

Evaluation of the Optimal Dosage for the Efficacy of Submucosal Midazolam Administration to Induce Sedation in Children Undergoing Diagnostic Procedures

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Abstract

Background: Preservation of sedation is vital and of great significance to successfully carry out diagnostic-therapeutic procedures in children and researchers believe that it is indispensable to offer a safe medication with appropriate administration in this regard. Hence, the present study aimed at evaluating the efficacy of different doses of submucosal Midazolam to induce sedation in children undergoing diagnostic procedures.

Methods: The present study was a clinical trial, in which 99 patients undergoing diagnostic procedures within the age range of 3 months to 5 years were selected and divided into three groups (n=33) of receiving submucosal Midazolam administration with doses of 0.3, 0.4, and 0.5 mg/kg. Then, the onset time of sedation, level of sedation, and duration of drug action were recorded and compared among the three groups.

Results: In the present study, the level of sedation 30 min after the administration of Midazolam 0.3 mg/kg with the mean value of 2.42 ± 0.83 was significantly lower than that of Midazolam 0.4 and 0.5 mg/kg with the mean values of 3.51 ± 0.62 and 3.36 ± 0.60 , respectively (p -value < 0.001). However, two doses of 0.4 and 0.5 mg/kg did not differ significantly.

Conclusion: The best sub-mucosal dosage of midazolam for sedation with the least complications for pediatric diagnostic procedures is 0.4mg/kg.

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Introduction

Relaxation and sedation have been considered as the most imperative and sometimes the most challenging part of diagnostic or therapeutic procedures in children as performing venipuncture for children is difficult due to thin and small size of the veins; even if it is carried out by a skilled personnel, it is time-consuming, may be failed to be performed in many cases

due to children's unconscious resistance and their parents' anxiety, and may result in serious delays in the diagnostic procedure in the emergency department (1,2). Moreover, the diagnostic procedure may fail due to child's non-cooperation. While the rate of failure in imaging has been reported by some researchers as a rare phenomenon with a frequency of 1-3% (3), other researchers have mentioned the rate of 10-20% in this

regard (4, 5). However, diagnostic procedures have been successful in all children that have undergone general anesthesia.

Therefore, sedatives and analgesics that are used alone or in combination with other drugs can be recommended in this regard (6). However, no medications or techniques are completely safe and reliable. In this regard, one of the safest drug categories is short-acting benzodiazepine receptor agonists that are associated with minimal drug side effects (7). Among these drugs, Propofol, Pentobarbital, Midazolam, Chloral Hydrate, Ketamine, and Nitrous Oxide that are used alone or in combination with other drugs can be mentioned (6, 8).

Midazolam, as a Benzodiazepine agonist, is a potent anti-convulsant that is usually administered intravenously or intramuscularly. The mentioned Benzodiazepine, which contains an imidazole ring, is water-soluble, does not convert to active metabolite, and is rapidly absorbed through the rectum, nose, and inner mucosa. The imidazole ring of Midazolam is highly lipophilic at physiologic pH, which facilitates its faster effect on the central nervous system (CNS) (9-12).

Although one of the best routes for administration of Midazolam is the buccal submucosal route, this route has not been well-investigated. Drug absorption via buccal mucosa is rapid because mucosal surfaces are relatively permeable and usually vascular-rich, which in turn lead to rapid transport of the drug to the systemic circulation. Moreover, the mentioned route is superior to intravenous or intramuscular injections as it is a non-invasive method, which means that it is not well-known to the child and even the parents. The mentioned point reduces the level of anxiety before injection and as already-mentioned the use of topical Benzocaine can minimize the child's anxiety.

Hence, buccal subcutaneous route may be more acceptable for children and even adults (13-15).

In previous studies, extensive use of Midazolam in dentistry (16), in controlling and treating epilepsy in children (14, 17), and in controlling seizure (18) has been reported. Moreover, the complications of buccal Midazolam injection have been reported to be very rare (17, 19, 13).

