and the peripheral actions of corticoids.<sup>[1]</sup> It releases vasotocin that lowers corticoid levels.<sup>[1]</sup> Other possible mechanisms for melatonin's anti-inflammatory effects include inhibition of COX-2 and iNOS enzymes, activation of NF- $\kappa$ B and inhibition of neutrophil infiltration.<sup>[27]</sup> It enhances thymocyte proliferation and IL-2 production.<sup>[28]</sup> Melatonin exhibits immunomodulatory properties and modulatory influence on the NO synthetase (NOS) and cytokine production in inflammatory and oncogenic processes.<sup>[29]</sup> It has been reported as effective in combating various bacterial and viral infections.<sup>[30]</sup>

#### **Anti-oxidative effects**

Melatonin is a powerful antioxidant.<sup>[31,32]</sup> Melatonin antagonises oxidative stress both in a direct and in an indirect way.<sup>[33-35]</sup> It prevents free radical-induced damage and increases the activity of several antioxidant enzymes like glutathione-S transferase, glutathione reductase and catalase.<sup>[36]</sup>

#### **Chronobiotic property**

Melatonin is an important regulator of the body circadian rhythm.<sup>[37,38]</sup> The circadian rhythm of pineal melatonin release is highly synchronised with the habitual hours of sleep and the daily onset of melatonin secretion is well correlated with the onset of the steepest increase in nocturnal sleepiness.<sup>[11]</sup> Anaesthesia in conjunction with surgery acutely disturbs the normal circadian rhythm of melatonin by delaying the onset of nocturnal melatonin secretion.<sup>[16,39]</sup>

#### **Antihypertensive effect**

Melatonin has a mild hypotensive effect. The mechanism of action on the circulation is complex and unclear. Melatonin may bind to specific melatonin receptors in the blood vessels, interfering with the vascular response to catecholamines.<sup>[24,40]</sup> It may interfere with the peripheral and central autonomic system, causing a reduction in adrenergic outflow and catecholamine levels.<sup>[16,41]</sup> It may induce relaxation of the smooth muscle of the arterial walls by increasing nitric oxide availability.<sup>[16,42]</sup> Night time melatonin supplementation reduced nocturnal blood pressure in otherwise untreated hypertensive men and in non-dipping hypertensive women in some studies.<sup>[27]</sup>

#### **Ocular hypotensive effect**

Melatonin has ocular hypotensive effect. The mechanism is not clear. It may have a complex, albeit undefined role in aqueous humour formation, since melatonin receptors (M2 and M3) were recognized in the ciliary body tissues in animals.<sup>[22,43,44]</sup>

### **POTENTIAL CLINICAL APPLICATIONS OF MELATONIN IN ANAESTHESIA AND CRITICAL CARE**

#### **Pre-medication before surgery**

Melatonin possesses sedative, hypnotic, analgesic, anti-inflammatory, anti-oxidative and chronobiotic properties that distinguish it as an attractive alternative pre-medicant.<sup>[45]</sup>

#### **In adult patients**

A systematic review of literature concerning the perioperative use of melatonin in adults provided

evidence that melatonin pre-medication is effective in ameliorating pre-operative anxiety, but its analgesic effects in the perioperative period remain controversial.<sup>[45]</sup> Pre-medication with 0.05, 0.1 or 0.2 mg/kg sublingual/oral melatonin is associated with pre-operative anxiolysis and sedation without impairment of orientation, psychomotor skills or impact on quality of recovery.<sup>[46,47]</sup> Ismail and Mowafi have found in a study that 10 mg oral melatonin pre-medication for patients 90 minutes before cataract surgery under topical anaesthesia provided anxiolytic effects, enhanced analgesia and decreased intraocular pressure with good operating conditions.<sup>[24]</sup> Compared to midazolam, pre-operative melatonin has a similar anxiolytic efficacy yet with less psychomotor impairment and fewer side effects.<sup>[18]</sup> Melatonin is an effective pre-medication before IVRA, since a single oral dose of melatonin 10 mg before IVRA reduced patient anxiety, decreased tourniquet-related pain and improved perioperative analgesia.<sup>[48]</sup>

Rana Altaf Ahmed *et al.* in a study found that sublingual melatonin 0.5 mg/kg pre-medication in adults undergoing cataract surgery under local anaesthesia significantly decreased anxiety levels with no amnesia, sleep and next day hangover effects.<sup>[18]</sup> In a study by Ionescu D *et al.*, 3 mg oral melatonin was used successfully as pre-medication for laparoscopic cholecystectomy and at this dose, it produced anxiolysis.<sup>[49]</sup>

In a study on 75 women, Naguib and Samarkandi found that patients who received pre-medication with 5 mg melatonin 100 minutes pre-operatively had a significant decrease in anxiety levels and increase in levels of sedation before operation with no amnesia for pre-operative events.<sup>[50]</sup>

