

Available online at www.sciencedirect.com

journal homepage: <http://www.elsevier.com/locate/medici>

Original Research Article

An evaluation of the effectiveness and safety of midazolam in children undergoing dental surgery

Lina Kalibatienė^{a,*}, Vytenis Kalibatas^b, Andrius Macas^a, Darius Trepenaitis^a

^a Department of Anesthesiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

^b Department of Health Management, Faculty of Public Health, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

ARTICLE INFO

Article history:

Received 23 September 2014

Received in revised form

4 April 2015

Accepted 22 April 2015

Available online 12 May 2015

Keywords:

Children

Premedication

Midazolam

Dental surgery

ABSTRACT

Objective: The aim of this study was to evaluate the effectiveness and safety of oral midazolam in children undergoing dental surgery.

Materials and methods: A prospective, randomized, controlled trial was conducted to assess the effectiveness and safety of midazolam in children. Patients aged 2–9 years who underwent dental surgery under general anesthesia were randomly allocated into one of the four groups: midazolam 0.2 mg/kg dose group ($n = 30$); midazolam 0.21–0.4 mg/kg dose group ($n = 15$); midazolam more than 0.41 mg/kg dose group ($n = 15$) or the placebo group ($n = 31$). The effectiveness of midazolam on sedation was assessed by the evaluation of vital signs, such as the respiratory and heart rate, oxygen saturation and the patients' reactive behaviors, in comparison with the placebo.

Results: The scores of the ratings for sleep, movement and crying, as well as patients' reactions at the moment of separation from their parents and their collaboration with the staff were statistically significantly better among patients who received oral midazolam compared with the placebo. There were statistically significant direct correlations between the doses of midazolam and higher sleep, movement, crying and reaction scores 30 min after premedication as well as higher scores of patients upon separation from their parents. There were only a few clinically insignificant side effects.

Conclusions: Oral midazolam, at a single dose from 0.2 to 0.6 mg/kg, is effective and safe, and provides the expected sedative effects in children required by premedication for dental surgery.

© 2015 Lithuanian University of Health Sciences. Production and hosting by Elsevier Sp. z o.o. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author at: Department of Anesthesiology, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50161 Kaunas, Lithuania. Tel.: +370 61809699; fax: +370 37326371.

E-mail address: lina.kalibatiene@gmail.com (L. Kalibatienė).

Peer review under the responsibility of the Lithuanian University of Health Sciences.



<http://dx.doi.org/10.1016/j.medici.2015.04.001>

1010-660X/© 2015 Lithuanian University of Health Sciences. Production and hosting by Elsevier Sp. z o.o. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Perioperative anxiety and the resulting lack of cooperation during the induction of anesthesia is a common problem for pediatric anesthesia [1]. For some children, premedication may be required to facilitate smooth separation from their parents [2]. Relieving preoperative anxiety is an important concern for the pediatric anesthesiologist. Data from a few studies showed that midazolam can be used for premedication in children [3,4] and that it improves the postoperative behavior and mood and reduces the incidence of nightmares, apathy, eating disorders, enuresis, stress and other forms of adverse postoperative behaviors [5]. Parents very often agree with premedication, but refuse the commercially available intravenous or intramuscular route of midazolam administration for their child due to the painful and frightening procedure. The oral form of midazolam for pediatric premedication presents an opportunity to solve this problem [6,7]. Research studies prove that the administration of oral midazolam shows the expected sedative effects on better post-administrative behavior and reduced preoperative anxiety among patients [7,8]. Data from a few clinical studies have supported the hypothesis that the oral administration of midazolam in a 0.5–1.0 mg/kg dose is an effective and safe medicine, significantly reduces anxiety and improves overall tolerance for the premedication of children undergoing dental surgery procedures [2,9,10].

The intravenous midazolam formulation has authorization in EU for use in children as an intravenous sedative before and during minor medical, dental and surgical procedures, such as gastroscopy, endoscopy, cystoscopy, bronchoscopy and cardiac catheterization. Midazolam tablets have authorization in the EU for the short-term treatment of insomnia and are contraindicated in children due to limited information about their effectiveness and safety. The oromucosal solution of midazolam hydrochloride has authorization in the EU for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents [11,12], but its use as a premedication is unlabeled due to a lack of effectiveness and safety data.