It is worth mentioning that very few studies have examined the use of this drug in critical diagnostic-therapeutic procedures such as CT scan in children (20). Hence, the present study aimed at evaluating the efficacy of buccal Midazolam administration to induce sedation in diagnostic-therapeutic procedures such as CT scan in children.

Materials and Methods

This study was a double-blind clinical trial. The study population was all children that referred to the emergency department of Kashani and Al-Zahra education training hospitals in Isfahan during 2017-2018 and underwent the diagnostic procedure (CT scan). Considering the confidence level of 95%, test power of 80%, error level of 0.17, and the results of previous studies reporting the ratio of 15% success in sedation with Midazolam, 33 patients were considered to be in each group (total number of 99).

The inclusion criteria to enter the study was the age range of over three months up to five years, children requiring diagnostic procedures such as CT scan, and agreement of a family care provider regarding the participation of the child in the study. Additionally, the patients with excessive sensitivity to Benzodiazepines, medical disorder of shock or blood pressure, alcohol intoxication, poor vital signs, pulmonary

diseases, and myasthenia gravis or musculoskeletal disorders were excluded from the study.

from the study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1396.829) and after obtaining written consent from the parents of children, they were included in the study.

It should be noted that as the very aim of this study was to specify the desired dose of Midazolam and level of sedation in children, three packets with A, B, and C labels that represented one of the 0.3, 0.4, and 0.5 mg/kg selective doses of Midazolam (21) were prepared. The children or their parents randomly selected one of the packets, as a result of which they were divided into three groups, each consisting of 33 patients.

Then, at the start of the study, children's primary information including age, gender, history of diseases, respiratory rate, heart rate, and arterial oxygen saturation percentage were recorded.

To apply the terms of a double-blind study, 0.4, 0.3, and 0.5 mg/kg doses of Midazolam were daily prepared by an emergency nurse (without the knowledge of the research), then placed inside a bag, marked with A, B, and C labels, and provided daily to the researcher. The researcher administered Midazolam with an insulin syringe into the patient's oral mucosa along the molar teeth (4-6 teeth).

Then, the onset time of the sedation in the child was recorded. The RAMSAY sedation scale (0-5) was used to measure the sedation level of the child. In this scoring scale, zero, one, two, three, four, and five indicate restless, completely awake, mildly drowsy, sleepy but responsive to an auditory stimulation, drowsy but responsive to a painful stimulation, and deep asleep and not responsive to a painful stimulation,

respectively. Moreover, as the child is supposed to be immobilized in the diagnostic procedures, reaching the sedation level of three and four was considered desirable so that the child would have no movement during the therapeutic-diagnostic procedures.

In addition, the duration of drug action (from the onset of sedation to the child's return to complete consciousness) was calculated and recorded. Moreover, the respiratory rate, heart rate, and arterial oxygen saturation percentage of the child were measured and recorded in all three groups after the administration of Midazolam.

Finally, the parents' rated the parental care provider and the patient's satisfaction levels during the diagnostic process from 1 to 4 (1: poor, 2: moderate, 3: good, and 4: excellent). In the mentioned rating scale, zero and four denote dissatisfaction and the highest level of satisfaction, respectively.

The collected data was analyzed using SPSS software, version 22. Descriptive statistics provided indicators such as mean, median, standard deviation, frequency, and percentage of frequency. Moreover, as the results of the Kolmogorov-Smirnov (KS) normality test indicated non-normal distribution of variables, Kruskal-Wallis, Mann-Whitney, and Fisher's exact tests were used. The significance level in all analyses was considered to be less than 0.05.

Results

In this study, 16 (48.5%) female and 17 (51.5%) male patients with the mean age of 1.74 ± 2.37 years received Midazolam 0.3 mg/kg. Moreover, 10 (30.3%) female and 23 (69.7%) male patients with the mean age of 1.37 ± 2.23 years were involved in the group receiving Midazolam 0.4 mg/kg. Finally, the group receiving Midazolam 0.5 mg/kg consisted of

16 (48.5%) female and 17 (51.5%) male patients with the mean age of 1.68 ± 2.73 years. The mentioned findings were indicative of no statistically significant difference among the three groups in terms of age and gender (p -value > 0.05).

