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A comparative study on Oral Dexmedetomidine and Midazolam as Premedication in Children Undergoing General Anesthesia for Dental Procedures

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Abstract

The most commonly used method for sedation before entering the operation room is using oral medication for children and the most commonly used medicine is midazolam. The purpose of the project was to examine the effect of dexmedetomidine as a prodrug on the mean scores of the Bispectral Index (BIS) in children aged 3-5 candidates of receiving dental treatment under general anesthesia compared to midazolam. In this randomized clinical trial, 75 children aged 3-5 years with ASAI candidates for dental treatment under general anesthesia were selected. Measuring BIS scores was the primary and main evaluation. Examining anxiety index scores during parental separation, sedation, behavior during venipuncture and behavior while waking up in recovery, postoperative analgesic need and changes in hemodynamic parameters were measured as secondary goals. The mean BIS score between the groups studied was significantly different and the dexmedetomidine group had lower values ($p<0.05$). Dexmedetomidine and midazolam groups were comparable regarding anxiety scores during separation from parents, behavior during venipuncture, and behavior during waking up in recovery ($p>0.05$), but both groups performed better than the control group ($p<0.05$). There was a significant difference between the sedation scores between dexmedetomidine and midazolam groups ($p=0.006$). Moreover, there was a significant difference between the two groups with the control group ($p<0.001$). Hence, given the results as well as fewer side effects, dexmedetomidine can be introduced as an alternative to midazolam.

Key words: Dexmedetomidine, Midazolam, Prodrug, General Anesthesia, BIS.

Introduction

One of the most significant issues faced in preparing children is the anxiety at entering the operating room (Ghali, Mahfouz and Al-Bahrani, 2011). At least, 60% of the child patients experience pre-operative anxiety (Kain et al., 1996). Children may be completely uncooperative while being separated from their parents, venipuncture, or applying masks. Untreated anxiety in children may cause more severe anesthesia, increased postoperative pain, more need for analgesics, agitation and even postoperative psychological effects and behavioral problems (Yuki and Daaboul, 2011; Aydin et al., 2008; Karling, Stenlund and Hägglöf, 2007). Many anesthetic practitioners use parental or pre-existing sedative supplements to relieve the physiological and psychological effects of pre-operative anxiety (Audenaert et al., 1995). Moreover, given the difficulty and specialty of anesthesia in children, prescribing drugs such as dexmedetomidine or midazolam for sedation, analgesic, stress relief, and the elimination of nervous and anxiety and fear, is necessary as a prodrug (Mukherjee et al., 2015). In particular, prodrugs facilitate general anesthesia in children and the patients who have difficulty communicating with them or who have experienced unpleasant experiences with the hospital (Segovia et al., 2014). Currently, the most commonly used way of sedatives before entering the operating room is using oral medication (Baygin, Bodur and Isik, 2010), where the most commonly used drug is midazolam (Shoroghi et al., 2011; Cao et al., 2009). Midazolam has several properties, like sedation, reducing vomiting, fast effect onset and short duration effect, but due to its side effects, such as post-operative behavioral changes, cognitive impairment, conflicting reactions, restlessness, forgetfulness, and respiratory depression, it cannot be an ideal anesthesia prodrug. One of the most inappropriate aspects of midazolam is the bitter taste that makes it less receptive (McGRAW and Kendrick, 1998). As a highly specific agonist on alpha-2 receptor with a short half-life, dexmedetomidine has sedative, anti-anxiety, sympathetic and analgesic properties without significant adverse effects of respiratory depression. Moreover, it has an antisialagogue effect and the ability to reduce nausea and vomiting (Bergendahl, Lönnqvist and Eksborg, 2006).