Midazolam, with its rapid onset and relatively short duration of action, could be a useful premedication for decreasing preoperative anxiety and facilitating separation from parents with fewer unwanted side effects, but further studies are required.

Due to the limited evidence on the use of oral midazolam for premedication prior to dental surgery, our research aimed to evaluate the effectiveness and safety of oral midazolam premedication in children undergoing dental surgery. The objectives were: (1) to evaluate the sedative effect of oral midazolam in children at doses from 0.2 to 0.6 mg/kg and to compare with the data from the placebo and (2) to evaluate the side effects of the same doses of oral midazolam in children.

2. Materials and methods

This study was designed as a single midazolam dose, blinded, prospective, randomized, controlled trial to evaluate the

effectiveness and safety of midazolam for the premedication of children. The sample size was calculated based on the hypothesis that the oral administration of midazolam as a premedication for children is clinically efficient and safe.

With the approval of the Kaunas Regional Bioethics Committee (approval No. BE-2-39) and written informed consent, 93 class I (normally healthy patients) or class II (patients with mild systemic disease) children according to the American Society of Anesthesiology (ASA) classification, from 2 to 9 years of age, who were undergoing dental surgery under general anesthesia were included in the study between January 2012 and October 2013. The exclusion criteria included: (1) a history of hypersensitivity to midazolam; (2) a history of chronic illness; (3) patients who refused to take medicine for sedation; and (4) patients whose parents were not present at any time during the period starting from the administration of the premedication medicine until the child left the operating room.

Patients whose parents agreed to their participation in the study were allocated randomly by the sealed envelope technique to one of four groups. The randomization and blinding procedures were performed by an individual with no clinical involvement in the study. To investigate the effectiveness of oral midazolam in children, we used the dose from 0.2 to 0.6 mg/kg and evaluated the response by monitoring vital signs and the behavior of patients. We randomly allocated the patients to one of four groups: the single midazolam 0.2 mg/kg dose group (Group 1, $n = 30$); the single midazolam 0.21–0.4 mg/kg dose group (Group 2, $n = 15$); the single midazolam 0.41 mg/kg or higher dose group (Group 3, $n = 15$) or the control group with the placebo (Group 4, $n = 31$). As the commercial soluble pharmaceutical form was not available on the market, we used the injectable midazolam prepared in a 5-ml needless syringe with colorful and cheerful pictures to administer the dose sublingually for the patients in Group 1. For the patients in Group 2 and Group 3, we used midazolam 7.5-mg tablets which are available on the market for premedication of adult patients. All patients received the test dose or the placebo 30 min before induction with anesthesia. The parents of all of the children were present from the start of premedication until transfer to the operating room. The patient characteristics, including sex, age, weight, ASA class and oral midazolam dose, are presented in Table 1 by group allocation.

The effectiveness of midazolam on sedation was assessed by an evaluation of vital signs, including respiratory and heart symptoms, pulse oxygen saturation (SpO_2) and the patients' reactive behavior, compared to those of patients on the placebo. Effectiveness and safety was monitored 30 min before premedication and repeatedly in the operating room every 30 min after the premedication for all four groups.

Patient behavior was assessed using a modified Houpt Behavior Rating Scale by rating sleep [score: 1 = anxious, excited; 2 = fully awake, alert; 3 = drowsy, disoriented and 4 = asleep], movement [score: 1 = violent movement, interrupting treatment, 2 = continuous movement making treatment difficult, 3 = controllable movement that does not interfere with treatment and 4 = no movement] and crying [score: 1 = hysterical crying that demands attention, 2 = continuous, persistent crying that makes treatment difficult,

Table 1 – Patient characteristics by group allocation.

