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ORIGINAL ARTICLES

Comparison of the effect of intravenous ketamine and midazolam as a premedication in children undergoing cochlear implantation at the time of separation from parents

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Abstract: *Background and aim: Preoperative anxiety and fear of separation from parents are some of the most important preoperative problems for children with deaf muteness. Here, the effect of intravenous administration of ketamine and midazolam was compared on sedation in children who candidates for choral cochlear implantation at the time of separation from parents.*

Patients and methods: This double-blind, prospective clinical study was performed on 74 children with deaf-muteness before cochlear implantation. Patients were randomly divided into two groups, midazolam (0.1 mg /kg) and ketamine (1 mg/kg). The sedation anxiety score scale (SASS) form was filled in to assess the anxiety and sedation status for each child. The children's relaxation score from recovery was assessed by the PACU sedation score scale (PACUSSS).

Results: The average of the children's anxiety score after the injection of both drugs during the separation from their parents was 3, and there was no significant difference in the mean of SASS between the two groups (p>0.05). The mean PACU sedation score scale in both ketamine and midazolam groups was 1.08 ± 0.89 and 1.32 ± 1.01, respectively (p = 0.27). The mean of extubation and recovery times in the ketamine group were 10.44 ± 4.47 and 30.27 ± 6.87, respectively, while the mean extubation and recovery times in the midazolam group were 11.83 ± 3.33 and 29.81 ± 6.31 minutes, respectively.

Conclusion: Both ketamine and midazolam caused equal sedation scores in children with deaf muteness at the time of separating from their parents.

Keywords: *deaf-muteness children, cochlear implantation, ketamine, midazolam, sedation, anxiety*

INTRODUCTION

According to the world health organization (WHO), more than 250 million people worldwide suffer from disabling hearing loss and 34 million of which are children [1, 2]. Pediatrics hearing loss, which often results from genetic defects, can be associated with multiple problems. Children with hearing impairment not only have difficulty talking, but also they do not respond to sounds [2]. Therefore, early diagnosis and treatment of this complication are very important for the disease improvement and quality of their life.

Cochlear implantation remains the only reliable therapeutic option for patients with hearing loss and deaf-mutism [3, 4]. However, this surgery is time-consuming and requires general anesthesia which may be associated with

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emergence agitation, restlessness, disorientation, and anxiety in children [5, 6]. Deaf-muteness children like healthy children recognize environmental events and preoperative anxiety and the fear of separation from parents are some of the most important preoperative problems for these children [5, 7]. Therefore, sedation or premedication is often needed for deaf-muteness children during their separation from parents and entrance to the waiting room.

Midazolam and ketamine are commonly used as premedication in children undergoing medical procedures [8]. Midazolam is an imidazole benzodiazepine that has depressant effects on the central nervous system and provides sedation, muscle relaxation, and amnesia before procedures [9, 10]. It has a rapid onset of action following oral, intravenous, intramuscular, nasal, and rectal administration [10]. A great number of studies have used midazolam as a safe premedication without any serious adverse effects for sedation of children during procedures [11, 12]. It has been also shown that preoperative oral midazolam reduces separation anxiety and emergence agitation in children following anesthesia [6].

Ketamine is a general anesthetic with sedative and analgesic properties which is commonly used as a premedication for sedation in children [13]. Its favorable effects on cardiovascular and pulmonary parameters are a reason by which physicians use this drug as a sedative [14, 15]. Therefore, these data indicated that both midazolam and ketamine are safe effective sedative premedication agents which can be used in children undergoing painful producers [16]. Although many studies have investigated the effect of midazolam and ketamine for sedation of children following medical surgery, no study evaluated the preoperative effect of these drugs on sedation in children with hearing loss and deaf mutism. Therefore, we designed this study, for the first time, to compare the preoperative effect of midazolam and ketamine as premedication on sedation in deaf-mutism children during their separation from parents and before cochlear implantation.

PATIENTS AND METHODS

Patients

This double-blinded, prospective clinical trial study was conducted on 74 children with deaf-muteness who were referred to Baqiyatallah Hospital for cochlear implantation from June 2019 to November 2019.

This study was registered in the Iranian Registry of Clinical Trials under no. IRCT20161022030421N3 cod. The protocol of the study was confirmed by the ethics committee of Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1397.031).

Written informed consents were signed by all parents. A questionnaire containing demographic data of all patients (e.g. age, sex, weight, and history of any previous illness) was filled before surgery. Children aged from 6 months to 5 years old, and American Society of Anesthesiology (ASA) Class I and II were included in the study. Children who met the following criteria were excluded from the study: (i) sensitivity to ketamine or midazolam, (ii) history of treatments with neuropsychiatric drugs, (iii) age less than 6 months, (iv) increased intracranial pressure (ICP), (v) history of seizure, and (vi) history of chronic diseases such as diabetes, liver disease, and upper and lower respiratory tract infection.