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BIS is a non-invasive marker of anesthetic depth and an electroencephalography (EEG)-based algorithm (Lo et al., 2011). BIS is used to measure the effect of anesthetic drug on the brain (Leslie et al., 1996). The BIS is graded from zero to 100 according to anesthesia depth. In awake and alert patients, the score is 90-100, whereas the stoppages of the cortical portion of the brain results in zero score (Sigl and Chamoun, 1994). To maintain the person in general anesthesia, BIS should be from 44 to 60 (Johansen and Sebel, 2000). BIS monitoring is a simple way to prevent the unwanted increase in anesthetic concentration, which will result in quick efficacy and short-term recovery (Wong et al., 2002).

Recently, dexmedetomidine has been extensively tested in the pediatric population. Although several RCTs have focused on dexmedetomidine as a prodrug in children, the sample size is relatively small and contradictory (Peng et al., 2014). As no similar studies have been done among the children to evaluate BIS index scores in relation to dexmedetomidine and midazolam prodrugs, the study is conducted given the necessity of examining the effect of dexmedetomidine as a prodrug on the mean scores of BIS index compared with midazolam. According to the results of previous studies regarding better properties and fewer side effects of dexmedetomidine, if the effect is favorable on the mean scores of the BIS index, this drug is considered as a good alternative to midazolam as prodrug for dental treatment under anesthesia.

Materials and Methods

The study was randomized clinical done on 75 healthy children aged 3-5 from both genders with ASAI, who were candidates for receiving full mouth dentistry treatment under general anesthesia admitted to the pediatric ward of Isfahan Dental School. The steps of conducting the study were explained to the child's parents prior to its implementation and written informed consent was obtained from them. The inclusion criteria were the patients with ASAI aged 3-5 years in need of Full Mouth dental treatment under general anesthesia. The exclusion criteria were the children, who according to the history received, had allergy to any of the medicines used (opioids, alpha 2 adrenoreceptors, propofol or localized anesthesia), or reported food allergy to eggs and soy (susceptible to propofol allergy). Moreover, they were the children who themselves or their parents refused to use the drugs, history of using drugs affecting the central nervous system (antipsychotics, antidepressants, sedatives and soporific) or suffering any disease that affects the central neural system (congenital or developmental). Those who had ASA more than I, or it was estimated that their treatment lasts less than one hour and more than two and a half hours, were not included in this study. All the patients were fasting 6 hours for solid food and for 2 hours for clear fluids. This study was double blind prospective, and the subjects in the study (dentist, patient parents, data recorder, and statistical counselor) were unaware of the nature of the drug given to each child. It should be noted that the color of the solutions did not differ in the three groups. The evaluation and scoring of the indices were done before and after the operation by the practitioner unaware of the prescribed drugs in each group and reading BIS scores during the operation was performed by the anesthetist nurse who did not know the study. Dental treatments of the patients were done under complete local anesthetic.

