Review Article

The Uses of Melatonin in Anesthesia and Surgery

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ABSTRACT

Melatonin is a hormone secreted by the pineal gland. It is available as a dietary supplement, taken primarily for the relief of insomnia. Increasing evidence from human and animal studies suggests that melatonin may be efficacious as a preoperative anxiolytic, a postoperative analgesic, and a preventative for postoperative delirium. It has also been reported to decrease intraocular pressure. Melatonin's high efficacy, wide safety profile in terms of dose, and virtual lack of toxicity make it of interest in anesthetic and surgical practice. This review examines clinical trial data describing the efficacy and safety of melatonin in the perioperative anesthetic and surgical settings. We shall, also, focus attention on animal and human experimental studies that concern these issues.

Key words: Anesthesia, analgesia, antioxidants, anxiolytics, melatonin

ملخص البحث :

الميلاتونين هرمون تفرزه الغدة الصنوبرية ويعتبر كمكمل غذائي ، ويستخدم أساسا كعلاج للأرق. هناك أدلة متزايدة من الدراسات على الإنسان والحيوان تشير إلى أن الميلاتونين يمكن أن يكون فعالا للتعامل مع القلق ولما بعد العمليات الجراحية ، وله تأثير وقائي لمنع هذيان ما بعد العمليات الجراحية. كما أتضح أنه يؤدي إلى خفض ضغط العين. وإن فعالية الميلاتونين العالية وقله آثاره الجانبية تجعله مفيدًا في التخدير والممارسات الجراحية. تبين هذه المقالة التجارب السريرية لفعالية وأمان الميلاتونين.

INTRODUCTION

It has been more than 50 years since an American dermatologist, Dr. Aaron Bunsen Lerner, extracted a few milligrams of N-acetyl-5-methoxy-serotonin from more than 100,000 cattle pineal glands.[1] It was called melatonin.[2]

Melatonin is secreted by the pineal gland in the brain when the body recognizes darkness.[3] Melatonin has intense effects on the sleep/awake cycle and in regulating the circadian rhythms of several biological functions.[4] Many biological effects of melatonin are produced through activation of melatonin receptors,[5] while others are due to its role as a pervasive and powerful antioxidant,[6] that protects the DNA.

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Although very promising in the field of anesthesia and surgery, preparations for perioperative use are not available yet. The US Food and Drug Administration, categorizes melatonin, not as a drug, but as a dietary supplement. A prescription-only, timed release melatonin product for people aged 55 and over was approved for use by the European Medicines Agency in 2007 and in Australia in 2009.[7]

In this review, we will focus on the effects of anesthesia and surgery on melatonin homeostasis and the potential benefits of melatonin in anesthesia and surgery.

EFFECT OF ANAESTHESIA AND SURGERY ON MELATONIN HOMEOSTASIS

Many studies have demonstrated that general anesthesia, alone or in conjunction with surgery, disturbs the circadian rhythm of melatonin secretion in humans and experimental animals.[8-21] Presumably, this disruption in melatonin levels may be the cause of postoperative sleep disorders occurring in patients following anesthesia and surgery.[9] However, the reports of the extent of these perioperative alterations in melatonin homeostasis are inconsistent and sometimes contradictory.

General anesthesia administered for hysterectomy operations reduced the nocturnal plasma concentrations of melatonin on the first postoperative night.[9] In another study of patients undergoing orthopedic surgery, the total urinary sulfatoxymelatonin (a major metabolite of melatonin) decreased on the first postoperative evening following thiopental and isoflurane anesthesia.[10] In addition, a reduction in the night: day ratio of urinary sulfatoxymelatonin level was found on the 4th postoperative day after major abdominal surgical procedures. This contradiction may be explained by a phase delay of the sulfatoxymelatonin rhythm.[22] Thus, general anesthesia may influence either the timing or amplitude of postoperative melatonin secretion.

