

Research Article

Anxiolytic and Analgesic Effects of Melatonin in Paediatric Dentistry

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Abstract

Aim: Fear and anxiety are the principal obstacles for dental treatment in children and can turn into dental phobia, leading to patients avoiding dental treatment. Melatonin, an endogenous indolamines produced and secreted by the pineal gland, is involved in many physiological functions such as regulation of circadian rhythm as well as possessing antioxidant, oncostatic, anti-inflammatory and anticonvulsant activity; it may be administered orally or sublingually, without any evidence of substantial side effects. After oral administration, melatonin undergoes first-pass effect, reaches the plasma peak after about 60 min and blood levels decrease in about 4 h.

Study Design: This is a retrospective case-control age and sex matched study. We collected data about first visit and treatment of 50 patients admitted to the Dental Clinic and to the Private Center of the investigators.

Methods: According to literature, 25 children received 0.5 mg/kg Melatonin 60' before being subjected to first visit and pedodontic treatment. No preventive treatment was given to 25 children. We compared the success of treatment and the pain experienced by the child assessed by FLACC behavioural pain scale.

Results: Both groups included 25 patients (15 male), mean age 7.6 yrs in Group A, 7.1 yrs in Group B. Melatonin treatment was well tolerated by 100% of children. According to FLACC scale categories, 42% of all children presented relaxed and comfortable or mild discomfort (FLACC scale 0-3), 42% moderate pain (FLACC scale 4-6), and 16% severe discomfort or pain or both (FLACC scale 7-10).

Statistics: Operators found greater compliance by children receiving melatonin with 96 % successful treatment versus 68% (p 0.012). We found 60% of children receiving melatonin experienced relaxed and comfortable or mild discomfort *versus* 40% in Group B (p 0.001).

Conclusions: Although a larger population study is needed, the anxiolytic and analgesic properties of melatonin seem to offer new therapeutic opportunity in the pedodontic field.

Introduction

Dental Fear and Anxiety (DFA), have a prevalence from 5 to 20% in children and adolescents [1]. DFA in children and adolescents has multifaceted manifestations, impacts and origins. Children and adolescents with DFA are often uncooperative during dental visits, thus rendering treatment difficult or impossible [2]. Such behaviour compromises the treatment outcome, creates occupational stress among dentist staff, and is often a cause of discord between dental professionals

and patients or their parents [3]. DFA acquired in childhood may persist to adulthood and is a significant predictor of avoidance of dental visits in adulthood [3]. This pinpoints childhood as a critical stage for preventing and intercepting DFA, thus helping people to protect their oral health in the long term.

Recently, Marseglia L. et al. suggested new potential uses of melatonin in pediatric patients for its analgesic, anxiolytic and anaesthetic effects [4]. This endogenous indolamines produced and secreted by the pineal gland, is involved in numerous physiological functions such as regulation of circadian rhythm, as well as having antioxidant, oncostatic, anti-inflammatory and anticonvulsant activity [5]. From a clinical standpoint, exogenous melatonin is mainly used for the treatment of sleep disorders, but given the hypnotic properties it has been suggested that it may be used at different stages of anesthesia procedures [4]. Numerous experimental studies promote further therapeutic possibilities: it has been shown that melatonin has a sedative and anticonvulsant action supporting GABAergic transmission at the central level [6]. In addition, it has been characterized by an analgesic activity of melatonin, which is now used in adult patients in the treatment of chronic pathology [7]. From a strictly pharmacokinetic point of view, exogenous melatonin may be administered orally or sublingually, both in adults and children, without any evidence of substantial side effects [8]. After oral administration, melatonin undergoes first-pass effect, reaches the plasma peak after about 60 min and blood levels decrease in about 4 h [9].