The patients were randomly assigned (through random numbers table) to one of three groups. The first group (n=25) received dexmedetomidine (Exir Co., Iran) at a dose of 4 g/Kg combined with a multivitamin syrup up to a volume of 3-5 ml 45 minutes prior to the operation as oral. The second group (n=25) received 0.5 mg/kg midazolam orally combined with multivitamin syrup up to 3-5 ml, 45 minutes before the operation. The third group (n=25) received multivitamin syrup orally as the control group only up to 3-5 ml 45 minutes before the operation. The patients were taken to the operating room 45 minutes after receiving the oral medication and placed on the bed of the venipuncture room. The relevant authority recorded the scores related to pre-anesthetic indices and venipuncture. Then, anesthesia was induced equally in all three groups using intravenous Propofol (5mg / Kg) (Lipuro 1%, B-Braun, Germany), Fentanyl (0.1mg / Kg) and Atracurium (0.8mg / Kg). The tracheal intubation was then nasally and the child was attached to the anesthetic machine, whose settings were set based on weight, number and volume of respiration. O_2 50% / N_2O 50% and Propofol (100 µg / Kg / min) were used for maintaining anesthesia. BIS monitoring was performed by placing the BIS sensor (BIS sys, Vista, Aspecmedial sys, USA) on a small size for children on their foreheads. BIS, Blood Pressure and Heart Rate were recorded in all 3 groups before the intubation, after intubation and then every 10 minutes to 60 minutes. Each of the hemodynamic parameters, besides measuring every 10 minutes during the operation and after operation, was monitored and recorded in the recovery and comparison of the status of these parameters, like arterial pressure and heart rate. In addition, the relevant authority recorded scores for post-operative indices. Then, the average of BIS values was compared in the studied groups. Moreover, studying and comparing the studied groups regarding anxiety while being separated from the parents, the degree of sedation caused by prodrug before anesthesia, cooperation during venipuncture, need for analgesic recovery, child behavior during recovery, and recovery time using the index. In the recovery room, besides hemodynamic status, the patients were monitored for side effects of drugs such as hypotension, bradycardia, respiratory depression, oxygen saturation, vibration, nausea and vomiting. In the case of ethical considerations, only the children were studies who according to the dental diagnosis, were in need of general anesthesia with informed consent of their parents about the purpose and method. This dissertation was approved by the Vice-Chancellor of Research and Technology of Isfahan University of Medical Sciences and approved by IR.MUI.RESEARCH.REC.1397.375.

Results

The study examined 75 patients (25 in each of the mentioned drug groups) whose demographic data and anesthesia time by group were presented in Table 1. In addition, the average values of BIS obtained in the studied groups were presented according to time in Table 2. In Table 3, the comparison of P value based on one way ANOVA (Tukey) in the studied groups was calculated by time.

Table 1: Demographic information of the patients and anesthesia time by groups

	Midazolam group	Dexmedetomidine group	Control group	P_v
Age (years)	3.72±0.77	4.02±0.85	0.67±3.72	0.79 (ANOVA)
Weight (kg)	15.43±3.40	15.36±2.82	14.90±2.42	0.786 (ANOVA)
Gender Girl-boy	12:13	9:16	14:11	0.326 (Chi^2)
Anesthetic Time (min)	112.80±13.31	112.60±18.67	117.60±14.00	0.52 (ANOVA)

Table 2: Average BIS values in the studied groups by time

Time / Group	Immediately after anesthesia	10 minutes later	20 minutes later	30 minutes later	40 minutes later	50 minutes later	60 minutes later	Pv (Analysis of the variance of repeated one-way data)
Midazolam	53.60±5.59	54.44±4.46	52.20±4.78	52.24±3.97	51.52±3.04	53.04±3.50	52.24±5.28	0.311
Dexmedetomidine	49.12±3.91	47.76±4.43	47.76±4.14	46.28±5.55	48.16±4.71	45.84±4.22	46.52±4.61	0.127
Control	55.00±3.81	54.76±4.35	52.96±3.74	53.12±3.77	54.48±4.67	53.84±4.18	55.16±2.98	0.221
P value	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	

Table 3: Comparing P value based on One Way ANOVA (Tukey)

Time / Group	Immediately after anesthesia	10 minutes later	20 minutes later	30 minutes later	40 minutes later	50 minutes later	60 minutes later
Midazolam- Dexmedetomidine	0.002	p<0.001	0.001	p<0.001	0.017	p<0.001	p<0.001
Dexmedetomidine-Control	0.520	0.965	0.803	0.770	0.040	0.758	0.056
Midazolam- Control	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

According to ANOVA for repeated data, BIS varied significantly between different times ($p = 0.035$), but the interaction was insignificant ($p = 0.446$). In addition, there was a significant difference between the three groups ($p < 0.001$). In Tukey test, this test showed a significant difference between midazolam and dexmedetomidine ($p < 0.001$), midazolam and control ($p = 0.011$), and dexmedetomidine and control ($p < 0.001$), but the effect of age ($p = 0.484$) and weight ($p = 0.765$) was insignificant.