In addition, the plasma melatonin concentration has been shown to decrease under general anesthesia and surgery,[13] and appeared to be unaffected during the immediate postoperative hours.[16] Other studies contradict these findings. For example, general intravenous anesthesia (fentanyl and thiopental or propofol) increased plasma melatonin levels during anesthesia[17] and during the first 8 h following propofol and isoflurane anesthesia.[8]

There is some evidence that the choice of anesthetic administered, intravenous or inhalational, may influence the plasma melatonin levels, intra- and postoperatively. For example, during the recovery period the elevation in plasma melatonin levels persisted in patients who had received inhalational isoflurane anesthesia, but gradually decreased in those who received intravenous propofol. In the same study, it appeared that altered melatonin levels following isoflurane and propofol anesthesia might also explain the differences in postoperative sedation scores in those patients.[8] According to another report, the different types of inhalational anesthetic influenced melatonin homeostasis differently; where isoflurane increased the intraoperative plasma level of melatonin sevoflurane reduced it.[12] It has been also reported that melatonin concentration did not change in the immediate postoperative hours in children who received intravenous thiopental or midazolam anesthesia for ambulatory surgery.[11]

The type of surgery also affects melatonin secretion. In one study, no significant effects after extra-corporal artificial circulation, using a heart-lung machine for open-heart surgery, were found on either perioperative circadian melatonin profile or on the postoperative mood changes.[19] However, in another study, there was a disruption in perioperative melatonin and cortisol secretions in patients who underwent coronary artery bypass grafting surgery with cardiopulmonary bypass. In that study, a circadian secretion pattern for melatonin, but not for cortisol, was restored on the 2nd postoperative day in most patients.[23] There was also severe disturbance in the circadian activity parameters and sleep after both laparoscopic cholecystectomy and major abdominal surgery, with the greater disruption following the latter.[20]

Recently, it was found that propofol anesthesia, *per se*, significantly decreased the plasma melatonin concentration during the immediate 3 h postoperatively and increased at 20 h following emergence from anesthesia in rats exposed to normal light conditions.[21]

It is evident that the growing data are somewhat contradictory. There is the possibility that such conflicting findings could be consequent to the diverse times of sampling and methodology for melatonin level assessment; differences in the duration and/or complexity of surgeries performed, variability in anesthetic techniques and perioperative management. Since variable anesthetic drugs and regimen were used in conjunction with surgery and premedication, it is hard to differentiate the general anesthesia effects from those of surgery and other perioperative medications.[18] Further studies are required to definitely establish, the immediate and late effects of anesthesia and/or surgery on melatonin secretion and its perioperative implications.

HYPNOTIC EFFECTS OF MELATONIN ADMINISTRATION

It has been demonstrated that melatonin markedly reduces the mean latency of sleep onset time in young and older subjects.[24-26] Oral melatonin was used as a preoperative medication in both pediatric[27] and adult surgical patients.[28,29] In older patients who were premedicated with oral melatonin 10 mg, preoperative anxiety decreased by 33% compared with a 21% reduction in the placebo group.[30]

Samarkandi *et al.*, Naguib and Samarkandi.[27-29] demonstrated that premedication with sublingual/oral melatonin, unlike midazolam, was associated with preoperative anxiolysis and sedation in adults and children, which did not impair psychomotor skills or impact the quality of recovery. A preoperative melatonin supplement was accompanied with a tendency toward faster recovery and a lower incidence of postoperative excitement than midazolam. In addition, administration of a single low dose of melatonin (0.3 or 1 mg) did not blunt rapid eye movement sleep.[24] Furthermore, unlike benzodiazepines, melatonin had no "hangover" effects.[24]

In a meta-analysis of randomized controlled studies on the effects of exogenous melatonin on sleep, it was reported that melatonin treatment significantly reduced sleep onset latency, increased sleep efficiency, and increased total sleep duration.[31] Variability in the activity of exogenously administered melatonin could be attributed to differences in the dose/preparation, subject profiles, and the time of administration.