Characteristics	Patients' groups				P value
	Liquid group 0.2 mg/kg (n = 30)	Tablets group 0.21–0.4 mg/kg (n = 15)	Tablets group 0.41 mg/kg and higher (n = 15)	Control group (n = 31)	
Sex (M/F), n	19/11	5/10	8/7	17/14	0.57
Age, years	3.97 ± 1.27	6.13 ± 1.5	3.73 ± 0.96	4.50 ± 1.63	0.44
Weight, kg	17.5 ± 4.06	23.07 ± 2.99	15.07 ± 1.88	19.03 ± 5.33	0.64
ASA class (I/II), n	26/4	14/1	13/2	28/3	0.46
Average dose of midazolam, mg/kg	0.2	0.3299 ± 0.04	0.4963 ± 0.06	0	–

Values are mean ± SD unless otherwise stated.

3 = intermittent, mild crying that does not interfere with treatment and 4 = no crying]. A higher score indicates better sedation effects.

The reaction of the patients was evaluated at the moment of separation from their parents in the ward, 20 min after premedication and just before leaving for the operating room [score: 1 = poor (cries and resists physically), 2 = fair (cries only), 3 = good (does not cry) and 4 = excellent (happy and satisfied)], and by their collaboration with the staff in the operating room in terms of face mask acceptance 30 min after premedication [score: 1 = poor (does not cooperate at all, markedly resistant, impossible to place the face mask despite coaxing), 2 = fair (does not cooperate, moderately resistant, the face mask is placed after extensive coaxing); 3 = good (cooperates, but is mildly resistant and allows the placement of the face mask with minimal coaxing) and 4 = excellent (cooperative, allows for the placement of the face mask without coaxing)]. Higher scores in these two domains indicate calmer conditions and cooperative behavior, respectively.

The potency of sedation was considered to be successful when the Houpt Behavior Rating Scale for sleep, movement and crying after premedication achieved scores of 3 and 4 for each variable or to be unsuccessful when the behavior scales for sleep, movement and crying 30 min after premedication received scores of 1 and 2.

The overall sedation effectiveness was considered to be successful when the sum of the Houpt Behavior Rating Scale score for sleep, movement and crying 30 min after premedication was 7 or more score for all three variables combined and to be unsuccessful when the sum of the Houpt Behavior Rating Scale score for sleep, movement and crying 30 min after premedication was 6 or less for all three variables combined. The overall reaction of the patients was considered to be positive when the sum of the patient behavior scores from the moment of separation from the parents to the collaboration with the staff in the operating room was evaluated to be 5 or more and was considered to be negative when the sum was 4 or less.

Statistical analysis was performed, and the results were tested for statistical significance using Statistica software v. 9.0. The sedation scores and clinical variables were reported as the mean and standard deviation (SD). Data were analyzed using Kruskal–Wallis test for analyzing multiple groups and t-test for the differences in means between two groups. Pearson's Chi-square (χ^2) test for association between two categorical variables or Fisher exact test when sample sizes

were small in a 2×2 contingency tables were calculated. Spearman rank correlation coefficient was used to determine the relationships between two variables. Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Effectiveness

There were no statistically significant differences in the before and 30 min after sedation respiratory rate, heart rate and pulse oxygen after sedation measures in all three midazolam groups compared with the placebo. However, the midazolam patients' reaction and behavior results were statistically significantly higher following premedication (i.e., better sedative effects) compared to the sleep, movement and crying scores of the control group (Table 2).

There were no statistically significant differences between the sleep, movement and crying scores prior to premedication. In a comparison of the sleep, movement and crying before and after premedication scores for each group, there was a statistically significant decrease in the sleep rating before premedication (average score 1.73) and after premedication (average score 1.5), in the movement rating before premedication (average score 3.53) and after premedication (average score 2.87) and in the crying rating before premedication (average score 3.4) and after premedication (average score 2.77) in the control group, while these scores increased in all three midazolam groups.

In a comparison of the individual behavioral and reaction changes after the administration of oral midazolam with the control group, there were statistically significant sedative effects on the sleep and movement scores of all patients who received oral midazolam. Statistically significant sedative effects were found between the individual patient reaction scores at the moment of separation from their parents and their collaboration with staff in the operating room among the patients who received doses of midazolam (0.21–0.4 and 0.41 mg/kg and higher) compared with the control group (Table 3).

An evaluation of the overall sedative effects of the administration of oral midazolam on behavior proves that there are statistically significant sedation effects in patients who received midazolam at doses of 0.21–0.4 and 0.41 mg/kg and higher compared with the control group (Table 4).