According to Kruskal-Wallis test, there was a statistically significant difference between the three groups according to PSAS ($p<0.001$). According to the Mann-Whitney test, there was a significant difference between midazolam prodrug and the control groups ($p<0.001$). Moreover, there was a statistically significant difference between the dexmedetomidine prodrug and the control groups ($p<0.001$). However, there were no significant differences between the two groups of midazolam and dexmedetomidine ($p=0.729$). In addition, according to Kruskal-Wallis test, there was a significant difference between the three groups in sedation score ($p<0.001$). Moreover, Mann-Whitney test showed a significant difference between the midazolam and the control groups ($p<0.001$). There was a significant difference between the dexmedetomidine prodrug group and the control group ($p<0.001$). In addition, there was a significant difference between dexmedetomidine and midazolam groups ($p=0.006$).

According to Kruskal-Wallis test, there were no significant differences between the three groups in terms of collaboration venipuncture ($p<0.001$). In addition, Mann-Whitney test showed a significant difference between the midazolam and the control groups ($p<0.001$). Furthermore, there was a statistically significant difference between the dexmedetomidine prodrug and the control groups ($p<0.001$). There were no significant differences between dexmedetomidine and midazolam groups ($p=0.665$). Regarding the behavior when waking up, according to Kruskal-Wallis test, there was a significant difference between the three groups in terms of behavior when awakening in recovery ($p=0.005$). Mann-Whitney test showed a significant difference between the midazolam and the control groups ($p=0.005$). In addition, there was a significant statistical difference between the dexmedetomidine prodrug and the control groups ($p=0.006$). There were no significant differences between dexmedetomidine and midazolam groups ($p=0.706$).

Chi-Square test showed no difference in the distribution of need for housing between midazolam and control groups (P = 0.529). However, according to the Fisher test, there was a significant difference between the need for housing between the dexmedetomidine and control groups (P=0.023). According to the Fisher test, there were no significant differences in the need for housing between dexmedetomidine and midazolam groups (P=0.098). In addition, Chi-Square test showed that there was no significant difference in the distribution of complications in recovery between the three groups (p = 0.424).

The results of one-way ANOVA showed that the time difference between the three groups was statistically insignificant (p = 0.549). However, the recovery time was significant between the three groups (p <0.001). Tukey test showed a significant difference between midazolam and dexmedetomidine groups in terms of recovery time (p=0.006). In addition, dexmedetomidine increased recovery time compared to control group significantly (p<0.001). Nonetheless, there were no significant differences between the midazolam and the control groups during recovery time (p = 0.299). ANOVA test for repeated data showed that the mean systolic blood pressure was significantly different between the three groups (p<0.001). In addition, there was a significant difference between different times (p<0.001). In addition, Tukey test showed a significant difference between midazolam and dexmedetomidine groups (p<0.001), midazolam and control (p <0.001), and dexmedetomidine and control (p <0.001). In addition, analysis of variance for repeated data showed that the mean heart rate was significantly different between the three groups (p <0.001). In completing the test, Tukey test showed a significant difference between midazolam and dexmedetomidine groups (p<0.001), and dexmedetomidine and control (p<0.001). However, midazolam and control groups showed no significant differences (p = 0.182).