Melatonin has its important clinical application in analgesia despite the biochemical mechanisms that have not been fully clarified; However, numerous experimental data have demonstrated the involvement of a series of endogenous substances and molecular targets [10]. For example, melatonin promotes the release of β -endorphins from the pituitary gland, favouring analgesia; naloxone is able to antagonize this effect as it prevents the binding of β -endorphins released with the opioid receptors, underlining its direct implication. The interactions of melatonin with membrane receptors, opioid 1-receptors, or Gamma-aminobutyric Acid- β (GABA- β) receptors, all of which are coupled to protein G, as well as having beneficial effects on pain perception, also result in anxiety. In addition, in view of the ability of melatonin to inhibit the production of nitric oxide, reduce the activation of the Nuclear Factor- κ B (NF- κ B) transcription factor, the expression of cyclooxygenase (COX) and prostaglandin and to recruit polymorphonuclear cells at the inflammation site Suggested a possible use of melatonin in the treatment of pain associated with pulp inflammatory processes [11]. Animal models demonstrated the existence of a circadian rhythm in the perception of pain finely regulated by melatonin: in an experimental study, the higher plasma levels of melatonin achieved at night in rats were associated with a lower sensitivity to pain but also higher morphine sensitivity than observed during waking hours [12]. The anxiolytic activity of melatonin demonstrated by animal models is confirmed by clinical trials conducted on adult patients undergoing stress, such as surgery and subsequent hospitalization [13,14]. Exactly as observed in animals, in these conditions, plasma melatonin levels were very low and oral administration in these patients proved to be useful

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in more than one aspect: It alleviated the state of preoperative anxiety, facilitated the induction of sleep, and improved post-operative pain control. Studies designed to investigate melatonin anaesthetic activity in adult patients have demonstrated the same pre-operative anxiolytic efficacy as midazolam (Gold standard) and furthermore, there was a lower incidence of postoperative excitement, sleep disturbance and delirium manifestations [15]. However, other studies have shown less efficacy of melatonin than midazolam [16]. The aim of the study was to evaluate the role which may be played by melatonin in the management of children in paediatric dentistry.

Materials and Methods

This is a retrospective case-control age and sex matched study. Participants were recruited among children attending the Dental Clinic and the Private Centre of the investigators from January 1st through July 1st, 2017. Inclusion criteria for patients were: Caucasian, aged 4-10, at their first pedodontic evaluation and without other diseases. We compared data collected during patient's first visit to evaluate the anxiolytic and analgesic effects of melatonin in paediatric dentistry.

GROUP A included 25 children who, according to literature [17], received Melatonin 0.5 mg/kg orally 60' before being subjected to first visit and pedodontic treatment and GROUP B included 25 children age and sex matched with patients of GROUP A who didn't received any preventive treatment. We collected data recorded by the operator at the end of each patient's visit, comparing success of treatment, anxiety and pain experienced by the child assessed by Face, Legs, Activity, Cry and Consolability (FLACC) behavioural pain scale according to literature [18].

Therefore, we identified 3 categories according to FLACC scale: relaxed and comfortable or mild discomfort (FLACC scale 0-3); moderate pain (FLACC scale 4-6); severe discomfort or pain or both (FLACC scale 7-10).

Statistical Analysis

Descriptive statistics were performed. Qualitative variables were summarised in terms of absolute frequencies or percentages, and quantitative variables were summarised in terms of mean \pm standard deviation. A comparison of frequencies was performed by the Chi-square test or by the Fisher Exact test (in case of expected frequencies less than 5). All tests were two-sided and $p \leq 0.05$ was considered as statistically significant. The software used for statistical analyses was Excel 2010 (Microsoft Corp. Redmond, WA, USA).

Results

Data of patients in the two groups are summarized in Table 1. Group A included 25 patients (11 male, mean age 6.7 yrs \pm 1.87; min 4.1 yrs, max 9.8 yrs), all pre-treated by administration of melatonin. Group

B included 25 patients (11 male, mean age 7.5 years \pm 1.89; min 4.0 yrs, max 9.7 yrs). Melatonin treatment was well tolerated by 100% of children. Physicians found greater collaboration with children of Group A: 96% successful treatment of the group receiving melatonin versus 68% in the group B (p 0.012). According to FLACC scale categories, 42% of all children presented relaxed and comfortable or mild discomfort (FLACC scale 0-3), 42% moderate pain (FLACC scale 4-6), and 16% severe discomfort or pain or both (FLACC scale 7-10). Moreover, in Group A, 60% of patients presented relaxed and comfortable or mild discomfort (FLACC scale 0-3), versus 24% in Group B; 32% of children of Group A showed moderate pain (FLACC scale 4-6) versus 52% in Group B; then, severe discomfort or pain or both (FLACC scale 7-10) was experienced by 8% of patients of Group A, versus 24% in Group B (p 0.025).

