Comparative Evaluation of Anxiolytic and Analgesic Effects of Melatonin in Paediatric Subjects

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Abstract: Aim: Dental phobia stems from fear and anxiety and is considered a major hurdle in dental treatment of pediatric patients who in turn resist or start avoiding treatment. Endogenous indolamines like melatonin which is produced by pineal gland has a chief role in regulation of circadian rhythms. Melatonin acts like an oncostatic agent, known to possess antioxidant, anti-inflammatory as well as anticonvulsant property. It is mainly administered through oral or sublingual route of drug administration. No substantial side effects have been reported by administration of melatonin. Soon after melatonin intake, it undergoes first-pass effect reaching in about 60 min to its peak plasma levels and within 4 h the blood level falls. Study Design: The present case-control study is a retrospective study with age and sex matched recruitments. Data collection was done as per first visit and then post treatment of 50 subjects who reported to the Department of Preventive and Pediatric dentistry. Methods: In accord with the literature, 25 pediatric subjects were administered with 0.5 mg/ kg body weight Melatonin 60’ prior to their first visit followed by their Pedodontic management. As per record no initial Pedodontic treatment was given to the rest of the 25 recruits. The successful management of treatment was assessed by analyzing their pain experience through FLACC behavioral pain scale. Results: A statistically significant number of children (n=50) both age and sex matched were included in the study and further divided into Group A and Group B with mean age of 7.56 years and 7.08 years respectively. Group A received Melatonin treatment while Group B was not given any preventive treatment. As per the FLACC scale categories, Melatonin was well tolerated by all the children of A Group, out of which 42% of subjects showed relaxed levels or slight discomfort (0-3), 42% presented with moderate discomfort or pain (4-6) while only 16% showed severe or intense pain or discomfort (7-10). Conclusions: The present study thus establishes a positive role of Melatonin on Pedodontic therapy as it has a potent analgesic and anxiolytic potential. Limitation of study is smaller sample size.

Keywords: Melatonin, analgesic, anxiolytic, FLACC scale.

INTRODUCTION

The prevalence rate of Dental Fear and Anxiety (DFA) is about 5-20% in pediatric subjects [1]. DFA has a wide range of manifestations, influences and origins. Children as well as adolescents have shown varying degree of DFA. They become very uncooperative during their visits to Pedodontic setups, avoiding treatments due to this fear and thus it...
becomes a very challenging task to manage such patients [2]. This consequently interferes with treatment and compromises the prognosis of the cases. Owing to this stressful environment, incoherence is often seen between dentists and parents of the patients [3]. There have been reported evidence of persistence of DFA in adulthood if acquired during childhood. The keystone stage for prevention and interception of DFA thus is childhood. This becomes crucial for maintenance of oral health in the long run.

In recent times, Marseglia L. has brought to our attention the benefits of using oral melatonin in pediatric patients due to their anesthetic properties besides anxiolytic and analgesic effects [4]. Melatonin is belongs to endogenous indolamines group. Melatonin acts like an oncostatic agent, known to possess antioxidant, anti-inflammatory as well as anticonvulsant property. It is mainly administered through oral or sublingual route of drug administration. No substantial side effects have been reported by administration of melatonin. Soon after melatonin intake, it undergoes first-pass effect reaching in about 60 min to its peak plasma levels and within 4 h the blood level falls [5].

In view of clinical perspective, exogenous variants of melatonin find their utility in sleep apnea and other sleeping disorders. Melatonin’s anesthetic potential is mainly due to various hypnotic properties that it harbors due to which it is used during anesthesia procedures [4]. Various in-vivo clinical trials have further established their therapeutic role; these studies have proven the role of melatonin as a sedative and also as an anticonvulsant. Melatonin has been found to act by supporting Gamma aminobutyric acid (GABAergic) neuro-transmission at the central nervous system level [6]. Besides, characteristic analgesic activity of exogenous melatonin is nowadays used for treating chronic pathologies in adult and geriatric patients [7]. In light of purely pharmacokinetic standpoint, routes of administration of exogenous melatonin are oral route and sublingual route with no potential side-effects [8]. Melatonin after its oral administration undergoes first-pass mechanism and then reaches its peak plasma levels after about an hour while its level in blood decreases in around four hours [9].

Biochemical mechanism of action of melatonin have not yet been clearly described but it’s a known fact now that it has wonderful analgesic effect. In-vitro experimental studies have set forward series of other endogenous substances with their target molecules [10]. As for instance, \( \beta \)-endorphins release from pituitary gland is promoted by melatonin which further favors analgesia. This effect is however nullified or antagonized by naloxone as it prevents \( \beta \)-endorphins to bind with their opioid receptors favoring its direct utility.