Table 2 – The patients' reaction and behavior scores after premedication in all groups.

Variables	1 group (0.2 mg/kg)	2 group (0.21–0.4 mg/kg)	3 group (0.41 mg/kg and higher)	4 group (Control)	P values comparing Control group with		
					1 group	2 group	3 group
<i>Reaction variables (scores)</i>							
Reaction at the moment of separation 20 min after premedication	3.12 ± 1.03	3.20 ± 0.86	3.40 ± 0.99	2.43 ± 1.30	0.11	0.04	0.017
Collaboration with the staff at the operating room 30 min after premedication	2.67 ± 0.76	2.89 ± 0.52	3.23 ± 0.62	2.07 ± 0.87	0.04	0.01	0.004
<i>Houpt Behavior Rating Scale variables (scores)</i>							
Rating for sleep 30 min after premedication	2.07 ± 0.83	2.20 ± 0.77	2.40 ± 0.74	1.5 ± 0.51	0.0024	0.007	0.002
Rating for movement 30 min after premedication	3.40 ± 0.85	3.42 ± 0.91	3.73 ± 0.79	2.87 ± 1.17	0.047	0.041	0.032
Rating for crying 30 min after premedication	3.66 ± 0.80	3.67 ± 0.49	3.73 ± 0.79	2.77 ± 1.22	0.045	0.007	0.003

Table 3 – A comparison of the behavioral and reaction changes after the administration of oral midazolam among children in the treatment groups compared with children in the control group.

Variables	1 group (0.2 mg/kg)	2 group (0.21–0.4 mg/kg)	3 group (0.41 mg/kg and higher)	4 group (Control)	P values comparing Control group with		
					1 group	2 group	3 group
<i>Houpt Behavior Rating Scale variables (no. of patients with changed/unchanged score)</i>							
Rating for sleep	16/14	7/8	9/6	1/30	0.000	0.000	0.000
Rating for movement	5/25	3/12	4/11	0/31	0.024	0.029	0.008
Rating for crying	2/28	2/13	3/12	1/30	0.610	0.244	0.098
<i>Reaction variables (no. of patients with score > 2/≤2)</i>							
Reaction at the moment of separation	21/9	14/1	14/1	17/14	0.22	0.016	0.016
Collaboration with the staff	19/11	13/2	10/5	16/15	0.35	0.026	0.005

Table 4 – A comparison of the overall sedative effects after the administration of oral midazolam in children in the treatment groups compared with children in the control group.

Variables	1 group (0.2 mg/kg)	2 group (0.21–0.4 mg/kg)	3 group (0.41 mg/kg and higher)	4 group (Control)	P values comparing Control group with		
					1 group	2 group	3 group
<i>No of patients with positive/negative changes</i>							
Behavior by Houpt Behavior Rating Scale variables ^a	23/7	13/2	14/1	17/14	0.072	0.049	0.016
<i>No of patients with score positive/negative changes</i>							
Behavior by reaction variables ^b	22/8	13/2	14/1	16/15	0.080	0.026	0.007

^a The change was considered to be negative or insufficient when the sum of the Houpt Behavior Rating Scale scores were 6 or less after premedication and was considered to be positive when the sum of the Houpt Behavior Rating Scale scores were 7 or more after premedication.

^b The change was considered to be negative or insufficient when the sum of the reactional scores were 4 or less after premedication and was considered to be positive when the sum of the reactional scores were 5 or more after premedication.

There were statistically significant direct correlations between the administration of midazolam and higher sleep and crying scores 30 min after premedication as well as higher scores of the patients' reactions upon separation from their parents. A statistically significant indirect correlation was

found with the respiratory rate 30 min after premedication. Also, there were statistically significant direct correlations between the doses of midazolam and higher sleep, movement, crying and reaction scores 30 min after premedication as well as higher scores of patients upon separation from their

Table 5 – The correlation between the administration of midazolam, the dose of midazolam and the clinical, behavioral and reaction changes in the patients after premedication.

