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Comparison of Oral Melatonin and Midazolam as Premedication in Children Undergoing General Anesthesia for Dental Treatment

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Abstract

Background: Dental anxiety is prevalent in children. This condition may cause uncooperative behavior and need a treatment under general anesthesia. The perioperative period, especially for children, is a stressing event. Premedication is commonly used to reduce perioperative anxiety and facilitate the induction of anesthesia.
Methods: 132 children candidates for dental treatment under GA were enrolled in this study and randomly divided into 3 groups. Oral melatonin, midazolam, and normal saline were administered as premedication. Patient's sedation score before GA, the ease of intravenous line establishment, patient's need for painkillers, and duration of recovery were evaluated and compared.
Results: Regarding the sedation score and response to IV access establishment, comparisons showed statistically significant differences between melatonin and midazolam groups ($P < 0.05$) as well as between midazolam and placebo groups ($P < 0.001$). The difference between melatonin and placebo groups was not significant ($P > 0.05$). The need for painkiller administration was statistically different between midazolam and placebo, melatonin and placebo, and midazolam and melatonin groups ($P < 0.05$). A statistically significant difference was also found between melatonin and midazolam as well as between melatonin and placebo groups ($P < 0.05$) with regard to the recovery duration while no significant difference was observed between midazolam and placebo groups ($P > 0.05$).
Conclusion: Midazolam is superior to melatonin for premedication regarding the patients' sedation score before anesthesia and the ease of IV access establishment. Premedication with midazolam decreases the need for painkillers and increases the rate of recovery in children undergoing GA for dental treatment.

Keywords: Melatonin, Midazolam, Dental Treatment

1. Background

Dental anxiety is prevalent in children. This condition may cause uncooperative behavior and subsequent failure of dental treatment (1). In today's world, traditional management techniques such as distraction and voice control are not adopted by parents (2).

An alternative is to perform dental treatment under general anesthesia. However, the perioperative period, especially for children, is a stressing event (3). Perioperative anxiety is an unpleasant state of uneasiness or tension. It is estimated that up to 65% of children experience intense anxiety in the perioperative period and during induction of anesthesia (3, 4).

Premedication is commonly used to reduce perioperative anxiety (3) and to facilitate induction of anesthesia (5).

Benzodiazepines mainly midazolam are most commonly used as premedication for anxiolysis. Midazolam has several adverse effects such as paradoxical reactions, respiratory disorder, cardiac arrhythmia, and involuntary muscle movement (5). Thus, it is appealing to find an alternative.

The pineal hormone melatonin has several functions, including hypnotic, anxiolytic, sedative, and anti-inflammatory actions. One of the proposed uses of melatonin is premedication preceding the anesthesia induction (6).

Melatonin has several advantages such as:

1. It is difficult to overdose since it is a natural hormone.

2. It may be more acceptable by patients.

3. It has a relatively short half-life and hence, prolonged sedation is unlikely.

Previous studies with melatonin to induce sedation in children and adults declared good results (5, 7).

However, therapeutic possibilities of melatonin as premedication in dentistry are still controversial (8).

Accordingly, the aim of this clinical trial was to assess the effect of melatonin as premedication in children undergoing general anesthesia for dental treatment in comparison with midazolam and placebo.

The effectiveness was evaluated by means of child sedation score before induction of anesthesia, the ease of intravenous cannulation for induction of anesthesia, recovery duration, and the child need for pain relievers after the operation.

2. Materials and Methods

After obtaining the ethics committee approval (from Isfahan University of Medical Sciences) and informed parental consent, 132 ASAI children aged 3 - 6 years who required dental treatment under general anesthesia as a result of uncooperative behavior were assessed by Frankl behavior scale (Table 1) at the dental examination.

Table 1. Frankl Behavior Scale

Score	Scoring	Observed Behavior
1	Definitely positive	Good rapport with the dentist, interested in the dental procedures, laughing and enjoying the situation
2	Positive	Acceptance of treatment; at times cautious, willingness to comply with the dentist, at times with reservation but patient follows the dentist's directions cooperatively.
3	Negative	Reluctant to accept treatment; uncooperative, some evidence of negative attitude but not pronounced, i.e. sullen, withdrawn
4	Definitely negative	Refusal of treatment, crying forcefully, fearful, or any other overt evidence of extreme negativism

Children who were taking medication within the last 2 weeks were excluded. Since melatonin could intensify the effect of anticoagulants, children taking these medications were excluded. The parents were advised to bring the child to the operating room an hour before the scheduled anesthesia time. Children had to eat or drink nothing for 6 hours before surgery.

Patients were premedicated in an isolated recovery room 40 minutes before induction of anesthesia.