The interactions of melatonin with G protein coupled receptors, opioid receptors or GABA- \( \beta \) receptors has thus a very important beneficial role in subsiding pain perception. Besides it also suppresses anxiety issues. Melatonin also has an inhibitory effect on release of nitric oxide. It further inactivates prostaglandin (Pg) expression, suppresses cyclooxygenase (COX) expression and inactivates Nuclear Factor- \( \kappa B \) (NF-\( \kappa B \)) transcription factor. It promotes the recruitment of PMNs at the site of inflammation. Expression of and prostaglandin and to recruit polymorphonuclear cells at the inflammation site is suggestive of possible role of melatonin in the management of pain related to pulpal inflammatory changes [11].

Studies on experimental animals (gnotobiotic rats) have elicited presence of circadian rhythm in pain perception which is well regulated or modulated by melatonin. In these animals higher plasma levels of melatonin were inversely proportional with pain perception. This was mainly seen during nights when rats were relatively less sensitive to pain perception. They also showed higher sensitivity to morphine that during day highlighting association of melatonin with circadian rhythms [12]. The anxiolytic effect of melatonin administration exhibited by animal studies is potentiated by clinical trials performed on adult subjects under stress of either undergoing any kind of surgery followed by hospitalization [13, 14].

Studies investigating anaesthetic effect of melatonin in adult subjects have demonstrated similar pre-operative anxiolytic efficacy as that of midazolam which is regarded as Gold standard with lower rate of postoperative anxiety, sleeping disturbances and manifestations of confusions or delirium [15]. However, other studies have concluded that melatonin is less efficient than midazolam [16].

The aim of the study was to comparatively evaluate anxiolytic and analgesic effects of Melatonin in Paediatric Subjects.

**Materials and Methods**

**Study Design**

The present case-control study is a retrospective study with age and sex matched recruitments. Data collection was done as per first visit and then post treatment of 50 subjects who reported to the Department of Preventive and Pediatric dentistry.
METHODS

In accord with the literature [17], 25 pediatric subjects were administered with 0.5 mg/kg body weight Melatonin 60’ prior to their first visit followed by their Pedodontic management. As per record no initial Pedodontic treatment was given to the rest of the 25 recruits. The successful management of treatment was assessed by analyzing their pain experience through (FLACC) Face, Legs, Activity, Cry and Consolability behavioral pain scale [18]. Therefore, 3 categories according to FLACC behavioral pain scale were identified namely:
- Comfortable and relaxed 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

Category of descriptive statistics were taken into account. Qualitative variables were recorded in relation to absolute frequencies or their percentages, while quantitative variables were recorded in terms of mean ± standard deviation. A comparison of frequencies was measured by the Chi-square test. All tests were two-sided and p value ≤ 0.05 was taken as statistically significant. The software used for statistical analyses was SPSS version 18.

RESULTS

A statistically significant number of children (n=50) both age and sex matched were included in the study and further divided into Group A and Group B with mean age of 7.56 years and 7.08 years respectively. Group A received Melatonin treatment while Group B was not given any preventive treatment. As per the FLACC scale categories, Melatonin was well tolerated by all the children of A Group, out of which 42% of subjects showed relaxed levels or slight discomfort (FLACC scale 0-3), 42% presented with moderate discomfort or pain (FLACC 4-6) while only 16% showed severe or intense pain or discomfort (FLACC 7-10) (Summarized in Table-1).

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

| Variables                                      | 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)                    |         |

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

DISCUSSION

The deep influence of DFA on children and adolescents promotes the idea that managing fear and anxiety should be a standpoint in patient management or else it can turn to dental phobia, leading to reluctance towards dental treatment. Midazolam considered as gold standard was introduced as a premedication for children around 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 potential 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 observations, Naguib M in 1999 proposed melatonin as alternative to midazolam as a pre-medication 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 post treatment [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 who received melatonin and higher rate of successful management. 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.

**CONCLUSION**

In view of its diverse origins, Dental Fear and Anxiety could be better prevented and intercepted through well-coordinated efforts of pediatric dentists, dental auxiliaries, pediatric patients, and their parents. Thoughtful approaches pre, par and post operatively of a dental visit contributes in one way or other to a pleasant and productive dental experience. Successful DFA management not only paves the road to satisfactory prognosis and better oral health, but also builds confidence in pediatric subjects and may in turn help them regulate their emotions in moderation while facing other challenges or situations in life. The present study thus establishes a positive role of Melatonin on Pedodontic therapy as it has a potent analgesic and anxiolytic potential. Limitation of study is smaller sample size.

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