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Role of Melatonin in Anesthesia and Intensive Care

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ABSTRACT

Background: delirium is an extremely common syndrome in the intensive care unit (ICU). It is characterized by acute fluctuations and alterations in attention and arousal. Critically ill patients are at particularly high risk, and those that develop delirium are more likely to experience poor clinical outcomes such as prolonged duration of ICU and hospital length of stay, and increased mortality. Melatonin and melatonin agonists (MMA) have the potential to decrease the incidence and severity of delirium

Aim of the study: to review and assess the role of melatonin in several clinical applications in perioperative management, critical care and pain medicine.

Conclusion: melatonin reported eight peri-operative outcomes: anxiety; analgesia; sleep quality; oxidative stress; emergence behavior; anesthetic requirements; steal induction; and safety. Evidence-based, multi modal, surgical and anesthetic approaches have reduced morbidity and mortality following surgical procedures.

Keywords: Delirium, Melatonin, Anesthesia, Intensive Care.

INTRODUCTION

Delirium, which is also known as an acute confusional state, is a syndrome characterized by disturbance in consciousness (i.e., reduced clarity of awareness of the environment), change in cognition including alteration in attention, disorganized thinking, disturbed psychomotor activity, and abnormal sleep-wake cycle [1].

Intensive care delirium is a well-recognized complication in critically ill patients. Delirium is an independent risk factor for death in the intensive care unit (ICU), leading to over sedation, increased duration of mechanical ventilation, and increased length of stay. Although there has not been a direct causal relationship shown between sleep deprivation and delirium, many studies have demonstrated that critically ill patients have an altered sleep pattern, abnormal levels of melatonin, and loss of circadian rhythms. Melatonin has a major role in control of circadian rhythm and sleep regulation and other effects on the immune system, neuroprotection, and oxidant/anti-oxidant activity. There has been interest in the use of exogenous melatonin as a measure to improve sleep [2].

Melatonin, once labelled as a master hormone, is a natural substance present in all major taxa of organisms. 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. Melatonin is also synthesized in a number of other organs and peripheral tissues from tryptophan. 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 anesthesiologist [3].

Exogenous melatonin has a number of beneficial actions, first and foremost is its use in the treatment of sleep disorders and jet leg. In addition to sleep promotion, melatonin exerts numerous other sedative and anti-excitatory effects that clearly go beyond sleep induction since they are also observed in nocturnally-active animals. This has been frequently studied in relation to its anticonvulsant actions, which have been linked to a facilitating role of melatonin on γ-aminobutyric acid (GABA) transmission. Experimental data support the analgesic and sedative role of melatonin. In adult human, its analgesic role has been employed for treatment of diseases with chronic pain.

The hypnotic property of melatonin supports its possible use in different stages during anesthetic procedures, from premedication to induction of general anesthesia for the modulating effects of melatonin on anesthesia drugs [4]. The present study aims at evaluating the role of melatonin in several clinical applications in perioperative management, critical care and pain medicine.

Role of Melatonin in Anesthesia

Evidence-based, multi-modal, surgical and anesthetic approaches have reduced morbidity and

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mortality following surgical procedures. New peri-operative interventions may further improve recovery.

A. Pre-procedural anxiolytic and sedative effects

In a study a 3mg oral melatonin was used successfully as pre-medication for laparoscopic cholecystectomy and at this dose, it produced anxiolysis [5]. In a study on 75 women, Naguib and Samarkandi [6] 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 [6]. Various drugs commonly used in anesthesia are also reported to alter melatonin secretion; benzodiazepines, non-steroidalanti-inflammatory drugs (NSAIDs), clonidine, corticosteroids and beta-blockers decrease plasma levels of melatonin. However,opioids may increase plasma melatonin by stimulating serotonin-*N*-acetyl transferase [7].

B. During Procedure

1. Hypnosis and analgesia as an anesthetic agent

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 [8]. Some researchers have found that oral melatonin 3 or mg as pre-medication reduced the induction dose of propofol without prolongation of the post-operative recovery room stay [9].

2. Analgesic effects

Melatonin interacts with multiple receptor sites including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α1-adrenergic, α2-adrenergic, and most importantly MT1/MT2 melatonergic receptors present in the dorsal horn of the spinal cord as well in the central nervous system [10].

C. Post-operative use of melatonin

1. Anxiolytic and analgesic effects

Melatonin may improve the control of post-operative pain by controlling the higher anxiety that accompanies surgical interventions. One study 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 in the first post-operative week after discharge [11]. 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 [12]. 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 [11].

