



Melatonin as Antianxiety drug in dentistry: A Review

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Abstract

Background: Anxiety is a barrier to dental care for many people. According to preliminary research, melatonin has sedative and anxiolytic effects. In dentistry, anxiety is a prevalent issue that may compromise the effectiveness of appropriate therapy. Many people with anxiety require oral premedication. Many people require heavy sedation or even general anesthesia to undergo dental care because they are so extremely nervous that oral sedation is ineffective. Even inserting an intravenous catheter can be challenging for these people because of their high levels of anxiety. The most often prescribed anxiolytic in these situations has been benzodiazepines, although several of these may cause paradoxical side effects. Since melatonin promotes natural drowsiness and enhances sedation, it has a strong chance of replacing benzodiazepines in this industry. This article aims to provide an overview of the use of melatonin as a dental premedication for patients who are uncooperative and apprehensive.

Keywords: Anesthesia, Dental Anxiety, Melatonin, Premedication

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Introduction

There is evidence linking general health issues to phobias, anxiety, or dread of the dentist. When you consider that 20% of patients delay going to the dentist because they need to, this is a significant fact. A dentist's dread is often persistent and challenging to overcome because of their own experiences or anxiety brought on by other patients' comments. 1. When a highly anxious patient has treatment under general anesthesia, their fear of needles may make it difficult to establish an intravenous line, or they may be afraid of being under anesthesia in addition to the dental surgery itself. One of the most efficient ways to assist patients in lowering their feelings of worry and panic is by oral premedication. Triazolam, midazolam, lorazepam, and diazepam are among the benzodiazepine class of medications that are most frequently used as oral anxiolytics for dental patients ². There are widely known side effects of benzodiazepines class, and rejection on acceptance of those drugs on several occasions. In order to combat this, a novel pharmaceutical known as melatonin has entered the dentistry science and practice sector. It can be used as a premedication and has demonstrated anxiolysis abilities comparable to those of benzodiazepines, but without the majority of their negative effects ^{3,4}. Thus,

this review focuses on the use of melatonin in the field of dentistry with various advantages.

Review

The primary secretory product of the pineal gland, melatonin (MT), is linked to the control of the human body's circadian dark/light cycle. This hormone possesses immunomodulatory and antioxidant properties. Furthermore, it has no toxicity, but it is a very lipophilic substance, which makes it easier for it to pass through cell membranes and compartments. This suggests that it may be used therapeutically, for example, locally (1) in oral cavity damage caused by bacteria, viruses, or fungi, and (2) in postsurgical wounds from tooth extractions and other oral surgeries, where it promotes bone formation and reduces gingival and periodontal inflammation. (3) to improve dental implant osteointegration, as well as in autoimmune conditions including Sjorgen syndrome, lichen planus, aphthous ulceration, and herpes lesions, and (4) even to prevent oral cancer ⁵. In this regard, melatonin may have a number of positive impacts on oral health, including lessening the severity of herpes, which has been shown to be at least as effective as the medication acyclovir. Its exact mode of action is unknown, although it may be because it stimulates NK CD4 cells ⁶. In terms of oral

health, melatonin may serve as a prognostic indicator for conditions like cancer. It may also be regarded as an onco-static agent of several cancer types, but low plasma levels of it are linked to mouth cancer: such is breast, stomach, colon, and lung cancer, all of which are associated with low melatonin plasma levels. It diffuses passively from the blood to the saliva. For this reason, it was observed that the concentration of this in saliva was around 30% of that in plasma⁷. When compared to blood levels, saliva contains less melatonin, most likely because it binds to albumin in almost 70% of plasma, preventing it from freely diffusing into saliva. Through the stimulation of type I collagen fiber formation and the control of osteoblastic and osteoclastic activity, local melatonin injection has been shown to have a number of possible effects in the oral cavity and may aid in the regeneration of alveolar bone. It should be taken into consideration because turning blood into saliva may help prevent oral infections and have positive effects on periodontal disease, herpes, and oral cancer. It is also significant for the treatment and prognosis of some tumors, such as epidermoid carcinoma⁸⁻⁹.