Patients were randomly divided into three groups (n = 44 in each) by using a computer-generated random allocation table. Each patient was recognized with a number and the numbers were allocated to each group randomly. The premedication in groups was:

Group 1: 15 ml oral midazolam solution (midazolex 15mg/3ml Amp from Neon Pharmaceutical company) at dose 0.5 mg/kg

A sugar cube was also added to the solution to solve its bitter taste.

Group 2: 15 ml oral melatonin (melatonin tablets 3mg from Aristo pharmaceutical company dissolved in water) at dose 0.5 mg/kg

Group 3: 15 ml combination of dextrose and normal saline in equal proportion orally administered (as placebo)

This study was double-blind and study drugs were given by a trained nurse. None of the researchers and parents was informed about the type of drug administered to the child.

40 minutes after drug administration, the patient was transferred to the operating room. Parental presence was allowed throughout anesthesia induction.

The sedation score of patients was assessed before induction according to Table 2. Then, an intravenous catheter was inserted. For anesthesia induction, sevoflurane 5% and N2O 30% in oxygen with a facemask were used. The child was intubated with a nasoendotracheal tube after administrating muscle relaxant.

Table 2. Sedation Scale

Score	Sedation Status
1	Alert
2	Awake
3	Drowsy
4	Asleep

The ease of intravenous access establishment was evaluated and patient's response was noted as one of these conditions: 1. Crying, 2. Yelling, 3. Limb moving, 4. No reaction.

Intravenous atracurium 0.5 mg/kg and an antiemetic were also administered.

Local anesthesia was not administered except for tooth extraction.

For each child, the types of performed dental treatment and anesthesia duration were noted.

After the operation, the child was extubated and kept in the recovery room under observation. The patients were discharged with the permission of the anesthesiologist (modified Aldrete criteria) (3).

The duration of recovery and need for painkiller administration for children in the recovery room until discharge were also evaluated (prescribed or not).

2.1. Statistical Analysis

Statistical evaluation was performed with SPSS20 using one-way analysis of variance (ANOVA) for intergroup comparisons of age and duration of anesthesia and Chi-square analysis for intergroup comparisons of sex.

The types of dental treatment, sedation score, the ease of IV access establishment, and recovery duration were compared by means of Kruskal-Wallis and Mann-Whitney tests.

Fisher's exact test was used to compare the need for painkillers between the groups.

3. Results

Patients in three groups were comparable in age, sex, and anesthesia duration ($P > 0.05$) (Table 3).

The types of dental treatment performed in each group were also comparable inter groups ($P > 0.05$).

The sedation score of children in each group was evaluated 40 minutes after premedication and provided in Table 4.

Table 3. Demographic Parameters in the Groups ($P > 0.05$ for all Inter Groups Comparisons)

	Midazolam	Melatonin	Placebo
Age (Mean ± SD)	4.3 ± 0.96	3.9 ± 0.98	4.1 ± 1.01
Gender (percentage of male, female)	45.7%, 54.3%	34.9%, 65.1%	44.7%, 55.3%
Duration of anesthesia (mean ± SD)	61.20 ± 27.0	63.37 ± 25.4	60.85 ± 26.8

The comparison of patient's response to IV access establishment between three groups is presented in Table 5.

Regarding the sedation score and response to IV access establishment, the comparisons showed statistically significant differences between melatonin and midazolam groups ($P < 0.05$) as well as between midazolam and placebo groups ($P < 0.001$).

The difference between melatonin and placebo groups was not significant ($P > 0.05$).

The need for painkiller administration for patients in each group is shown in Table 6.

A statistically significant difference was observed between midazolam and placebo, melatonin and placebo, and midazolam and melatonin groups ($P < 0.05$).

The three groups were also compared based on recovery duration (Table 7). A statistically significant difference was found between melatonin and midazolam as well as between melatonin and placebo groups ($P < 0.05$) while no significant difference was observed between midazolam and placebo groups ($P > 0.05$).

4. Discussion

In our study, we compared the effect of orally administered melatonin versus midazolam and placebo on sedation score, intravenous access establishment, the need for painkillers after the operation, and recovery duration in children undergoing general anesthesia (GA) for dental treatment.