2. Anti-Delirium effect

Melatonin has been used successfully to treat and prevent post-operative delirium [13]. Disrupted sleep wake cycle after surgery leads to post-operative delirium. Melatonin can regulate this cycle which is disrupted after surgery [1]. The pre-operative administration of melatonin may accelerate the resynchronization of circadian rhythms in the post-operative period, suggesting better recovery quality [11]. In a study by Kain ***et al.*** [14] children who receivedpre-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 [14].

The effect of melatonin as emergence delirium prophylaxis has been investigated in three randomized controlled pediatric studies. Melatonin administration was compared to inactive and/or active placebo (midazolam/placebo, midazolam, dexmedetomidine/midazolam/placebo). All three studies demonstrated that melatonin reduced the incidence of emergence delirium [15].

Role of Melatonin in Critical Care

Delirium is a syndrome characterized by acute fluctuations and alterations in attention and

arousal. Critically ill patients in particular are at increased risk, with reported rates of up to 80% in those who are mechanically ventilated [16]. Delirium is associated with increased mortality, prolonged duration of intensive care unit (ICU) and hospital length of stay, greater risk of unplanned extubation and device removal. The pathophysiology of ICU delirium remains unclear. It is hypothesized that gamma aminobutyric acid or dopamine neurotransmitter pathways are involved in its development and that cytokine passage across the blood-brain-barrier aggravates the condition [17].

Although disturbances of the sleep-wake cycle are not diagnostic of delirium, changes in sleep patterns are incorporated into delirium screening tools, and studies indicate that sleep changes occur in >75% of delirious patients**.** Critically ill patients, irrespective of delirium status, display abnormal sleep architecture [18]. Sedative drugs such as benzodiazepines, propofol, α2-agonists, and opioids, which are frequently administered in the context of critical care, decrease rapid eye movement, the restorative component of sleep [18].

Although melatonin regulates sleep, the correlation between levels of melatonin and the different sleep phases is weak. In subjects with a free-running pattern of release, melatonin induces sleep during its peak secretion in daytime. After melatonin administration, 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 (TST), sleep efficiency, and stage 2 sleep with a reduction in slow wave sleep.

In addition to the effects on sleep phases, melatonin maintains synchronization in situations where the circadian rhythms are jeopardized and resynchronizes subjects after a period of free-run release [19].

Role of Melatonin in management of ICU-related delirium

It is known that patients admitted to ICU develop impaired sleep patterns.

Typical findings include increased latency and arousals, reduced rapid eye movement (REM) sleep. Factors, which contribute to sleep impairment in the ICU, include the use of opioids and benzodiazepines which disrupt REM sleep, the impact of specific patient therapies such as asynchrony to mechanical ventilation, arousal related to patient care-related activities.

Adverse effects associated with sleep deprivation include impaired lung mechanics, sympathetic–parasympathetic imbalance; cellular and humoral immunosuppression, impaired endocrine responses, and significant psychological abnormalities such as inattention, impaired intellectual performance, and delirium [19].

There are strong associations between sleep deprivation and delirium in the elderly, postoperative patients, and the critically ill. It remains uncertain if sleep deprivation is a cause of delirium or whether both represent aspects of 'ICU syndrome' with apathetic delirium misinterpreted as a state of over-sedation or sleep (Fig. 5).