Nevertheless, in a study by Capuzzo *et al.*, oral melatonin 10 mg pre-medication did not significantly reduce anxiety in elderly patients undergoing elective surgery.<sup>[51]</sup>

#### **In children**

The use of melatonin, especially in children younger than 3 years, has decreased significantly the number of youngsters undergoing GA for diagnostic exploration like brainstem audiometry.<sup>[52]</sup> Pre-procedure 10 mg melatonin 30 minutes before MRI examination improved the success rate of procedure in sleep-deprived children. However, in another study, in children pre-treated with melatonin 3-6 mg

and undergoing MRI examination, melatonin did not contribute to sedation.<sup>[53]</sup>

Clinical trials with melatonin as a pre-medication agent in anxious children under nitrous oxide-oxygen sedation for dental treatment have shown good results, but so far, only limited data are available.<sup>[54]</sup> Few clinical studies have shown that melatonin is as effective as midazolam in reducing pre-operative anxiety in children and is associated with a more rapid recovery, a reduced incidence of emergence delirium and decreased incidence of sleep disturbances 2 weeks after surgery when compared to midazolam.<sup>[46,55]</sup> Currently, there is no consensus on the appropriate dose of melatonin for sedation in children. Melatonin dosing for children is reported to be between 0.3 and 20 mg.<sup>[55]</sup>

Thus, in view of its many benefits as a pre-medication, patients on melatonin supplements should continue taking them perioperatively.<sup>[56]</sup>

#### **Hypnosis and analgesia as an anaesthetic agent/adjuvant**

The hypnotic, anti-nociceptive and anticonvulsant properties of melatonin endow melatonin with the profile of a novel hypnotic anaesthetic agent. Anton-Tay and co-workers were the first to demonstrate clearly that orally administered 0.2 mg/kg melatonin produced loss of consciousness in human beings accompanied by a pattern of EEG activity similar to that seen during intravenous and volatile anaesthetic-induced loss of consciousness.<sup>[16]</sup> It significantly reduced the induction dose of propofol and thiopental.<sup>[16]</sup> Some researchers have found that oral melatonin 3 or 5 mg as pre-medication reduced the induction dose of propofol without prolongation of the post-operative recovery room stay.<sup>[57]</sup>

Orally administered melatonin has been shown to potentiate the anaesthetic effects of thiopental and ketamine and ether in rats.<sup>[58]</sup> Intra-peritoneal injection of 100 mg/kg melatonin significantly reduced MAC for isoflurane in rats by 24% when compared to control.<sup>[16]</sup> Melatonin and melatonin analogs possess hypnotic properties when injected intravenously, comparable to the properties of propofol and thiopental including the EEG effects with the additional advantage of providing analgesia, at least in animal studies.<sup>[59,60]</sup>

However, in a study on women undergoing hysteroscopy on day care basis, sublingual melatonin

9 mg as pre-medication 30 minutes before induction did not enhance the inhalation induction of anaesthesia with sevoflurane.<sup>[61]</sup>

The IV administration of 2-bromomelatonin can exert hypnotic effects and anti-nocifensive effects with a profile similar to that induced by propofol in that it exerts a rapid onset and short duration of action.<sup>[62]</sup>

Melatonin on its own does not seem to possess sufficient efficacy to warrant consideration as a general anaesthetic, but it may be used as a general anaesthetic adjuvant.<sup>[63]</sup>

### Miscellaneous peri-operative uses

#### *In patients with hypertension*

In a study by Ismail and Mowafi, mean arterial pressure decreased after melatonin pre-medication and extended to the early post-operative period. This mild hypotensive effect of melatonin may be beneficial in elderly patients, particularly those at cardiovascular risk.<sup>[24]</sup>

#### *For neuroprotection and as an anticonvulsant*

Melatonin by virtue of its antioxidant properties protects against oxidative stress, prevents neuronal damage associated with epilepsy, has putative neuroprotective effects and can be used as an anticonvulsant.<sup>[35]</sup>

#### *To reduce intraocular pressure*

10 mg oral melatonin 90 minutes before cataract surgery under topical anaesthesia has been reported to decrease intraocular pressure and produced good operating conditions.<sup>[24]</sup>

#### *To improve surgical outcomes*

Melatonin in surgical neonates resulted in improvement of clinical outcomes by virtue of its ability to reduce oxidative stress related to surgical procedures.<sup>[64]</sup> A pre-operative single dose of melatonin 50 mg/kg body weight dissolved in 250 ml of milk and administered through gastric tube after intubation for general anaesthesia was effectively absorbed, safe and well tolerated and decreased inflammatory changes after major liver resection.<sup>[65]</sup> Melatonin has been shown to be effective in preventing post-surgical adhesion formation in rat uterine horn adhesion model.<sup>[66]</sup>