Intervention and measurements

After preliminary considerations and patient selection based on inclusion and exclusion criteria, using a computer-generated randomization list, children were divided into two groups of midazolam (n=37) and ketamine (n=37). Intravenous (IV) access was performed using local anesthetic cream 1 hour before their admission in the operating room. The sedation anxiety score scale (SASS) questionnaire was filled out by an observer who was unaware of the study groups. The questionnaire was filled out based on children's behavior in the pre-operative preparation room when they were with their parents. The SASS score ranged from 1 to 5 based on the child's status (Table 1).

Table 1: The SSAS scoring questionnaire

Score	Status	More details
1	Unconscious	Sleepy, no response to mild motor stimulations
2	Sleepy	Sleepy, may have closed eyes but react to mild stimulations
3	Normal	Calmly, comfortable sited or sleeping with eyes open
4	Anxious	Looks afraid, no adhesion to parents, without crying
5	Very rest less	Crying, stomping, or adhesion to parents

After SASS scoring, midazolam (0.1 mg/kg) or ketamine (1 mg/kg) drugs were intravenously injected into children by another person who was unaware of the study groups. Following the injection of the drug, pulse oximetry monitoring was provided for patients. Furthermore, the SASS form was filled out again following the drug's injection just after children felt calming and when they were separating from their parents. Children were then transferred to an operating room and the observer measured the extent of child tolerance during the anesthetic

induction by SASS.

Pethidine (1 mg/kg) and atropine (0.2 mg/kg) were injected into children as premedication and then anesthesia induction was performed with propofol and atracurium. Sevoflurane was applied to maintain the anesthesia. Cefazolin, hydrocortisone, and dexamethasone were injected into all children. All children also received ondansetron (1 mg/kg). Children were transferred to the recovery room after surgery and the observer assessed the sedation rate by the post-anesthesia care unit (PACU) sedation score scale (PACUSSS) (Table 2). The PACUSSS score ranged from 0 to 4 based on the child's status. When children obtained the safe discharge criteria from the recovery room, they were transferred to the section. The observer also recorded any postoperative side effects or complications such as nausea, vomiting, emergence agitation, and decreases in arterial oxygen saturation below 92%. The duration of surgery, extubation time, and recovery time was also recorded.

Table 2: The PACU sedation score scale questionnaire

Score	Status
0	Slept, calmly, and without crying
1	Whining, Not rest less
2	Crying, Slightly rest less
3	Continuous crying

Statistical analysis

The results of this study were analyzed by SPSS software (IBM, version 19). Quantitative data were analyzed using the descriptive program and presented as Mean ± SD. Crosstabs and Chi-Square tests were used to compare the percentages or frequencies between the two groups. The comparison of the mean of parametric data between midazolam and ketamine groups was compared by independent student samples-test. In this study, $p< 0.05$ was considered statistically significant.

RESULTS

In this study, 74 patients were entered into the survey. 32 patients were boys (43.2%) and 42 patients (56.8%) were girls. There was no significant difference in the percentage of male and female genders between midazolam and ketamine groups (p=0.24; Table 3).

The mean age of all participated patients was 29.55 ± 16.92 months. There was no significant difference in the mean age of patients between the ketamine and midazolam groups (p=0.94; Table 3).

The mean weight of all participated patients was 13.18 ± 3.74 kg. There was no significant difference in the mean weight of patients in the ketamine and midazolam groups (p=0.72; Table 3).

Table 3: Demographic characteristics of patients in both groups

Parameters	Midazolam	Ketamine	p-value
Age (months)	29.7 ±17.68	29.4 ±16.36	0.94
Gender			
Male (%)	18 (48.64%)	14 (37.83%)	0.24
Female (%)	19 (51.35%)	23 (62.16%)	
Weight (kg)	13.33 ± 4.3	13.02 ± 3.13	0.72

A comparison of the mean of SASS between the ketamine and midazolam groups is shown in Table 4. There was no significant difference in the mean of each score between the two groups. The mean score of children status in the waiting room with their parents was approximately 4, indicating they were anxious. The mean score of children's status after drug injection, when separating from their parents was decreased to around 3, which suggests the normal status of the patients in both groups. Furthermore, the mean score of the patient's condition at the anesthetic induction time ranged from 2.5 to 3, which indicates they had sleepy or normal conditions.