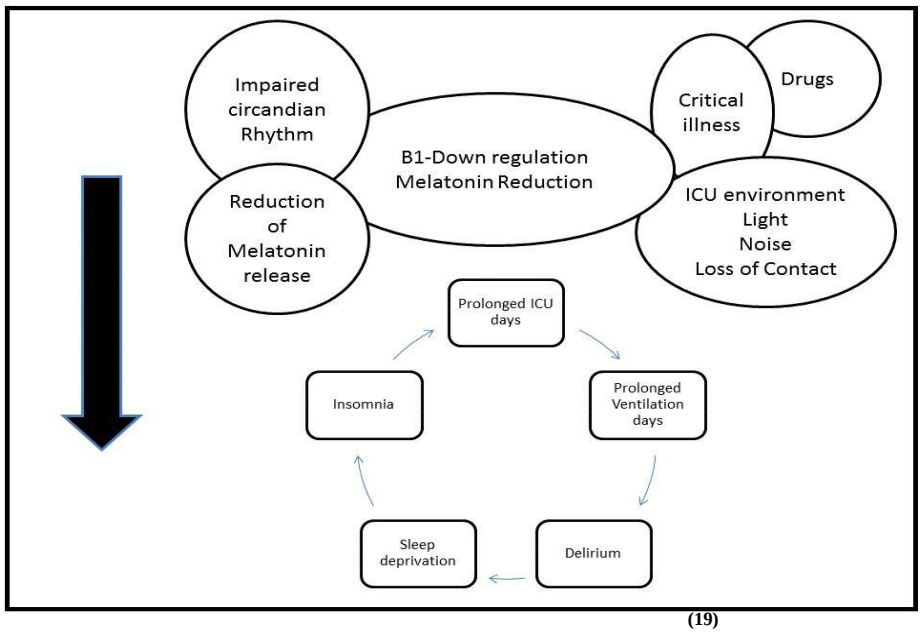

Fig 5: Proposed pathophysiology of ICU delirium [19].

During critical illness, there is abnormal release of melatonin and its plasma concentration and that of its urinary metabolite are altered**.** Although lower levels of melatonin and disrupted circadian release of melatonin have been correlated with ICU delirium**.** Causality has not been established. Surgical stress reduces melatonin release from the pineal gland **.** But this is confounded by the effects of perioperative medications such as opioids [19]. A variety of doses and preparations of melatonin have been used in the studies assessing the efficacy of melatonin to improve sleep in critically ill patients [19].

Ibrahim and colleagues study confirms that melatonin levels increased significantly in the melatonin group compared with the placebo group. The incidence of agitation was non-significantly higher in the melatonin group (31% v 7%), while the requirement for extra sedation or use of haloperidol was slightly higher in the placebo group (57% versus 46%) [20].

Similarly, Shilo and colleagues study confirms that melatonin administration to patients in intensive care units may be indicated as a treatment for sleep induction and resynchronization of the "biologic clock." This treatment may also help in the prevention of the "ICU syndrome" and accelerate the healing process [21].

Role of Melatonin in 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 [22]**.** Abnormal sleep–wake cycle is considered as one of the critical symptoms of delirium. Restoration of normal sleep–wake cycle by administration of melatonin may be a key in treating delirium [1]**.**

Importantly, it was approved by the US Food and Drug Administration (FDA) as a drug in 2005 for treatment of insomnia in adults**.** Administration of melatonin at 2 to 4 mg or ramelteon at 8 mg has some beneficial effects leading to prevention and management of delirium and has showed no adverse effects [23]**.**

Strong chronobiotic and hypnotic properties and the ability to correct sleep-wake rhythm disturbances, make melatonin as a drug choice for decreasing sleep latency. It has been observed that when administered at the right time and dose, melatonin was able to effectively correct the circadian rhythms in children with sleep disorders and because of this; melatonin is commonly used in children of all ages with sleep-related issues. There are no clinical guidelines for proper prescription of melatonin in children suffering with different neurological disorders, albeit many pediatricians currently prescribe melatonin to their patients, considering this as a naturally occurring sleeping aid. Timing of melatonin administration is critical in achieving expected results of treatment, because of its biological rhythm-based secretion and effects. It is important to administer melatonin earlier than the dim-light melatonin onset for optimal administration 2-3 h after this onset has no effects [24]**.**

Role of Melatonin in sepsis

The anti‑oxidative properties of melatonin are being investigated for use in sepsis and reperfusion injuries **,** 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**.** 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 [25]**.** Melatonin has been found to be beneficial in treating premature infants suffering distress syndrome and septic shock. It has been found to be effective in combating various bacterial and viral infections [25]**.**

Role of Melatonin in treatment and prevention of stress‑induced gastric ulcers

Melatonin is generated in the GIT and serves as a local antioxidant and protective factor. Melatonin has ulcer‑healing and gastro-protective effects [26]**.**

Role of Melatonin in 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 [27].

Role of Melatonin in patients with hypertension

In a study, mean arterial pressure decreased after melatonin pre-medication, this mild hypotensive effect of melatonin may be beneficial in elderly patients, particularly those at cardiovascular risk [28].

Role of Melatonin in 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 [29].

Role of Melatonin in pain management

The precise mechanisms underlying the analgesic effects of melatonin are not known although several possibilities have been suggested, which include the involvement of β -endorphins, GABA receptor, opioid l-receptors and the nitric oxide (NO)-arginine pathway**.** Melatonin increases the release of β-endorphin from pituitary gland, and it has been observed that naloxone, which blocks β-endorphin binding to opioid receptors, may antagonize the melatonin-induced antinociceptive effects [30].