### Post-operative use of melatonin

Anxiolytic and analgesic effects of melatonin may improve the control of post-operative pain by controlling the higher anxiety that accompanies surgical interventions.<sup>[67]</sup> Caumo *et al.* found that

5 mg oral melatonin, the night before and 1 hour before surgery in patients undergoing abdominal hysterectomy, decreased pain and anxiety during the first 24 hours after surgery. Also, they had better recovery of the rhythmicity perceptual in the first post-operative week after discharge.<sup>[22]</sup>

In a clinical study, it was found that a pre-emptive oral dose of 6 mg of melatonin reduced the pain scores and pethidine requirements in the first post-operative 24 hours in patients undergoing abdominal surgery.<sup>[67]</sup> In another study, pre-operative oral melatonin 6 mg, the night before and 1 hour before surgery, decreased pain scores and tramadol consumption and enhanced sleep quality and sedation scores during the post-operative period in patients undergoing elective prostatectomy.<sup>[68]</sup>

Disrupted sleep wake cycle after surgery leads to post-operative delirium. Melatonin can regulate this cycle which is disrupted after surgery.<sup>[69]</sup> The pre-operative administration of melatonin may accelerate the resynchronization of circadian rhythms in the post-operative period, suggesting better recovery quality. This could be a consequence of melatonin's effects on pain and anxiety which enhance rhythmicity disruption in stressful situations such as surgeries.<sup>[22]</sup> Clinical trials on the effect of melatonin on delirium in hip fracture patients are going on. Melatonin has been used successfully to treat and prevent post-operative delirium.<sup>[70]</sup>

In a study on pre-medication in children, oral melatonin 0.1 mg/kg, oral dexmedetomidine 2.5 µg/kg and oral midazolam 0.5 mg/kg were equally efficient in reducing the incidence of emergence agitation in children after sevoflurane anaesthesia.<sup>[71]</sup> In a study by Kain ZN *et al.*, children who received pre-operative oral melatonin 0.05 mg/kg developed less emergence delirium compared with those who received oral midazolam (0.5 mg/kg) and the effects were dose related.<sup>[72]</sup>

However, in a study by Gogenur *et al.*, on patients undergoing laparoscopic cholecystectomy, oral 5 mg melatonin for three nights after surgery did not improve sleep quality, fatigue or increased well being. Nevertheless, it decreased sleep latency on the first post-operative night.<sup>[73]</sup>

### In intensive care

#### *In sepsis*

The anti-oxidative properties of melatonin are being investigated for use in sepsis and reperfusion injuries.<sup>[56]</sup>

Melatonin 3 mg/kg IV 3 hourly in rats with peritonitis-induced septic shock with multi organ dysfunction syndrome (MODS) significantly attenuated hyporeactivity to nor-epinephrine and delayed hypotension, reduced plasma index of hepatic and renal dysfunction, reduced infiltration of polymorphonuclear neutrophils in the lung and liver tissue and promoted survival rate at 18 hours to two fold.<sup>[74]</sup> Melatonin has well-documented protective effects against the symptoms of severe sepsis/shock in both animals and in human beings; its use for this condition significantly improves survival. Melatonin clearly arrests cellular damage and prevents multi organ failure, circulatory failure and mitochondrial damage in experimental sepsis, and reduces lipid peroxidation, indices of inflammation and mortality in septic human newborns.<sup>[30,75]</sup> Melatonin has been found to be beneficial in treating premature infants suffering from severe respiratory distress syndrome and septic shock.<sup>[34]</sup> It has been found to be effective in combating various bacterial and viral infections.<sup>[30,76]</sup> In a study, 20 mg oral melatonin in two divided doses of 10 mg each, with a 1-hour interval, improved the clinical outcome of septic newborns.<sup>[77]</sup>

However, Bagci *et al.* stated that further investigations are needed to identify whether treatment with melatonin may have beneficial effects in paediatric intensive care unit patients with sepsis/septic shock.<sup>[78]</sup> Melatonin has been proposed to be used as a pharmacological support in burn patients where it reduced oxidative damage.<sup>[79]</sup>

#### **For protection against organ injury**

Melatonin has been found to be protective against glycerol-induced renal failure in rats. It was also found to be protective against lung injury in an animal study. This is because of its antioxidant effects.<sup>[1,80]</sup>

#### **Sleep disorders in critically ill patients**

The reduction in plasma melatonin levels and loss of circadian rhythm observed in critically ill patients receiving mechanical ventilation may contribute to an irregular sleep wake pattern and sleep disturbances in them with compromise of nocturnal sleep time. Oral melatonin at 9 pm every night was associated with a 1 hour increase in nocturnal sleep and increased nocturnal sleep efficiency.<sup>[81]</sup>