Oral premedication with 0.2 mg/kg melatonin significantly reduced intravenous propofol and thiopental doses required for loss of responses to verbal commands and eyelash stimulation.[32] At the ED50 values reflecting loss of responses to verbal command and eyelash reflex, the relative potency of propofol after melatonin premedication was 1.7-1.8 times greater than that of propofol after placebo.[32] Similarly, the relative potency of thiopental following melatonin premedication was 1.3-1.4 times greater than that of thiopental after placebo.[32] In rats, it has been shown that orally administered melatonin potentiated the anesthetic effects of thiopental and ketamine.[33] Furthermore, intraperitoneal injection of 100 mg/kg melatonin significantly reduced the minimum anesthetic concentration of isoflurane in rats by 24%, when compared with controls.[34]

Melatonin might be promising as an anesthetic induction agent. Data from *in vivo* rat models have revealed that melatonin and its analogs, 2-bromomelatonin and phenylmelatonin, have anesthetic properties.[35-38] Anesthetic doses of melatonin produced effects on processed electroencephalographic variables similar to those of thiopental and propofol in rats.[35,36] The profile of the hypnotic properties of 2-bromomelatonin and phenylmelatonin was similar to that induced by propofol, and the similarity lies on the rapid onset and a short duration of action of these compounds. Unlike propofol and thiopental, melatonin and its analogs have potent antinociceptive effects.[35,36] Evidence suggests that melatonin-induced analgesia could be attributed to the release of β-endorphin.[39] These data support the concept that melatonin, or one of its analogs, might be used as an anesthetic agent. However, in a recent study, melatonin premedication did not enhance sevoflurane induction of anesthesia in women undergoing hysteroscopy as assessed by bispectral index.[40]

MELATONIN ANALGESIC EFFECTS

Melatonin has a promising role as an analgesic drug that could be used for alleviating pain associated with surgical procedures.

Several animal studies have shown that systemic melatonin provided dose-dependent antinociception and enhanced morphine analgesia.[41] In a clinical study of female patients undergoing abdominal hysterectomy under epidural anesthesia, Caumo *et al*.[42] proved that melatonin premedication enhanced postoperative analgesia. It has also been demonstrated that melatonin improved tourniquet tolerance and enhanced postoperative analgesia in patients receiving intravenous regional anesthesia.[43] Moreover, after melatonin premedication in patients undergoing cataract surgery under topical anesthesia, the study group had lower pain scores and fewer subjects needed supplemental fentanyl resulting in reduction in the intraoperative fentanyl consumption.[44] In another study, the preoperative melatonin had anxiolytic and postoperative analgesic effects similar to that of clonidine but greater than placebo, in patients undergoing abdominal hysterectomy.[45]

In a recent study, oral administration of melatonin the night before and 1 h prior to surgery was effective in decreasing both postoperative pain and patient-controlled analgesia with tramadol. It also improved sleep quality and subjective analgesic efficacy in patients undergoing prostatectomy.[46] The precise mechanism and site of action of melatonin antinociception are not known. However, the proposed mechanism of analgesic effects of melatonin could be through controlling the release of proinflammatory mediators, suppressing the activation of nociceptors and pain perception in the brain, and promoting sleep, which is extremely essential for modifying pain perception. Glutamate, γ-aminobutyric acid, opioid neurotransmission, or melatonin receptors may be involved in melatonin's analgesia. Other alternative mechanisms may be through scavenging of free radicals or nitric oxide synthase inhibition.[47]

MELATONIN ANXIOLYTIC EFFECTS

Several studies reported that melatonin was useful for reducing anxiety prior to surgery, presumably due to its sedative effects.[30,31,34,44] The anxiolytic effects of melatonin may be mediated through γ-aminobutyric acid system activation. However, other researchers have been unable to confirm these results. Melatonin did not significantly reduce anxiety in older patients undergoing elective surgery.[32] Similarly, in anxious children, oral 0.5 mg/kg melatonin premedication was similar to placebo for sedation during dental treatment.[48] In more recent study, it was shown that oral melatonin given to children before surgery in doses up to 0.4 mg/kg was less effective than oral midazolam in reducing preoperative anxiety.[49] However, methodological concerns may have limited the validity of these studies. These include discrepancies in the time of day in which the studies were performed, the lack of valid evaluative tools for anxiety, and variability in the bioavailability of the formulations used.

MELATONIN AND POSTOPERATIVE DELIRIUM

Postoperative delirium is a common problem and can be a result of sleep/wake cycle disruptions that occurs in the hospital environment. Plasma melatonin levels, essential in regulation of the sleep/wake rhythm, are decreased after surgery and in hospitalized patients. The reduction in postoperative melatonin secretion triggers sleep disturbances in the older patients, which in turn causes delirium.[50] Profound sleep disturbance in postoperative patients could be prevented by exogenous melatonin supplementation.[9] It may be useful to use melatonin as a treatment or prophylaxis for postoperative delirium in patients with a history of postoperative confusion.