In addition, the mean of oxygen saturation percentage, respiratory rate, and heart rate of children before the

intervention was not significantly different from the obtained percentages 15 and 30 minutes after the Midazolam administration (in all three doses). In other words, three groups did not indicate any significant differences in this regard (p -value > 0.05, Table 1).

Table 1. Determination and comparison of the means of oxygen saturation percentage, heart rate, and respiratory rate among the three studied groups

Variables	Time	Midazolam 0.5 mg.kg ⁻¹	Midazolam 0.4 mg.kg ⁻¹	Midazolam 0.3 mg.kg ⁻¹	P value
Oxygen saturation percentage	before the intervention	94.94±0.35	95.00±0.25	95.00±0.25	0.372
	15 minutes after the intervention	94.94±0.24	95.00±0.25	94.97±0.17	0.362
	30 minutes after the intervention	94.89±0.38	94.91±0.38	94.85±0.51	0.804
Heart rate	before the intervention	85.97±12.84	87.27±11.84	89.79±11.33	0.426
	15 minutes after the intervention	108.24±21.79	119.82±16.75	90.67±11.69	0.601
	30 minutes after the intervention	86.11±12.79	87.06±11.30	89.57±10.78	0.463
Respiratory rate	before the intervention	23.15±4.65	23.09±0.83	22.21±3.87	0.589
	15 minutes after the intervention	21.36±4.63	21.54±3.27	20.30±3.87	0.392
	30 minutes after the intervention	23.24±4.55	23.48±3.22	22.58±3.75	0.617

Furthermore, the level of sedation during the first five minutes after the administration of Midazolam was at under sedation level in all three groups and did not differ significantly among the three groups (p -value > 0.05). However, 15 and 30 minutes after the administration of Midazolam, the level of sedation in the Midazolam 0.3 mg/kg group was significantly lower than that in the Midazolam 0.4 and 0.5 mg/kg groups (p -value < 0.05). Moreover, the level of sedation was not

significantly different between the two doses of Midazolam 0.4 and 0.5 mg/kg (p -value > 0.05). In addition, within 30 minutes after the intervention, the two groups of Midazolam 0.4 and 0.5 mg/kg demonstrated the adequately sedated (AS) level in 93.9% of their children, while Midazolam 0.3 mg/kg group revealed the adequately sedated (AS) level in 48.5 % of the children (Table 2, Fig. 1).

Table 2. Determination and comparison of the means of sedation level at different time intervals among the three studied groups