More clinical evidence is required to confirm the potential benefits of melatonin supplementation before it can be routinely used in the critically ill patient.<sup>[82]</sup>

#### **Treatment and prevention of stress-induced gastric ulcers**

Melatonin is generated in the GIT and serves as a local antioxidant and protective factor.<sup>[28]</sup> Melatonin has ulcer-healing and gastroprotective effects. This involves hyperaemia at ulcer margin and numerous mechanisms including activation of brain gut axis, sensory afferent nerves and certain gut hormones, especially gastrin.<sup>[29]</sup>

#### **Pain management**

The melatonin dose with analgesic potential is undefined.<sup>[24]</sup> Melatonin has been associated with the relief of pain in patients with extensive tissue injuries.<sup>[22]</sup>

Melatonin has analgesic benefits in patients with chronic pain – fibromyalgia, inflammatory bowel syndrome, migraine. Disturbances in melatonin secretion have been proposed to be part of the pathophysiology leading to fibromyalgia.<sup>[19]</sup> Melatonin when given in doses of 3 mg orally for 4 weeks, 30 minutes before sleeping time, significantly improved sleep quality and resulted in significantly fewer painful trigger points.<sup>[19,83]</sup> Melatonin alleviates abdominal pain in patients with inflammatory bowel syndrome (IBS).<sup>[84]</sup> Melatonin 3 mg for 2 weeks attenuated abdominal pain and bloating and reduced rectal pain sensitivity in patients with IBS.<sup>[84]</sup> The urinary melatonin concentration was found to be low in subjects suffering from migraine and trials have shown that melatonin may have both therapeutic and prophylactic benefit in patients suffering from migraine headaches.<sup>[85,86]</sup>

Melatonin reduces tactile allodynia in neuropathic rats after intrathecal and oral administration.<sup>[87]</sup>

#### **SAFETY OF MELATONIN**

Melatonin is reported to have a high and an excellent safety profile.<sup>[45,88]</sup> It is usually remarkably well-tolerated. Very high doses (300 mg/day) were given orally for up to 2 years and found to be safe.<sup>[89]</sup> Sugden reported a potential for motor incoordination when using melatonin in high doses in experimental studies.<sup>[83,90]</sup> The reported side effects of melatonin include 4% fatigue and 3% nausea. Doses of melatonin as great as 20 mg were administered to children without producing adverse side effects apart from sedation.<sup>[55]</sup> Dizziness, headache and irritability may be other adverse effects seen with very high doses.<sup>[13]</sup> The interaction of melatonin with other drugs has not been systematically evaluated.<sup>[1,13]</sup>

## AVAILABILITY OF EXOGENOUS MELATONIN

Exogenous melatonin is available in a range of preparations for sublingual and oral administration.<sup>[56]</sup> It is available over the counter in several countries including USA and India.<sup>[4]</sup> It is widely available as a nutritional adjunct and over-the-counter supplement marketed by different companies. These supplements may contain additional vitamins.<sup>[1]</sup>

Although melatonin has potential therapeutic value in operative and critical care settings, it has not been approved by the FDA as a therapeutic drug.<sup>[16]</sup>

Melatonin analogs have been synthesized.<sup>[4]</sup> There are two melatonin agonists on the market today, ramelteon and agomelatine.<sup>[4,11]</sup> Ramelteon has been approved by the US FDA for long-term use for the treatment of insomnia.<sup>[4,11]</sup> Additionally, two melatonin agonists, Tasimelteon and TIK-301, have been granted orphan drug designation and are going through clinical trials in the USA.<sup>[11]</sup> The main advantage of melatonin analogs is their good safety profile because of specificity for either or both of the two principal melatonin membrane receptors: MT<sub>1</sub> and MT<sub>2</sub>.<sup>[4]</sup> Slow release forms of melatonin are being developed.<sup>[11]</sup>

## CONCLUSIONS

Melatonin by virtue of its multiple functions has the potential to take a place in the anaesthetic drug armamentarium, because it can be an attractive option for pre-medication as an anxiolytic and sedative, for the induction of general anaesthesia as a hypnotic or as an induction adjuvant and peri-operatively for analgesia, reducing inflammation and for providing favourable operative conditions. Melatonin can also be used post-operatively to restore sleep rhythm and prevent delirium, in the intensive care unit for sepsis management and neuroprotection and in the pain clinic for the management of some painful conditions. The surgical and ICU patients may benefit from an evening meal that is rich in melatonin. Data support the notion that melatonin, or one of its analogs, might find use as an anaesthetic agent or adjuvant. As anaesthesiologists, intensivists and pain physicians, we may benefit multimodally from melatonin. Well-designed randomised controlled trials are warranted to further investigate the use of melatonin in anaesthesia, intensive care and pain medicine.

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