Finally we compared two categories of FLACC scale: relaxed and comfortable or mild discomfort (FLACC scale 0-3), versus moderate pain and severe discomfort or pain or both (FLACC scale 4-10). We found 60% of children receiving melatonin experienced relaxed and comfortable or mild discomfort versus 40% in Group B (p 0.001).

Conclusions

The deep impacts of DFA on children and adolescents reinforce the idea that managing fear and anxiety should be a starting point in patient management otherwise it can turn to dental phobia, leading to patients avoiding dental treatment. Midazolam was introduced as a premedication for children since 1980s. Although it can be administered via multiple routes, it is currently preferred as oral medication because of its rapid absorption and low incidence of nausea vs. other benzodiazepines [19]. However, midazolam has several side effects, including paradoxical reactions, interactions with opioids, variable bioavailability and elimination half-life, excessive sedation, disorientation, impaired psychomotor performance and amnesia [20]. In light of these findings, Naguib M in 1999 proposed melatonin as alternative to midazolam as a premedicant in procedures preceding anaesthesia induction [21]. Samarkandi et al. reported that 0.25 and 0.5 mg/kg melatonin was not only as effective as midazolam in alleviating preoperative anxiety in children but also associated with a tendency toward faster recovery, lower incidence of excitement postoperatively [22]. But according to Isik B. et al., in terms of effectiveness of the sedation in melatonin groups were not similar to that of these research [17].

Our data showed better compliance in children receiving melatonin and higher rate of successful treatment. Interestingly, in our experience melatonin significantly reduced FLACC score both reducing pain than anxiety. Then, although studies about use of melatonin on children have provided conflicting results, our experience shows the analgesic and hypnotic properties of melatonin offer new therapeutic possibilities in the pediatric dentistry.

	All patients (N=50) N (%)	Patients Group A (N=25) N (%)	Patients Group B (N=25) N (%)	P
Gender: Males	22 (44.0)	11 (44.0)	11 (56.0)	1 [§]
Females	28 (56.0)	14 (44.0)	14 (56.0)	
successful treatment: yes	41 (82.0)	24 (96.0)	17 (68.0)	0.012 [#]
No	9 (18.0)	4 (4.0)	8 (32.0)	
scale FLACC: 0-3 (Relaxed and comfortable o mild discomfort)	21 (42.0)	15 (60.0)	6 (24.0)	0.025 [§]
4-6 (Moderate pain)	21 (42.0)	8 (32.0)	13 (52.0)	
7-10 (Severe discomfort or pain or both)	8 (16.0)	2 (8.0)	6 (24.0)	
scale FLACC: 0-3 (Relaxed and comfortable o mild discomfort)	21 (42.0)	15 (60.0)	6 (24.0)	0.001 [§]
4-10 (Moderate pain, severe discomfort or pain or both)	29 (58.04)	10 (40.0)	19 (76.0)	

[§]P refers to the Chi-square test; [#]P refers to the Fisher Exact

Table 1: Patients' characteristics and relationships between successful treatment and scale FLACC and patient's treatment.

In light of its diverse origins, DFA could be better prevented and intercepted through coordinated efforts of pediatric dentists, dental auxiliaries, pediatric patients, and their parents. Thoughtful approaches before, during, and after the dental visit contribute in one way or another to a pleasant and productive dental experience. Successful DFA management not only paves the road to satisfactory clinical outcome and better oral health, but also builds confidence in pediatric patients and may help them regulate their emotions while facing other challenges in life. In our opinion, analgesic and hypnotic properties of melatonin seem to offer new therapeutic possibilities in the pedodontic field, however larger population study is needed.