Biosynthesis

Tryptophan is transformed into melatonin in pinealocytes. This synthesis is carried out in four phases¹⁰. Melatonin production occurs through a two-step mechanism after tryptophan first transforms into serotonin. These enzymes are hydroxyindole-O-methyltransferase (HIOMT)¹¹ and N-acetyl transferase (NAT), which inhibits the melatonin molecule. The pattern of day and night determines how this synthesis is managed, and night¹² is when it peaks. A number of factors affect how quickly this process proceeds. For example, norepinephrine and b1 adrenergic receptor activation play crucial roles in this synthesis. Under these conditions, melatonin production increases¹². Folate and vitamin B6 are also essential for this process. For the methylation process to occur, folate is required. Vitamin B6 is also involved in the decarboxylation of tryptophan. Melatonin synthesis won't happen if they're not in the environment.

Pharmacokinetics

Melatonin is quickly distributed (distribution half-life of 0.5 to 5.6 minutes) and excreted following intravenous injection¹³. Within 60 minutes of oral treatment, a peak in plasma concentration occurs. The decrease in plasma concentrations is biphasic, with half-lives of two and twenty minutes, respectively. Melatonin concentrations 10–100 times greater than the physiological nocturnal peak can be achieved within an hour of consumption when a typical dose of 1–5 mg is taken; the concentrations revert to their baseline levels within 4–8 hours. Melatonin is rapidly metabolized, mostly in the liver and subsequently in the kidney, following intravenous or oral administration. However, because there is no hepatic first pass following intravenous injection, the hepatic bio-degradation is less significant. It is converted to 6-hydroxymelatonin by the cytochrome P450 enzyme CYP1A2, conjugated with either 90% sulfuric acid or 10% glucuronic acid, and then eliminated

in the urine. Urine contains around 5% of the unmetabolized melatonin that is expelled from the body.

Mechanism of action as sedation and antianxiety

Because melatonin binding to the MT1 receptor appears to affect the GABA_A receptor via the G-coupled protein pathway¹⁷, MT's anesthetic action is comparable to that of other anesthetics like propofol and benzodiazepines, enhancing the binding of GABA to the GABA_A receptor¹⁷. Faster recovery times and a lower incidence of postoperative excitement and sleep disturbances are linked to melatonin premedication, which can be taken orally in doses of 3 or 5 mg. This reduces the amount of propofol needed to achieve a bispectral index score of 45, which indicates a sufficient level of hypnosis for tracheal intubation without extending the length of the postoperative recovery room stay¹⁸. 2 weeks after surgery compared to midazolam¹⁹. Melatonin can reduce preoperative anxiety 50–100 minutes after administration, and it may be just as effective as standard treatment with midazolam in reducing preoperative anxiety (50–100 minutes after administration) in adults twenty, according to a recently published review evaluating the effect of melatonin on pre- and postoperative anxiety in adults when compared to MT given as premedication to placebo²⁰. Oral melatonin does not affect general cognitive and psychomotor abilities like midazolam does²¹. Six hours after surgery, melatonin may help individuals feel less anxious. When children require general anesthesia for oesophageal dilatation procedures, oral melatonin appears to reduce postoperative agitation²². Melatonin added to alprazolam may provide better anxiolysis than other medications in the same group, according to a randomized controlled factorial experiment²³. The time of premedication with melatonin may also be significant. Oral melatonin has been shown to have a sleep-onset impact within 30 minutes. However, Naguib and Samarkandi¹⁹ found that 60 and 90 minutes after sublingual melatonin premedication, melatonin-treated patients had higher degrees of drowsiness. Melatonin appears to have strong potential for usage in lowering anxiety and inducing drowsiness in dental patients receiving general anesthesia without any notable side effects when compared to other drugs, such as benzodiazepines, which are currently the gold standard. An observational study was also carried out by Gupta S et al.²⁴ and found that postoperative anxiety decreased in correlation with cognitive and psychomotor scores. Their study also supported that melatonin can be used as a potent premedication drug in children as an anti-anxiety drug.

Premedication in Dentistry

Because oral sedation reduces tension and excitement and relaxes the patient for subsequent procedures, it can be useful in dentistry. Barbiturates had a low therapeutic index, the potential for addiction, and negative effects on the heart and lungs, despite their effectiveness in sedation. Benzodiazepines' broad margin of safety and efficacy in sedation, anxiolysis, and forgetfulness led to the ultimate replacement of barbiturate use for sedation.