Melatonin may also mediate its analgesic activity by interacting with opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, and α1 and α2-adrenergic receptors located in the central nervous system and also in the dorsal horn of the spinal cord [10]**.**

In several experimental animal models of pain, melatonin has been shown to be efficacious. Thus, in models of electrically induced pain, intraperitoneal (i.p.) injection of melatonin was able to increase the anti-nociceptive effect up to 210 min[31]. In a hot-plate model of pain induction in mice, it was observed that melatonin exerted maximal analgesic effect, when administered to the mice in the evening and that these effects of melatonin could be blocked by an opiate antagonist naloxone or central benzodiazepine antagonist flurmazenil, indicating interplay of these receptor pathways in melatonin action[32]

.In a model of mechanically induced pain via tail clamping, 2-bromomelatonin was found to induce dose-dependent analgesic effect. In all these different animal models of pain, administration of melatonin had no adverse effects [24]**.**

Melatonin and migraine

Considering that there is strong relationship between sleep and headache, the ability of melatonin to regulate sleep disorders may also be useful in improving headache patho-physiology**.**

It has been reported that properly timed melatonin treatment with appropriate dosing, decreased headaches in 78.6% of 328 patients suffering with circadian rhythm sleep disorders and headache [33]**.**

Melatonin at a dose of 3 mg twice daily, given to children with primary headache, was able to reduce the number, intensity and duration of headache attacks [34].

It has been suggested that melatonin may be considered an effective prophylactic medication for use in children with migraine. In an open-labeled clinical trial with 34 patients suffering from migraine, prophylactic use of melatonin at 3 mg, given 30 min before bedtime, was found to reduce headache intensity as well as frequency and duration, with significant clinical improvement by 1 month**.**

Melatonin and Fibromyalgia

Fibromyalgia is characterized by tenderness, altered sleep pattern and a number of painful trigger points. In an open-label, randomized-clinical trial that included 21 female patients, oral therapy of melatonin at doses of 3 mg/day, 30 min before sleeping time, for 1 month led to significant improvement, not only in sleep quality, but also in much less painful trigger points as compared to the situation prior to treatment. Results of that study also suggested that melatonin treatment has the potential to improve pain, fatigue and symptoms of depression [35]**.** A more recent randomized clinical study thatincluded 63 female patients with FM tested the efficacy of 6-week treatment with melatonin versus melatonin plus amitriptyline, another serotonin reuptake inhibitor and the results showed that a combined therapy of amitriptyline and melatonin, and melatonin as a monotherapy were more efficient than amitriptyline monotherapy in improving pain, morning stiffness, and sleep disorders[36].

Melatonin and Irritable bowel syndrome

Irritable bowel syndrome that affects the GI tract is a painful condition characterized by abdominal pain, flatulence, constipation and diarrhea in association with sleep disturbances. GI tract is known to create and release an almost 400-fold higher amount of melatonin than the pineal gland, but without circadian rhythms as is the case in the pineal body. Although the precise physiological

function of melatonin from GI tract is not clear, food intake affects melatonin synthesis and release**.** Considering that irritable bowel syndrome affects11-20% of the adult population. In two separate randomized placebo-controlled clinical trials, women with irritable bowel syndrome were treated with melatonin for 4-6 weeks and in both the trials, it was observed that melatonin was able to improve the symptoms and lower the associated pain [(37)].

Safety of Melatonin

Melatonin is reported to have a high and an excellent safety profile**.** 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**.** The reported side effects of melatonin include fatigue 4% and nausea 3%.

Doses of melatonin as great as 20 mg were administered to children without producing adverse side effects apart from sedation [(38)].

CONCLUSION

Critically ill patients are at particularly high risk, and those that develop delirium are more likely to experience poor clinical outcomes such as prolonged duration of ICU and hospital length of stay, and increased mortality. Melatonin and melatonin agonists (MMA) have the potential to decrease the incidence and severity of delirium through their hypnotic and sedative-sparing effects, thus improving health-related outcomes. Chronic pain such as fibromyalgia (FM), inflammatory bowel syndrome and migraine, melatonin has been found to be effective in reducing pain. Although it has been suggested that melatonin may have analgesic and anxiolytic effects in the perioperative and postoperative period.

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