Discussion

The study examined the effect of oral prodrug dexmedetomidine and midazolam on BIS mean scores in children as well as some other variables such as sedation, parental anxiety, separation from the parent and behavior while venipuncture and waking up in recovery. The results showed that dexmedetomidine prodrug, compared to midazolam, significantly increased the pre-operative sedation rate, but in case of anxiety during separation from parents, collaboration in venipuncture and behavior when waking up in recovery, while no significant differences were reported between the midazolam and dexmedetomidine group. In a consistent study, Liu et al. reported that using dexmedetomidine could be recommended as a suitable alternative because of the absence of side effects such as delusions, neurodegenerative changes, and reversible behavior (Liu et al., 2015). According to the results of the current study, the mean BIS scores in the dexmedetomidine group at all times was significantly lower than that of the midazolam and control groups. However, midazolam did not significantly differ from the control group, so we found that the dexmedetomidine increases the anesthetic depth compared to midazolam, and because of this positive effect in the depth of anesthesia, it can reduce the need for anesthetic drug to reach the desired anesthetic depth for proper dental practice of children under general anesthesia and reduce the dose-dependent effects. As some studies have reported the relationship between BIS values and the age of patients, a small age range in children who were also the most likely candidate group for dental treatment under anesthesia was selected to compare the BIS score without age. In a study, Le Guen et al., France reported the value of anesthetic used to induce anesthesia was significantly lower in patients receiving dexmedetomidine. The study used BIS monitoring method. They concluded that dexmedetomidine is useful as an anesthetic to reduce anesthetic substance and cause postoperative analgesic effects (Le Guen et al., 2014). This conclusion is close to that of the current study. However, the study of the recovery time showed no effect on the recovery and prolonged duration of the study, different from those of ours regarding the prolongation of recovery time in the dexmedetomidine group. The reason for this difference can be due to the administration of the dexmedetomidine drug performed during the study. In a review study (2014), dexmedetomidine has proven more satisfactory in parental separation compared with midazolam (Peng et al., 2014). As the studies reviewed had heterogeneity, and some of them prescribed the drug nasally, the difference in the results of this study with ours could be justified. In this study, the sedation rate with midazolam at 30, 45 and 60 minutes was significantly higher than the starting dose of prodrug compared to dexmedetomidine, but there were no differences between the groups, which may be due to the onset of the effect and peak effect of midazolam compared to dexmedetomidine. In a study in this area, it has been reported that the onset of the dexmedetomidine effect is 30 minutes and the onset of the effect of midazolam is 15 minutes (Kumari et al., 2017). These results are not in line with the results of our study, which was more satisfactory concerning dexmedetomidine sedation at 45 minutes post-prodrug. Another study showed that more patients with dexamethomidine prodrug at the time of separation from their parents, as well as induction of anesthesia, had a good degree of sedation compared to those receiving midazolam. In addition, patients' behavior while waking up in recovery was comparatively satisfactory in both studies (Kumar et al., 2017). The results of this study were consistent with those of ours in these three areas. Almost all the studies similar to ours, showed an analgesic effect after dexmedetomidine administration significantly better than other sedative medications, due to the pharmacological properties mentioned for this drug. Moreover, dexmedetomidine is associated with shortening postoperative care time and reduces PACU time, which is not in line with our results that recovery of dexmedetomidine was prodrug by dose regimens compared to midazolam (Feng et al., 2017). Other clinical studies also reported improvement in sedation and separation from parents, as well as reduction of PACU duration with dexmedetomidine compared to other sedative agents, such as midazolam or propofol, and were not in line with our results in terms of PACU time and separation from parents, but in terms of sedation were similar (Pasin et al., 2013; Ali and Abdellatif, 2013; Hadi et al., 2015). A meta-analysis study due to the use of dexmedetomidine prodrugs reported a longer wake up time and discharged from PACU, which was similar to the results of our study (Amorim et al., 2017). The present study compares dental procedures under general anesthesia in the range of 1 to 2.5 hours, so BIS results cannot be completely generalized to longer

processes. As studies in the field of dental anesthesia prodrug have been less prevalent, the study used the results of surgical and other medical procedures, which may be inappropriate in terms of pain and the level of anesthesia required at dentistry.

Conclusion

Prescribing dexmedetomidine as a prodrug reduces BIS scores significantly during general anesthesia and the increase in the anesthetic depth of midazolam. Thus, it can reduce the anesthetic depth during the maintenance phase with less anesthetic drug. Given other features of this drug that are comparable to midazolam and comparable to less side effects, it can be introduced as an alternative to midazolam.

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