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References

- Chhabra N, Chhabra A, Walia G. Prevalence of dental anxiety and fear among five to ten year old children: a behaviour based cross sectional study. *Minerva Stomatol.* 2012; 61: 83-89.
- Klingberg G, Broberg AG. Dental fear/anxiety and dental behaviour management problems in children and adolescents: a review of prevalence and concomitant psychological factors. *Int J Paediatr Dent.* 2007; 17: 391-406.
- Hakeberg M, Berggren U, Gröndahl HG. A radiographic study of dental health in adult patients with dental anxiety. *Community Dent Oral Epidemiol.* 1993; 21: 27-30.
- Marseglia L, D'Angelo G, Manti S, Aversa S, Arrigo T, Reiter RJ, Gitto E. Analgesic, anxiolytic and anaesthetic effects of melatonin: new potential uses in pediatrics. *Int J Mol Sci.* 2015; 16: 1209-1220.
- Reiter RJ, Tan DX, Fuentes-Broto L. Melatonin: a multitasking molecule. *Prog Brain Res.* 2010; 181: 127-151.
- Naguib M, Gottumukkala V, Goldstein PA. Melatonin and anesthesia: a clinical perspective. *J Pineal Res.* 2007; 42: 12-21.
- Chen WW, Zhang X, Huang WJ. Pain control by melatonin: Physiological and pharmacological effects. *Exp Ther Med.* 2016; 12: 1963-1968.
- Gordon N. The therapeutics of melatonin: A paediatric perspective. *Brain Dev.* 2000; 22: 213-217.
- Reiter RJ. Pineal melatonin: Cell biology of its synthesis and of its physiological interactions. *Endocr Rev.* 1991; 12: 151-180.
- Srinivasan V, Pandi-Perumal SR, Spence DW, Moscovitch A, Trakht I, Brown GM, Cardinali DP. Potential use of melatonergic drugs in analgesia: mechanisms of action. *Brain Res Bull.* 2010; 81: 362-371.
- Li JG, Lin JJ, Wang ZL, Cai WK, Wang PN, Jia Q, Zhang AS, Wu GY, Zhu GX, Ni LX. Melatonin attenuates inflammation of acute pulpitis subjected to dental pulp injury. *Am J Transl Res.* 2015; 15(7): 66-78.
- Christina A, Merlin N, Vijaya C, Jayaprakash S, Muruges N. Daily rhythm of nociception in rats. *J Circadian Rhythms.* 2004; 2: 2.
- Golombek DA, Martini M, Cardinali DP. Melatonin as an anxiolytic in rats: Time dependence and interaction with the central GABAergic system. *Eur J Pharmacol.* 1993; 237: 231-236.
- Andersen LP, Werner MU, Rosenberg J, Gögenur I. A systematic review of peri-operative melatonin. *Anaesthesia.* 2014; 69: 1163-1171.
- Impellizzeri P, Vinci E, Gugliandolo MC, Cuzzocrea F, Larcian R, Russo T, Gravina MR, Arena S, D'Angelo G, Gitto E, Montalto AS, Alibrandi A, Marseglia L, Romeo C. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients. *Eur J Pediatr.* 2017; 176: 947-953.
- Isik B, Baygin O, Bodur H. Premedication with melatonin vs midazolam in anxious children. *Paediatr Anaesth.* 2008; 18: 635-641.
- Kurdi MS, Muthukalai SP. A comparison of the effect of two doses of oral melatonin with oral midazolam and placebo on pre-operative anxiety, cognition and psychomotor function in children: A randomised double-blind study. *Indian J Anaesth.* 2016; 60: 744-750.
- von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. *Pain.* 2007; 127: 140-150.
- Marshall WR, Weaver BD, McCutcheon P. A study of the effectiveness of oral midazolam as a dental pre-operative sedative and hypnotic. *Spec Care Dentist.* 1999; 19: 259-266.
- Acil M, Basgul E, Celiker V, Karagöz AH, Demir B, Aypar U. Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. *Eur J Anaesthesiol.* 2004; 21: 553-557.
- Naguib M, Samarkandi AH. Premedication with melatonin: a double-blind, placebo-controlled comparison with midazolam. *Br J Anaesth.* 1999; 82: 875-880.
- Samarkandi A, Naguib M, Riad W, Thalaj A, Alotibi W, Aldammas F, Albassam A. Melatonin vs. midazolam premedication in children: a double-blind, placebo-controlled study. *Eur J Anaesthesiol.* 2005; 22: 189-196.