Variables	Administration of midazolam		Dose of midazolam (mg/kg)	
	r	P value	r	P value
Respiratory rate	-0.29	<0.05	-0.24	<0.05
Heart rate	-0.11	>0.05	0.02	>0.05
Pulse oxygen saturation	-0.04	>0.05	0.01	>0.05
Rating for sleep	0.42	<0.05	0.43	<0.05
Rating for movement	0.15	>0.05	0.14	<0.05
Rating for crying	0.29	<0.05	0.22	<0.05
Reaction at the moment of separation	0.23	<0.05	0.18	<0.05
Collaboration with the staff at the operating room	0.06	>0.05	0.00	>0.05

parents. A statistically significant indirect correlation was found between the dose and the respiratory rate 30 min after premedication (Table 5).

3.2. Safety

Only a few clinically insignificant side effects were observed during the study: two cases of hiccups occurred in Group 1 and one case of salivation occurred in Group 3. There were no allergic reactions, no episodes of severe bradycardia and/or severe respiratory depression, no desaturations of less 93% and no fainting, nausea or vomiting occurred in any of the groups.

4. Discussion

There is limited evidence from clinical trials that midazolam at a dose of 0.5–1.0 mg/kg via different routes is suitable for the premedication of children [2,8,13,14].

This study showed that oral midazolam used at a dose of 0.2–0.6 mg/kg did not have negative effects on the respiratory and/or heart rate or the pulse oxygen saturation (SpO₂) before premedication and 30 min after premedication in comparison with the placebo. These results confirm that the effect of midazolam on the vital functions of the patient, including the cardiovascular system and respiration, is negligible and of no pharmacological significance [15]. Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur in adults over 60 years of age and patients with pre-existing respiratory insufficiencies or impaired cardiac function [16]. This study proves that there is not a significant effect of oral midazolam used in single doses from 0.2 to 0.6 mg/kg on the vital functions of pediatric patients.

The results of the study demonstrate the desirable sedative effect of oral midazolam for premedication in children prior to dental surgery operations. The reactions of the midazolam patients, measured upon separation from their patients 20 min after premedication, had statistically significantly higher scores (demonstrating superior sedative effects) compared with the control group. Collaboration with staff in the operating room, as assessed by mask acceptance, also showed that the patients in the midazolam groups had statistically significant higher scores (demonstrating superior sedative effects) compared with the control group. Comparisons of behavioral and reaction

changes after the administration of oral midazolam demonstrate that there is a statistically significantly superior effect of sedation in the midazolam groups compared to the control group, while the overall sedative effects were statistically significantly higher in children who received a 0.21 mg/kg and higher midazolam dose compared to the control group.

Savla et al. [17] reported that children who received oral midazolam doses of 0.5 mg/kg with honey 30 min after premedication scored a 4.0 (i.e., the patients responded quickly to a light glabellar tap or loud auditory stimulus) on the Ramsay sedation scale (with a maximum score of 6, in which higher scores indicate better sedation); while Baygin et al. [18] reported that children who received 0.7 mg/kg oral midazolam by inhalation scored a 2.5 at the start of the operation on the Ramsay sedation scale. Arai et al. [19] reported that children who were premedicated with 0.5 mg/kg oral midazolam 40 min before the induction of anesthesia scored a 2.0 (i.e., they were asleep, but responded to movement or stimulation) on a 5-point scale (lower scores indicate better sedation) for mask induction with or without parental presence.

Patient behavior, as evaluated by a modified Houpt Behavior Rating Scale assessing sleep, movement and crying, rated statistically significantly higher among patients who received oral midazolam compared with the control group 30 min after sedation. The measures of the behavior of the patients in this study are similar with the results of Tazeroualti et al. [20], who reported that children who received a 0.5 mg/kg oral dose of midazolam with syrup had a 6.5 modified objective pain score (for movement, tears and behavior in terms of sleeping, with a maximum score of 30, in which lower scores indicate better effects) with high quality anesthesia induction in 70% of children, as well as the results of the study by Lima et al. [21] on the effects of oral midazolam, in which children who received 1.0 mg/kg oral midazolam received a score of 1.7 (with a maximum of 3.0, and higher scores indicating better sedation) for sleeping; 3.4 (with a maximum of 4.0; and higher scores indicating better sedation) for movement and 3.6 (with a maximum of 4.0; and higher scores indicating better sedation) for crying after 30 min of premedication. Lima et al. reported that the overall behavior of children who received midazolam received a score of 5.2 according the Houpt behavior scale after premedication (with a maximum of 6.0; and higher scores indicating better behavior).