MELATONIN AND POSTOPERATIVE COGNITIVE DYSFUNCTION

It was found that patients with postoperative cognitive dysfunction had poorer sleep, but without significant differences in 6-sulfatoxymelatonin levels compared with the control patients who were free from cognitive dysfunction.[14,15] The 6-sulfatoxymelatonin rhythm was disturbed after surgery with a significantly reduced night/day ratio and higher daytime excretion. Further studies are required for more comprehensive analysis of the melatonin rhythm.

MELATONIN AND REGIONAL ANAESTHESIA

Melatonin is an effective premedication before intravenous regional anesthesia since it reduces patient anxiety, decreases tourniquet-related pain, and improves perioperative analgesia.[43] Although still under trial, melatonin seems to be effective in the relief of postdural puncture headache in humans (Ismail and Mowafi, ongoing study).

MELATONIN AND OPHTHALMOLOGIC SURGERY

Oral melatonin premedication for patients undergoing cataract surgery under topical anesthesia provided anxiolytic effects, enhanced analgesia, and decreased intraocular pressure, resulting in better operating conditions.[44]

MELATONIN AND SURGICAL OXIDATIVE STRESS

Both experimental and human studies suggest that modulation of oxidative stress that results from surgical intervention can improve organ function and probably reduce morbidity and mortality. Melatonin has potent antioxidant properties. As proven experimentally, it is more effective than the classical antioxidants with minimal toxicity. Studies showed that melatonin reduced the oxidative damage related to surgical insults and ischemia/reperfusion and improved morbidity and mortality.[51]

The effect of melatonin as an antioxidant in relation to surgery on humans has only been tested in newborns. The drug was safe and reduced oxidative stress caused by surgery. Melatonin reduced cytokines levels and modified serum inflammatory parameters in neonates undergoing major operation with a significant improvement in clinical parameters.[52] Similar beneficial effects of melatonin in the adult population remain to be documented.

MELATONIN AND ORGAN TRANSPLANTATION

Melatonin is a versatile preparation that has immune-stimulatory, antioxidative, antiapoptotic, antibiotic, and antiviral properties that could modulate several pathological and physiological processes associated with organ transplantation. It could protect against ischemia — reperfusion injury and prolong graft survival following transplantation, as demonstrated in animal models.[53] However, more studies are required to evaluate melatonin's beneficial effects for transplantation of different organs and to assess it as a potential adjuvant therapeutic drug in humans.

MELATONIN AND WOUND HEALING

In 2003, Soybir *et al*. demonstrated that the administration of melatonin in rats significantly improved angiogenesis and wound healing, probably secondary to release of growth factors.[54] However, further randomized clinical trials are required before final confirmation of its beneficial effects, especially in patients with disturbed wound healing.

MELATONIN AND BONE HEALING

It has been shown that both fibroblast growth factor two and melatonin have similar stimulatory effects on osteogenesis. Together, they synergistically enhanced new bone formation around titanium implants in rats.[55] However, further clinical trials in humans may be performed to confirm this effect.

MELATONIN AND POST-PINEALECTOMY SYNDROME

It had been reported that the tumors of the pineal gland distinctly decreased the circadian rhythm of melatonin before surgery. The lack of melatonin rhythm in these tumors may help in the diagnosis of this condition. Moreover, postoperative melatonin deficiency could justify melatonin supplementation to prevent a sleep/wake cycle disturbance occurring following surgery and the probable post-pinealectomy syndrome in patients with resected pineal gland.[56]

MELATONIN AND INTRA-ABDOMINAL ADHESIONS

Melatonin may be a valuable agent in preventing peritoneal adhesions in rats.[57] Intra-abdominal adhesions following abdominal surgery could induce intestinal obstruction or infertility. However, randomized clinical studies are required in humans to evaluate its potential clinical benefits.