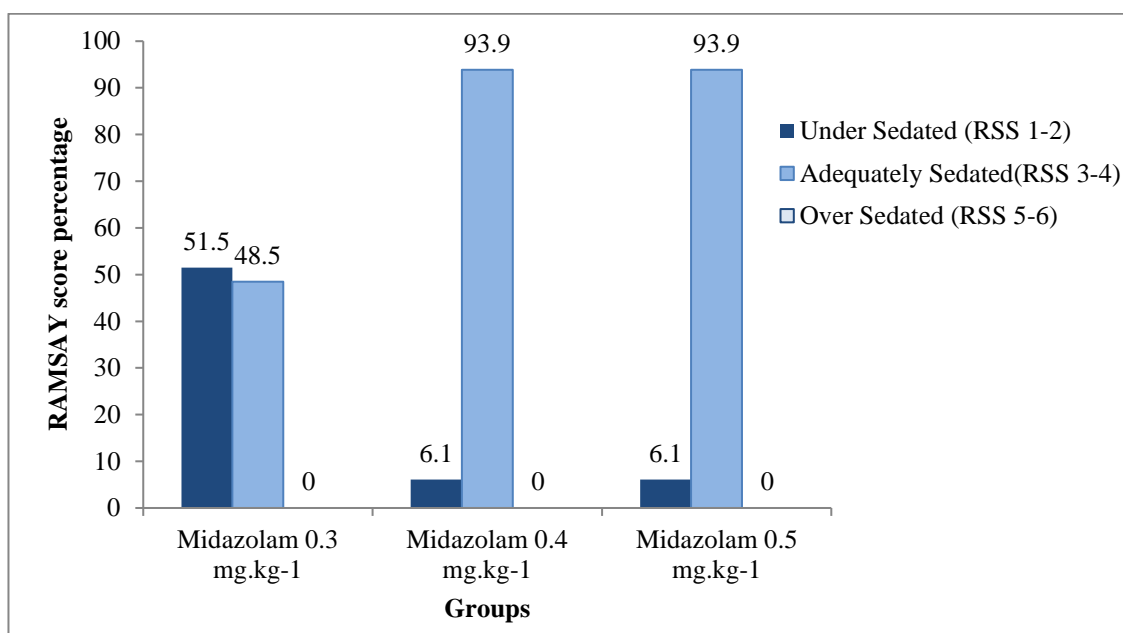
Level of Sedation	Midazolam 0.5 mg.kg ⁻¹	Midazolam 0.4 mg.kg ⁻¹	Midazolam 0.3 mg.kg ⁻¹	P value ¹	P value ²	P value ³
5 minute	1.45±0.50	1.48±0.51	1.30±0.47	0.134	0.208	0.807
AS*	0(0%)	0(0%)	0(0%)			
US**	33(100%)	33(100%)	33(100%)			
15 minute	2.88±0.74	2.73±0.94	2.15±1.03	0.024	0.003	0.463
AS*	22(66.7%)	17(51.5%)	12(36.4%)			
US**	11(33.3%)	16(48.5%)	21(63.6%)			
30 minute	3.51±0.62	3.36±0.60	2.42±0.83	<0.001	<0.001	0.452
AS*	31(93.9%)	31(93.9%)	16(48.5%)			
US**	2(6.1%)	2(6.1%)	17(51.5%)			

*: adequately sedated (RSS 3-4), **: under sedated (RSS 1-2)

1: Significant level obtained from the comparison of the mean values of two groups of Midazolam 0.3 and 0.4 mg/kg

2: Significant level obtained from the comparison of the mean values of two groups of Midazolam 0.3 and 0.5 mg/kg

3: Significant level obtained from the comparison of the mean values of two groups of Midazolam 0.4 and 0.5 mg/kg

**Figure 1.** Frequency percentage of the sedation level 30 min after the intervention in the three studied groups

Moreover, the onset time of sedation was not significantly different in the three groups of Midazolam 0.3, 0.4, and 0.5 mg/kg (p -value > 0.05). Evaluation of the duration of drug action in three doses of Midazolam indicated that the duration of drug action in the Midazolam 0.3 mg/kg group with a mean of 11.36 ± 33.33 minutes was significantly less than those in Midazolam 0.4 and 0.5 mg/kg groups with the means of $9.29 \pm$

38.39 and 11.82 ± 40.15 minutes, respectively (p -value < 0.05).

In contrast, the duration of drug action of two doses of 0.4 and 0.5 mg/kg Midazolam did not differ significantly (p -value = 0.766, Table 3).

Finally, the satisfaction levels of parental care providers and patients regarding their sedation level during the diagnostic procedure did not differ significantly among the three doses of

3.0, 0.4 and 0.5 mg/kg Midazolam with means of 2.55 ± 0.62 , 2.70 ± 0.58 , and 2.65 ± 0.67 respectively (p -value >0.05). In other words, administration of the lowest possible dose of

Midazolam can be effective in performing a diagnostic process with more tranquility.