Additionally, individuals with respiratory, hepatic, renal, or cardiovascular diseases require extra attention¹⁵. Despite their effectiveness, these medications have a higher sedative impact that could cause a delay in recovery after sedation^{3,28}. Disorientation, decreased psychomotor performance, paradoxical reactions, excessive sedation that interacts with opioids, and sleep disturbance after surgery are some of the negative effects of midazolam. As a result, melatonin has been proposed as a pre-medication alternative to midazolam²⁸. Melatonin sublingual administration (0.05 mg kg⁻¹ or 5 mg) has been linked to preoperative anxiety reduction in adults without psychomotor impairment or recovery effects. 5–7.5 mL, or 3–4.5 mg of melatonin tablets, is the recommended dosage for syrup oral melatonin^{25,26}. Children can safely take up to 0.4 mg/kg of oral melatonin without experiencing any serious negative effects²⁷. Doses of up to 10 mg of melatonin have been used for youngsters who are uncooperative and as an alternative to traditional sedatives. However, a study found that premedication with 5 mg of melatonin was linked to drowsiness and pre-operative anxiolysis without causing post-operative impairment of psychomotor performance⁴. Exogenous melatonin has a peak effect between 45 and 90 minutes²⁴. In addition to providing sedation, oral melatonin (0.4 mg/kg) administered 60–90 minutes before to surgery offers sufficient anxiolysis on par with oral midazolam (0.2 mg/kg)²¹. For elective procedures using oral melatonin, the 2-4-6 fasting rule is applied. For clear foods, breast milk, formula milk, and solids, fasting before appointment should be of 2-3 hours, 4 hours, 6 hours and 6-8 hours respectively²⁹.

Other benefits of melatonin include: (1) it may also be more palatable to people who might find synthetic drugs uncomfortable, and (2) it has a short half-life, which reduces the likelihood of extended drowsiness compared to benzodiazepines¹⁶. The only short-term side effect of oral administration of exogenous melatonin is drowsiness; however, the long-term effects of melatonin use are still unknown. Melatonin use is generally safe without significant adverse effects in healthy adults over the age of 18, who are not pregnant, and who do not have psychiatric disorders.

Advantages of Melatonin

Melatonin offers a number of potential advantages such as reduced post-operative sedation & less sleep disturbance, faster recovery, improved post-operative analgesia, and avoidance of respiratory depression, short half-life, dose dependent effect, offers greater taste expectance, Difficult to overdose Melatonin since it is a natural hormone.

Disadvantages of Melatonin

Regardless of the level of sedation, it's vital to fast before the session since stomach contents can be re-aspirated or vomited, which might cause pneumonia or pneumonitis²⁹. Headache, Nausea, Daytime drowsiness may also occur in some patients.

Safety Profile

In contrast to midazolam, which causes weariness, drowsiness, and dizziness, melatonin has a few negative side effects, such as drowsiness. When comparing the safety profile of Melatonin to Midazolam³⁰, Ansari et al. (2017) found that children who were premedicated with Melatonin experienced a considerably decreased incidence of nausea, vomiting, and dizziness. In addition, Angelo et al. compared the safety profiles of melatonin and midazolam as premedication and found that the former was just as effective as the latter without causing any cognitive or psychomotor impairments. Additionally, compared to midazolam, melatonin in children can be used without significant adverse effects and requires less preoperative monitoring, according to Kain et al. and Tushar et al³⁰.

Conclusion

Melatonin has significance of oral sedation as a pharmacological behaviour management technique in pediatric dentistry. If it is given prior to pre operative dental treatment to uncooperative or fearful patient, it provides adequate anxiolysis and sedation. Oral Melatonin at 0.75 mg/kg appears to be the most effective drug for allaying pre-operative anxiety in children followed by 0.5 mg/kg. Even the doses of 0.5 mg/kg and 0.75 mg/kg does not cause sedation or cognition and psychomotor dysfunction. In addition, new clinical studies are needed to improve therapeutic efficacy of this drug. Further experimental and well-designed clinical studies are required to explore the protective and therapeutic effects of melatonin as premedication in dentistry.

Conflict of Interest: No

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