There were only a few non-serious and non-severe side effects among the patients who received oral midazolam during the follow-up period. These results confirm the

statement of another group of authors, who concluded that significant side effects associated with oral midazolam usage for behavior management in children appear to be rare [22], although some authors have identified some side effects of oral midazolam [23,24].

There is an ongoing discussion of the effectiveness of oral midazolam for the premedication of children: Lourenço-Matharu et al. [25] state that “there is some weak evidence that oral midazolam is an effective sedative agent for children undergoing dental treatment” and Sheta et al. [26] and Kapur et al. [27] state that the liquid form of midazolam given orally as premedication is acceptable, effective and safe at 0.5 and 0.75 mg/kg doses, respectively. Our results show that the main outcomes of premedication, anxiolysis [22,28], a smooth separation from the parents [2] and good cooperation with medical staff before general anesthesia [29], can be achieved by giving oral midazolam in a single 0.2–0.6 mg/kg dose.

This study has a few limitations, including the small sample size, the short duration of follow-up and that the level of premedication measured by clinical diagnostic or laboratory techniques among the patient groups in this study were not measured and compared. Therefore, further studies should be conducted with larger sample sizes, longer follow-up periods and the use of clinical diagnostic and laboratory techniques to evaluate the level of premedication.

5. Conclusions

The results of this study demonstrate that there are sedative effects of oral midazolam in children who receive 0.2, 0.21–0.4 mg/kg or 0.41 and higher doses, and the higher dose of oral midazolam correlates with better sedation effects in terms of the patients' behaviors and reactions. There are not statistically significant changes in the clinical measures after the administration of oral midazolam in children receiving 0.2, 0.21–0.4 mg/kg and 0.41 and higher doses compared with the control group, while the behavioral and reactional changes after the administration of oral midazolam had a statistically significant sedative effect compared with the control group. There were only a few clinically insignificant side effects of oral midazolam.

Overall, oral midazolam at a single dose of 0.2–0.6 mg/kg is effective and safe and provides the expected sedative effects in children for the premedication of dental surgery.

Conflict of interest

The authors state no conflict of interest.