Table 3. Determination and comparison of the mean values of the onset time of sedation and duration of drug action among the three groups

Variables	Midazolam 0.5 mg.kg ⁻¹	Midazolam 0.4 mg.kg ⁻¹	Midazolam 0.3 mg.kg ⁻¹	P value ¹	P value ²	P value ³
Onset time of sedation; min	14.33±6.44	15.67±4.09	18.48±8.38	0.319	0.085	0.071
Duration of drug action; min	40.15±11.82	38.39±9.29	33.33±11.36	0.028	0.017	0.766

Discussion

The present study aimed at addressing the effect of Midazolam 0.3, 0.4, and 0.5 mg/kg on induction of sedation in children undergoing diagnostic procedures and the obtained results revealed adequately sedated (AS) level in more than 90% of the children 30 minutes after the intervention in the two groups of Midazolam 0.4 and 0.5 mg/kg. Moreover, Midazolam 0.3 mg/kg group revealed the adequately sedated (AS) level of 48.5 % with no complications for children, which in turn resulted in parents' high level of satisfaction regarding the mentioned procedure.

In this respect, some previous studies have also highlighted the prominence of using sedative medications to increase the success rate of diagnostic-therapeutic procedures in children. Regarding the therapeutic success, in McIntyre et al.'s study on 177 children with epilepsy, therapeutic success was achieved in more than 92 patients treated with buccal Midazolam as compared with 85 patients treated with rectal Diazepam. In addition, the percentage of patients whose visible seizure symptoms stopped within 10 minutes in the buccal Midazolam group was 29% higher than that in the rectal Diazepam group (56% versus 27%). Moreover, there was no increase in the

onset of respiratory depression (17). In another clinical trial, buccal Midazolam was found to be as effective and safe as rectal Diazepam (12).

In line with the findings of the current study, a large prospective study addressing the success of diagnostic procedures in diagnostic MRI or CT scan procedures for children undergoing sedation (922 patients) or general anesthesia (140 patients), relief and relaxation rates were inadequate in only 16% of children. Moreover, only 7% failure was reported in this regard. In addition, the mentioned study evaluated the administration of Benzodiazepines to control anxiety and sedation induction in children (22).

In this regard, the American Academy of Pediatrics (AAP) has specified the objectives of sedation for diagnostic and therapeutic procedures in the pediatric patient as follow: to protect the patient's safety and comfort, to minimize the physical pain and discomfort, to control anxiety, to minimize psychological trauma, and to control the child's behavior and/or movements to adopt a safe method (23).

The desired level for depth of anesthesia varies according to the method of imaging as well as the characteristics of the patient. For example, the existence of a modern multifunction

scanner in CT scan allows the operator to capture a rapid image so that the mentioned diagnostic procedure requires a moderate level of sedation. However, to carry out long-term procedures such as MRI and nuclear medicine imaging, it is necessary for the child to be asleep, which may last up to 1 hour (8, 24). Hence, consideration of the diagnostic procedure and administration of the appropriate dose of the drug are of great significance to induce sedation in children and minimize the drug complications (25) as in a small number of studies, severe respiratory problems have been reported after the administration of buccal Midazolam, which may be due to the administration of high doses of the drug (17, 19). However, no drug complications were observed in the present study.

In addition, the effect of submucosal Midazolam administration with three different doses on the onset of sedation did not differ significantly in the present study. In other words, the onset of sedation in children with a minimum (0.3 mg/kg) and maximum (0.5 mg/kg) doses of Midazolam was not different. Generally, the initiation of sedation was 14-18 minutes after the submucosal administration. However, the level of sedation and the duration of drug action for 0.4 and 0.5 mg/kg doses were significantly higher than those for 0.3 mg/kg dose. Moreover, the level of sedation and duration of drug action at 0.4 and 0.5 mg/kg doses were not significantly different. In fact, it may be concluded that submucosal Midazolam administration at a dose of 0.5 mg/kg is not preferable to the dose of 0.4 mg/kg. Therefore, the minimum dose of 0.4 mg/kg can be used to avoid potential risks and the side effects of the drug.