MELATONIN AND MAJOR VASCULAR SURGERY

Treatment of patients undergoing major aortic surgery with intravenous melatonin in a dose up to 60 mg intraoperatively was demonstrated to be safe and lacks adverse effects.[58] Melatonin may decrease oxidative damage resulting from this surgery, but randomized clinical trials are required before definitive conclusions can be drawn regarding its clinical benefit in these circumstances.

MELATONIN AND CARDIAC SURGERY

It has been found that melatonin may have a protective effect against ischemic — reperfusion injury during coronary artery bypass grafting, as high plasma levels of melatonin may be associated with low levels of reperfusion injury markers.[59] However, additional studies may be required for the preoperative administration of melatonin in cardiac surgery patients with cardiopulmonary bypass to improve myocardial protection. Melatonin administration effectively reduced postoperative pericardial adhesions in dogs.[60] The potential use of melatonin for the prophylaxis of pericardial adhesions following cardiac operations in human subjects warrants further investigations.

MELATONIN AND HAEMORRHAGIC SHOCK

Treatment with melatonin suppresses the release of the proinflammatory cytokines, tumor necrosis factor-α and interleukin (IL-6). The levels of markers of organ injury associated with hemorrhagic shock are decreased; thereby ameliorating hemorrhagic shock — induced organ damage in rats.[61] However, further studies are required to elucidate these effects in patients with hemorrhagic shock.

MELATONIN AND SEDATION DURING DIAGNOSTIC PROCEDURES

Clinically, it has been used to induce sleep to facilitate performing electroencephalography in children.[62] Melatonin may also be useful for magnetic resonance imaging (MRI) examination and has been reported to be successful in 55-76% of children.[63] However, this study included a series of cases and lacked control group for comparison.

In a further study, melatonin tablets of 3 or 6 mg doses given 10 min before MRI were not valuable for sedation of children. Children tended to be sedated more quickly after melatonin and were slower to recover. These findings may denote that there was wide variation in the onset of sedation following melatonin premedication. In addition, inter-individual variations in children who needed MRI and contrasting criteria for sedation, could explain some of the differences in sedation times.[64]

MELATONIN AND THERMAL INJURY

There is good evidence that melatonin therapy possesses potential advantage in reducing the morbidity and mortality in patients with thermal injury.[65] It is a powerful free radical scavenger and antioxidant, particularly in the skin. It has some influence on intracellular organelles that improve the cells' ability to resist damage associated with burn. Melatonin has also immune-modulatory and inhibitory effects on proinflammatory cytokines. Therefore, it ameliorates the immune disorders that often result following thermal injury. Finally, melatonin triggers sleep mechanisms that are disturbed in patients with burn.

MELATONIN AND LIVER RESECTION

Experimental data suggest that preoperative melatonin, as a potent immune-modulator and antioxidant, would decrease postoperative infectious and noninfectious complications induced by major abdominal surgery. Therefore, a clinical trial is ongoing to determine if melatonin can improve the general outcome after liver resection.[66]

Because of melatonin's antioxidant effects and its capacity to cross physiological barriers, it may be administered therapeutically against surgically induced oxidative stress. In the work of Ochoa *et al*., who studied the effects of melatonin during cardiopulmonary bypass surgery, their findings provided grounds for the use of melatonin for preventive and therapeutic purposes in open-heart surgery.[67]

MELATONIN AND THYROID SURGERY

In an interesting study, diurnal serum melatonin profiles in patients with a very large goiter were assessed before and after surgery. The authors found that nocturnal serum melatonin concentrations were significantly higher after the surgery than before the operation. They concluded that the manipulations of very large goiters during its surgical resection might compress the superior cervical ganglia, indirectly altering melatonin synthesis, although other mechanisms cannot be excluded.[68]

CONCLUSION

Based on the available evidence in clinical and experimental studies, with melatonin's beneficial effects in anesthetic and surgical settings, it is highly likely that its dietary supplementation will be a safe and inexpensive option for perioperative clinical practice. Melatonin has significant potential for clinical uses as a premedication in adults and children for several perioperative settings. However, further studies are required to definitely identify the short- and long-term effects of anesthesia, alone and combined with surgery, on melatonin secretion. Moreover, clinical trials are needed to verify the clinical usefulness of melatonin in humans for the different experimental surgical models.

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