REFERENCES

- [1] Zutter A, Frei FJ. Uncooperative children during induction of anesthesia: theory and practice. *Anaesthesist* 2011;60(8):743–50 [in German].
- [2] Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, Ortega R. *Clinical anesthesia*. 7th ed. Lippincott Williams & Wilkins; 2013, 1240 pp.
- [3] Ghali AM, Mahfouz AK, Al-Bahrani M. Preanesthetic medication in children: a comparison of intranasal dexmedetomidine versus oral midazolam. *Saudi J Anaesth* 2011;5(4):387–91.
- [4] Rosenbaum A, Kain ZN, Larsson P, Lönnqvist PA, Wolf AR. The place of premedication in pediatric practice. *Paediatr Anaesth* 2009;19:817–28.
- [5] Kain ZN, Mayes LC, Wang SM, Hofstadter MB. Postoperative behavioral outcomes in children: effects of sedative premedication. *Anesthesiology* 1999;90:758–65.
- [6] Kazak Z, Sezer GB, Yilmaz AA, Ates I. Premedication with oral midazolam with or without parental presence. *Eur J Anaesthesiol* 2010;27:347–52.
- [7] Cox RG, Nemish U, Ewen A, Crowe MJ. Evidence-based clinical update: does premedication with oral midazolam lead to improved behavioural outcomes in children? *Can J Anaesth* 2006;53:1213–9.
- [8] Tyagi P, Tyagi S, Jain A. Sedative effects of oral midazolam, intravenous midazolam and oral diazepam in the dental treatment of children. *J Clin Pediatr Dent* 2013;37(3):301–5.
- [9] Rafeey M, Ghajzadeh M, Feizo Allah Zadeh H, Majidi H. Use of oral midazolam in pediatric upper gastrointestinal endoscopy. *Pediatr Int* 2010;52(2):191–5.
- [10] Munro A, Machonochie I. Midazolam or ketamine for procedural sedation of children in the emergency department. *Emerg Med J* 2007;24:579–80.
- [11] State Medicines Control Agency of Lithuania. Register of medicinal products. Available at: http://extranet.vvkt.lt/paieska/index.php?thislanguage=lang_en.
- [12] Medicines Compendium (eMC). Product Characteristics of Buccolam. Available at: <https://www.medicines.org.uk/emc/medicine/25538>.
- [13] Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. *Paediatr Anaesth* 2002;12(8):685–9.
- [14] Kattoh T, Katome K, Makino S, Wakamatsu N, Toriumi S. Comparative study of sublingual midazolam with oral midazolam for premedication in pediatric anesthesia. *Masui* 2008;57(10):1227–32. Abstract available at: <http://www.ncbi.nlm.nih.gov/pubmed/18975537>.
- [15] *Dormicum ampoules for anesthesiology and intensive care*. Basel, Switzerland: F. Hoffman-La Roche Ltd.; 1992, 185 pp.
- [16] New Zealand Medicines and Medical Devices Safety Authority. Product characteristic of Hypnovel. Available at: <http://www.medsafe.govt.nz/profs/datasheet/h/Hypnovelinj.pdf>.
- [17] Savla JR, Ghai B, Bansal D, Wig J. Effect of intranasal dexmedetomidine or oral midazolam premedication on sevoflurane EC₅₀ for successful laryngeal mask airway placement in children: a randomized, double blind, placebo-controlled trial. *Paediatr Anesth* 2014;24:433–9.
- [18] Baygin O, Bodur H, Isik B. Effectiveness of premedication agents administered prior to nitrous oxide/oxygen. *Eur J Anaesthesiol* 2010;27:341–6.
- [19] Arai YCP, Ito H, Kandatsu N, Kurokawa S, Kinugasa S, Komatsu T. Parental presence during induction enhances the effect of oral midazolam on emergence behavior of children undergoing general anesthesia. *Acta Anaesthesiol Scand* 2007;51:858–61.
- [20] Tazeroualti N, De Groote F, De Hert S, De Ville A, Dierick A, Van der Linden P. Oral clonidine vs midazolam in the prevention of sevoflurane-induced agitation in children. A prospective, randomized, controlled trial. *BJA* 2007;98(5):667–71.
- [21] Lima AR, da Costa LR, da Costa PS. A randomized, controlled, crossover trial of oral midazolam and hydroxyzine for pediatric dental sedation. *Pesqui Odontol Bras* 2003;17(3):206–11.

- [22] Papineni A, Lourenço-Matharu L, Ashley PF. Safety of oral midazolam sedation use in paediatric dentistry: a review. *Int J Paediatr Dent* 2014;24(1):2-13.
- [23] Sinha C, Kaur M, Kumar A, Kulkarni A, Ambareesha M, Upadya M. Comparative evaluation of midazolam and butorphanol as oral premedication in pediatric patients. *J Anaesthesiol Clin Pharmacol* 2012;28:32-5.
- [24] Akin A, Bayram A, Esmoğlu A, Tosun Z, Aksu R, Altuntas R, et al. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. *Paediatr Anaesth* 2012;22(9):871-6.
- [25] Lourenço-Matharu L, Ashley PF, Furness S. Sedation of children undergoing dental treatment. *Cochrane Database Syst Rev* 2012;3:CD003877.
- [26] Sheta SA, Alsarheed M. Oral midazolam premedication for children undergoing general anaesthesia for dental care. *Int J Pediatr* 2009;2009:274380.
- [27] Kapur A, Chawla SH, Goyal A, Gauba K, Bhardwaj N. Efficacy and acceptability of oral-transmucosal midazolam as a conscious sedation agent in pre-school children. *J Indian Soc Pedod Prev Dent* 2004;22:109-13.
- [28] Raugale A. Pharmacology and pharmacotherapy of clinical paediatrics. Vilnius University; 2008 (in Lithuanian). ISBN 978-9955-33-283-1.
- [29] McCann ME, Kain ZN. The Management of preoperative anxiety in children: an update. *Anesth Analg* 2001;93: 98-105.