The results demonstrated that in anxious children who were scheduled for dental treatment under GA, oral melatonin (0.5 mg/kg) and oral midazolam (0.5 mg/kg) administration compared to placebo administration before induction of anesthesia were both effective to sedate patients. However, midazolam was more effective than melatonin. There is scarce evidence regarding melatonin reducing anxiety for dental treatment (1). A randomized controlled study investigated melatonin in dental surgery and could not demonstrate any sedative effect compared to placebo (1). In this study, we found midazolam is superior to melatonin in premedication for sedating children before induction of anesthesia. Five studies compared sedation levels after premedication with melatonin, midazolam, or placebo (7, 9-11). Naguib and Samarkandi revealed increased levels of sedation in melatonin and midazolam groups versus placebo group at 60 and 90 minutes after premedication (7, 9). In our study, the difference between preoperative sedation scores of 3 groups was statistically significant. The intergroup comparison revealed that midazolam produced the most favorable degree of sedation and most children premedicated with midazolam were awake. This outcome was in contrast to the findings of some other studies (1, 12).

The ease of intravenous (IV) line establishment in children was also assessed in this study after premedication with melatonin, midazolam, and placebo.

The results revealed that in the midazolam group, the most observed response of children was limb movement followed by yelling, no reaction, and crying. In the melatonin group, 'voice producing" was mostly found, followed by limb movement, crying, and no reaction. The response observed in the placebo group was comparable with that of the melatonin group, although significantly different from that of the midazolam group. One of the adverse effects of midazolam is unusual and involuntary muscle movement (5), which can justify the most observed response in children. However, "no reaction" that is the favorable response was mostly found in the midazolam group.

Anxiety during induction of anesthesia after midazolam premedication has been evaluated in previous studies. Some studies revealed a reduction in induced anxiety with midazolam (4, 13, 14). To our knowledge, no previous study is found to assess and compare the effects of premedica-

Table 4. Preoperative Sedation Scores in the Groups (Percentage of Patient's Scores in Each Group)[a]

	Alert	Awake	Drowsy	Asleep
Midazolam	6.5%	82.6%	8.7%	2.2%
Melatonin	18.6%	67.4%	14.0%	0.0%
Placebo	53.2%	46.8%	0.0%	0.0%

[a] $P < 0.05$ for comparing melatonin with midazolam group

Table 5. The Ease of IV Access Establishment (Percentage of Patient's Type of Response in Each Group)[a]

	Crying	Yelling	Limb Moving	No Reaction
Midazolam	4.3%	23.9%	56.5%	15.2%
Melatonin	11.6%	51.2%	34.9%	2.3%
Placebo	21.3%	55.3%	21.3%	2.1%

[a] $P < 0.05$ for comparing melatonin with midazolam group

Table 6. The Need for Analgesics Administration (Percentage of Patients in Each Group)[a]

	Need of Analgesics	No Need of Analgesics
Midazolam	8.7%	91.3%
Melatonin	7.0%	93.0%
Placebo	31.9%	68.1%

[a] $P < 0.05$ for comparing melatonin with midazolam group

Table 7. Recovery Duration in Minutes (mean ± SD)[a]

	Mean ± SD
Midazolam	79 ± 29
Melatonin	93 ± 30
Placebo	78 ± 30

[a] $P < 0.05$ for comparing melatonin with midazolam group

tion with midazolam and melatonin on the ease of IV access establishment.

The need for pain relievers until patient discharge was also evaluated in this study. Our results revealed a significant difference between the three groups. The need for painkiller administration was observed in 31.9%, 8.8%, and 7% of placebo, melatonin, and midazolam groups, respectively. Anxiety reduction caused by midazolam and melatonin administration could increase pain perception threshold and decrease the need for painkillers in the patients.

Experimental animal studies have demonstrated the anti-nociceptive effect of melatonin (15).

A meta-analysis demonstrated that melatonin reduced postoperative pain scores compared to placebo (16).

A meta-analysis of randomized controlled trials revealed that Dexmedetomidine is more effective than midazolam in providing postoperative analgesia (3). However, to our knowledge, no study was found to compare melatonin and midazolam. Our study revealed that melatonin-induced postoperative analgesia is superior to midazolam-induced analgesia when used as premedication.

The duration of recovery was compared between midazolam and melatonin groups and showed a significant intergroup difference.

Patients in the midazolam group exhibited faster recovery than those in the melatonin group and the rate of recovery in the melatonin group was comparable with that of the placebo group. In contrast to this study, Acil et al. declared that recovery after premedication with melatonin was faster than after premedication with midazolam (11). In their study, 5 mg melatonin was administered and showed comparable results with 15 mg midazolam. Different prescribed doses can justify the difference in the results of the previous and present studies.

4.1. Conclusion

We concluded that midazolam (0.5 mg/kg) was superior to melatonin (0.5 mg/kg) in premedication regarding the patients' sedation score before anesthesia and the ease of IV access establishment. Premedication with oral midazolam decreased the need for painkillers and increased the rate of recovery in children undergoing GA for dental treatment.

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