In accordance with this study, in a study conducted by Majidinejad et al. addressing the effect of oral administration of Midazolam along with Ketamine versus Midazolam to induce

sedation in children undergoing CT scan, the level of adequate sedation was achieved in five (15.2%) and 15 (45.5%) patients out of 33 children who had received Midazolam and Midazolam along with Ketamine, respectively (20).

The findings of many studies on sedation and anxiety control in therapeutic procedures are consistent with those of the present study. According to many clinical trials, Midazolam has been well-documented in the field of dentistry. It has been indicated that buccal Midazolam can reduce the anxiety level in patients with dental problems. In addition, the positive effect of Midazolam administration via nasal mucosa has been reported despite its negative reception by some patients (11, 26-28).

In this regard, it can be stated that drug absorption via buccal mucosa is rapid because mucosal surfaces are relatively permeable and usually vascular-rich, which in turn lead to rapid transport of the drug to the systemic circulation. In addition, stratum corneum epidermidis that is a major barrier to absorption throughout the skin does not intervene in the submucosal administration. Moreover, the absorption rate is much higher in the subcutaneous administration and is resulted from the high bioavailability due to the lack of the first-pass effect in the liver. The mouth has a large surface area and the amount of blood supply is high in the mouth. Moreover, subcutaneous administration is preferable to intravenous or muscular injection as it is a non-invasive method, and it is possible to reduce the level of anxiety before injection due to the parents' lack of acquaintance with this route of administration (11, 18, 19).

Recent reports have indicated that submucosal route is the most widely used route for injection of sedative medications in pediatric dentistry (20). Another common use of Midazolam is in the control and treatment of epilepsy in children. The study

conducted by Scott et al. addressing the safety and efficacy of buccal Midazolam versus intravenous diazepam in controlling seizures in children revealed that administration of Midazolam via buccal route was as effective as the administration of Diazepam via rectal route in controlling acute seizure. The mentioned study indicated that administration of Midazolam via buccal route can be used to control seizure (9). In another study conducted in India, buccal Midazolam was as effective as intravenous Diazepam in controlling seizure (22).

Finally, it should be mentioned that the major advantage of the present study is that to date no study has evaluated and specified the effective dose of drug administration via this route. But, on the other hand, comparing the results of the present study with those of other studies in this regard is not possible.

References

1. Rothman DL. Sedation of the pediatric patient. *J Calif Dent Assoc* 2013; 41(8):603-11.
2. Ares G, Hunter CJ. Central venous access in children: indications, devices, and risks. *Curr Opin Pediatr* 2017; 29(3):340-6.
3. Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. *Ann Emerg Med* 1998; 31(6):688-97.
4. Cahoon GD, Davison TE. Prediction of compliance with MRI procedures among children of ages 3 years to 12 years. *Pediatr Radiol* 2014; 44(10):1302-9.
5. Martin ML, Lennox PH. Sedation and analgesia in the interventional radiology department. *Journal of Vascular and Interventional Radiology*. 2003; 14(9):1119-28..
6. Yaster M. Multimodal analgesia in children. *Eur J Anaesthesiol* 2010; 27(10):851-7.
7. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J* 2013; 13(2):214-23.
8. Rabach I, Peri F, Minute M, Aru E, Lucafò M, Di Mascio A, et al. Sedation and analgesia in children with cerebral palsy: a narrative review. *World J Pediatr* 2019; 15(5):432-40.
9. Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *The Lancet*. 1999; 353(9153):623-6.
10. Lam JK, Xu Y, Worsley A, Wong IC. Oral transmucosal drug delivery for pediatric use. *Adv Drug Deliv Rev* 2014; 73:50-62.
11. Southerland JH, Brown LR. Conscious intravenous sedation in dentistry: a review of current therapy. *Dent Clin North Am* 2016; 60(2):309-46.

Hence, it is recommended to conduct more similar studies to offer a single and definitive conclusion in this regard.