Table 4: Comparison of the mean of SASS between ketamine and midazolam groups

Parameters	Midazolam	Ketamine	p-value
In the waiting room with parents	4 ± 0.78	3.89 ±0.9	0.58
After drug injection, when separating from parents	2.91 ± 0.49	2.83 ± 0.55	0.5
Anesthetic induction time	2.62 ± 0.68	2.59 ± 0.68	0.86

The prevalence of each SSAS item in the waiting room before pre-medication is presented in Table 5. There was no significant difference in the frequency of each item in patients between the two groups (p=0.6). Most of the children (40.54% in the ketamine group and 48.64% in midazolam groups) had the anxious condition before premedication. Furthermore, 27.02% of children in the both ketamine and midazolam groups were very restless. The percentage of normal conditions in children in the midazolam and ketamine groups was 21.62% and 29.72%, respectively.

The prevalence of each SSAS item after drug injection, when separating from their parents is presented in Table 5. No significant difference was found in the frequency of each item between the two groups (p=0.68). Most of the patients (67.56% in the ketamine group and 75.67% in midazolam groups) had the normal condition. 24.32% of children in ketamine and 16.21% of patients in the midazolam group were sleepy. Only 8.1% of patients in both groups had

anxiety conditions.

The percentage of each SSAS item at the time of anesthetic induction is shown in Table 5. There was no significant difference in the frequency of each item between the two groups (p=0.69). Most of the patients (54.05% in the ketamine group and 48.64% in midazolam groups) had the normal condition at the time of anesthetic induction, while 40.54% of children in ketamine and 45.94% of patients in the midazolam group were sleepy. Only 2.1% of patients in both groups were very resting less.

Table 5: The prevalence of pediatrics SSAS in different conditions

Parameters	Midazolam	Ketamine	p-value
Before pre-medication			
Unconscious	0	1 (2.7%)	
Sleepy	1 (2.7%)	0	
Normal	8 (21.62%)	11 (29.72%)	0.6
Anxious	18 (48.64%)	15 (40.54%)	
Very rest less	10 (27.02%)	10 (27.02%)	
Separating from parents			
Unconscious	0	0	
Sleepy	6 (16.21%)	9 (24.32%)	
Normal	28 (75.67%)	25 (67.56%)	0.68
Anxious	3 (8.1%)	3 (8.1%)	
Very rest less	0	0	
Anesthetic induction time			
Unconscious	0	1 (2.7%)	
Sleepy	17 (45.94%)	15 (40.54%)	
Normal	18 (48.64%)	20 (54.05%)	0.69
Anxious	1 (2.7%)	0	
Very rest less	1 (2.7%)	1 (2.7%)	

The prevalence of children's relaxation scores during the recovery time can be seen in Table 6. There was no significant difference in the prevalence of children's condition between the two groups (p=0.64). Most of the patients (37.83% in ketamine and 32.43% in midazolam groups) had to whine without rest less, whereas 29.72% of patients in ketamine and 24.32% in midazolam groups were kept without crying. Only 5.4% of children in ketamine and 13.5% in midazolam were continuously crying.

Table 6: The prevalence of children relaxation scores during the recovery time

Children status	Midazolam	Ketamine	p-value
Slept, calmly and without crying	9 (24.32%)	11 (29.72%)	0.64
Whining, Not rest less	12 (32.43%)	14 (37.83%)	
Crying, Slightly rest less	11 (29.72%)	10 (27.02%)	
Continuous crying	5 (13.51%)	2 (5.4%)	

There was no significant difference in the mean of extubation (p=0.2) and recovery times (p=0.76) between the two groups. The mean of extubation and recovery times in the ketamine group were 10.44 ± 4.47 and 30.27 ± 6.87 minutes, respectively, while the mean extubation and recovery times in the midazolam group were 11.83 ± 3.33 and 29.81 ± 6.31 minutes, respectively.

We didn't observe any significant side effects from both studies' drugs. In the waiting room, no child showed a drop in SPO2 below 92% and there was no need for mask ventilation for these patients. Nausea and vomiting were the most important complications after recovery. Three patients (8.1%) in the ketamine group had nauseous and 10 (27.02%) in the midazolam group suffered from nausea (p=0.023). Also, one patient in the midazolam group had vomiting. None of the patients in both groups experienced emergence agitation and decreased arterial oxygen saturation in recovery time.

Interestingly, our findings showed that 37.03% of children in the midazolam group start laughing after receiving premedication (Figure 1), but this condition was not observed in patients in the ketamine group.

Figure 1: Children's reaction after premedication with midazolam. About 37% of children in the midazolam group start laughing after receiving this premedication, but this status was not observed for children in the ketamine group

DISCUSSION

In this study, we compared the intravenous administration effect of ketamine and midazolam as a premedication in children undergoing cochlear implants at the time of separating from their parents. To the best of our knowledge, the use of intravenous midazolam and ketamine for sedation of children with deaf-muteness before cochlear implantation has not been investigated yet. Our data have revealed that there was no significant difference in the mean anxiety score between the ketamine and midazolam groups. Children were anxious (mean sedation anxiety score of 4) before premedication with ketamine and midazolam, while they reached normal status (mean sedation anxiety score of 3) after premedication. Furthermore, most children had sleepy and normal status after premedication at the time of anesthetic induction. There was no significant difference in the mean PACU sedation score between the ketamine and midazolam groups. Furthermore, we didn't find any serious adverse effects in each group; however, nausea occurred more frequently in the midazolam group. More importantly, we found that 37.03% of children in the midazolam group started laughing after receiving the premedication, while this condition was not observed in patients in the ketamine group. However, this mechanism is unclear.

A great number of studies compared the effect of ketamine and midazolam as premedication in the prevention of anxiety, pain score, and emergence agitation in children and adults before entering the operating room. For example, Jeong et al. [17] demonstrated that intravenous administration of ketamine (1 mg/kg) before entering the operating room significantly reduces separation anxiety, postoperative pain score, and also the incidence of emergence agitation in children following ophthalmic surgery. Ozdemir et al. [18] reported that intravenous, oral, and rectal administration of ketamine and midazolam had equal sedation effects in children with malignancy. Several studies compared the combination of ketamine and midazolam as premedication in different groups. For example, Golpayegani et al. [19] compared the oral administration of ketamine and midazolam as sedative agents in pediatric dentistry. They found that the Ketamine-Midazolam combination provides sufficient sedative effect in children's behavior. In another study, Wathen et al. [20] found that intravenous ketamine and its combination with midazolam had equal effective sedation in children. They also found that vomiting occurred more frequently in the ketamine group, while oxygen desaturation occurred more frequently in the ketamine-midazolam group. Barkan et al. [21] evaluated the efficacy of oral midazolam alone and oral midazolam-ketamine combination in 60 children requiring laceration repair. They didn't find a significant difference in the mean pain score between the two groups; however, midazolam and ketamine combination caused deeper sedation than midazolam alone. Additionally, no clinically significant adverse effects were found in either group which was in agreement with the results of our study. In another study, the effect of high dose oral ketamine (10 mg/kg) with midazolam (0.7 mg/kg) was evaluated in children during laceration repair [12]. The results showed better tolerance to local anesthetics and deeper sedation in children treated with ketamine with no serious adverse events in both groups [12]. Kim et al. [6] investigated the intravenous effect of ketamine (1 mg/kg) and midazolam (0.1 mg/kg) on emergence agitation in children at the postanaesthetic care unit. They showed that premedication with these drugs significantly decreases preoperative anxiety. However, they found that premedication with ketamine was more effective than midazolam in the prevention of early post-operative emergence agitation. Similarly, in this research, we used the same doses of ketamine and midazolam for the improvement of preoperative anxiety and sedation in children. Our data showed that premedication with ketamine and midazolam significantly improves anxiety and sedation in children without any serious side effects.

Our findings have also revealed that there is no significant difference in the mean of extubation and recovery times between the two groups. Similarly, Kim et al. [6] didn't found a significant difference in the mean of extubation and recovery times between children in midazolam and ketamine groups. Ozdemir et al. [18] reported that ketamine and midazolam are equally effective in recovery time improvement. Recent evidence has proposed that the recovery time in patients receiving ketamine and midazolam is dependent on multiple factors such as drugs dosage, kind of surgery, and the physician on call. For example, previous studies didn't observe a significant improvement in recovery times when children were treated with higher doses of

ketamine (2.5-3 mg/kg) and midazolam (0.25-0.5 mg/kg). Several studies reported higher recovery times in children treated with higher doses of midazolam (0.5 mg/kg) and ketamine (5 mg/kg) [21]. Abdolahi et al. [22] reported that low dose administration of ketamine (0.5 mg/kg) during anesthesia induction did not affect postoperative pain score, postoperative nausea, and vomiting, as well as perioperative additional analgesic requirements in ophthalmic surgery. However, premedication with ketamine improved the extubation time. Based on these data, in our study, children were treated with 0.1 mg/kg midazolam and 1 mg/kg ketamine. Therefore, these data suggest that both drugs are equally effective for the prevention of anxiety in children before surgery and separating from their parents. However, the dose of drugs and kind of surgery are important factors affecting sedation and anxiety which should be considered before administration.

CONCLUSION

In summary, the results of the current clinical study indicated that both midazolam and ketamine are equally safe with desirable sedation effects on children with deaf-muteness before separating from their parents for cochlear implantation. Premedication with 0.1 mg/kg midazolam or 1 mg/kg ketamine decreases preoperative anxiety in these cases. Both drugs improved recovery and extubation times without any serious adverse effects. However, nausea occurred more frequently in the midazolam group. More importantly, children in the midazolam group start laughing after premedication with this drug which caused their parents felt well, while children in the ketamine group didn't show this reaction. Further studies with a larger sample size should be conducted to determine the optimal dose and to establish the safety of the combination therapy.

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