Conclusion

The results of the present study revealed that subcutaneous administration of three Midazolam doses of 0.3, 0.4, and 0.5 mg/kg did not result in a significant difference in terms of the onset time of sedation. However, the effectiveness of two doses of 0.4 and 0.5 mg/kg on the level of sedation and duration of drug action was significantly higher than that of Midazolam 0.3 mg/kg. Moreover, no significant difference was observed between the two Midazolam doses of 0.4 and 0.5 mg/kg in terms of the level of sedation and duration of drug action. Hence, it can be suggested to use the minimum dose of 0.4 mg/kg in subcutaneous administration of Midazolam.

12. Mula M. The safety and tolerability of intranasal midazolam in epilepsy. *Expert Rev Neurother* 2014; 14(7):735-40.
13. Milnes AR, Wilson S. Alternatives to Oral Sedation. In *Oral Sedation for Dental Procedures in Children* 2015 (pp. 141-155). Springer, Berlin, Heidelberg.
14. Coulthard P, Craig D, Holden C, Robb ND, Sury M, Chopra S, et al. Current UK dental sedation practice and the 'National Institute for Health and Care Excellence' (NICE) guideline 112: sedation in children and young people. *Br Dent J* 2015; 218(8):E14.
15. Ghai B, Jain K, Saxena AK, Bhatia N, Sodhi KS. Comparison of oral midazolam with intranasal dexmedetomidine premedication for children undergoing CT imaging: a randomized, double-blind, and controlled study. *Paediatr Anaesth* 2017; 27(1):37-44.
16. Jo CW, Park CH, Lee JH, Kim JH. Managing the behavior of a patient with autism by sedation via submucosal route during dental treatment. *J Dent Anesth Pain Med* 2017; 17(2):157-61.
17. McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; 366(9481):205-10.
18. Momen AA, Azizi Malamiri R, Nikkhah A, Jafari M, Fayezi A, Riahi K, et al. Efficacy and safety of intramuscular midazolam versus rectal diazepam in controlling status epilepticus in children. *Eur J Paediatr Neurol* 2015; 19(2):149-54.
19. Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics* 2008; 121(1):e58-64.
20. Majidinejad S, Taherian K, Esmailian M, Khazaei M, Samaie V. Oral midazolam-ketamine versus midazolam alone for procedural sedation of children undergoing computed tomography; a randomized clinical trial. *Emerg (Tehran)* 2015; 3(2):64-9.
21. Smith R, Brown J. Midazolam for status epilepticus. *Aust Prescr* 2017; 40(1):23-5.
22. Malviya S, Voepel-Lewis T, Eldevik OP, Rockwell DT, Wong J, Tait A. Sedation and general anaesthesia in children undergoing MRI and CT: adverse events and outcomes. *Br J Anaesth* 2000; 84(6):743-8.
23. Coté CJ, Wilson S, American Academy Of Pediatrics, American Academy Of Pediatric Dentistry. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures: update 2016. *Pediatrics* 2016; 138(1):e20161212.
24. Sury M, Bullock I, Rabar S, Demott K, Guideline Development Group. Sedation for diagnostic and therapeutic procedures in children and young people: summary of NICE guidance. *Bmj* 2010; 341:c6819.
25. Ahmed SS, Unland T, Slaven JE, Nitu ME. High dose dexmedetomidine: effective as a sole agent sedation for children undergoing MRI. *Int J Pediatr* 2015; 2015:397372.
26. Sunbul N, Delvi MB, Zahrani TA, Salama F. Buccal versus intranasal midazolam sedation for pediatric dental patients. *Pediatr Dent* 2014; 36(7):483-8.
27. Manoj M, Satya Prakash MV, Swaminathan S, Kamaladevi RK. Comparison of ease of administration of intranasal midazolam spray and oral midazolam syrup by parents as premedication to children undergoing elective surgery. *J Anesth* 2017; 31(3):351-7.
28. Musani IE, Chandan NV. A comparison of the sedative effect of oral versus nasal midazolam combined with nitrous oxide in uncooperative children. *Eur Arch Paediatr Dent* 2015; 16(5):417-24.