

Intranasal Midazolam Compared with Intravenous Diazepam in Patients Suffering from Acute Seizure: A Randomized Clinical Trial

Mohsen Javadzadeh¹, MD; Kourosh Sheibani^{*2}, MD; Mozhgan Hashemieh¹, MD, and Hedyeh Saneifard¹, MD

1. Department of Pediatrics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Clinical Research and Development Center, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: Jan 17, 2011; Final Revision: Jul 16, 2011; Accepted: Oct 02, 2011

Abstract

Objective: Acute seizure attack is a stressful experience both for health care personnel and parents. These attacks might cause morbidity and mortality among patients, so reliable methods to control the seizure preferably at home should be developed. This study was performed to measure the time needed to control seizure attacks using intranasal midazolam compared to the common treatment (intravenous diazepam) and to evaluate its probable side effects.

Methods: This study was conducted as a not blind randomized clinical trial among 60 patients coming to Imam Ali Hospital, Zahedan, Iran. The patients were 2 months to 15 years old children coming to our emergency department suffering from an acute seizure episode. Intranasal midazolam was administered 0.2 mg/kg equally dropped in both nostrils for case group and intravenous diazepam was administered 0.3mg/kg via IV line for control group. After both treatments the time needed to control the seizure was registered by the practitioner. Pulse rate and O₂ saturation were recorded at patients' entrance and in minutes 5 and 10 after drug administration.

Findings: The time needed to control seizure using intranasal midazolam (3.16 ± 1.24) was statistically shorter than intravenous diazepam (6.42 ± 2.59) if the time needed to establish IV line in patients treated by intravenous diazepam is taken into account ($P < 0.001$). The readings for O₂ saturation or heart rate did not indicate a statistically significant difference between two groups of patients either at entrance or 5 and 10 minutes after drug administration.

Conclusion: Considering the shorter time needed to control acute seizure episodes compared to intravenous diazepam and its safety record, intranasal midazolam seems to be a good candidate to replace diazepam, as the drug of choice, in controlling this condition.

Iranian Journal of Pediatrics, Volume 22(Number 1), March 2012, Pages: 1-8

Key Words: Midazolam; Diazepam; Seizures; Clinical Trail

Introduction

Acute seizure attack is a stressful experience both for health care personnel and parents [1]. Most parents believe these epileptic episodes to be

dangerous and half of them are afraid of their child dying when these attacks happen for the first time [2]. Prolonged or recurrent seizure activity might cause morbidity and mortality among patients specially those persisting more than 30 minutes

*** Corresponding Author;**

Address: Imam Hossein Medical Center, Shahid Madani St, Tehran, Iran

E-mail: sh_kourosh@hotmail.com

© 2012 by Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, All rights reserved.

[3,4], so reliable methods to control the seizure preferably at home should be developed. The use of the main anticonvulsant drug (diazepam) by injection is not possible by most parents at home and rectal diazepam, being the most common method of controlling the seizure at home, is associated with adverse social and personal effects[5-8], so the intranasal application of anticonvulsants have been considered in recent years. The vascular nasal mucosa facilitates the rapid absorption, a fact known by cocaine addicts for years [1], and drugs administered this way have been utilized in a variety of treatment methods. The ease of intranasal midazolam administration to treat episodes of seizure makes it a good candidate to replace the conventional treatment methods not only for use at home but also for health professionals [5].

Diazepam has been widely used to treat different kinds of seizure episodes both in children and adult patients. The drug has a short half life and should be administered via intravenous injection or rectal application. Rectal gel (Desitin) might also be used. The main advantages of diazepam are rapid response, wide safe range and its ability to control seizures with cortical and centerencephalic origins [9]. The main side effects are respiratory depression and hypotension which is more frequent in patients receiving multi-drug treatment (diazepam+phenobarbital) or multiple administrations of the drug [9]. Diazepam tends to accumulate in body after multiple usages and might cause brain stem depression, bradypnea, and even apnea in rare cases [9]. One other disadvantage of intravenous diazepam is that securing an IV line might be hard in patients with tonic- clonic seizure or high fever.

Midazolam is a water soluble benzodiazepine which is an effective anticonvulsant agent after IV or IM injection. Intranasal midazolam is directly absorbed by nasal mucosa and rapidly enters the blood and cerebrospinal fluid (CSF). The drug absorption is influenced by blood circulation of nasal mucosa, the spread of mucosa in contact with drug, and concentration of the drug. The half life of the drug is usually between 1.5 and 3.5 hours[10]. After administration of 0.2 mg/kg intranasal midazolam its plasma concentration reaches 100ng/ml in about six minutes[11]. Within a few minutes of delivery, serum levels of

intranasal midazolam are comparable with injectable levels [12]. The intranasal form controls seizure episodes better than rectal diazepam and is easier to administer with higher overall satisfaction [5,8,13-18]. It is a safe and comparatively cheap drug and its ease of use makes it a perfect candidate for use at home [8,19-22].

O'reagan et al have outlined the usage of intranasal midazolam to treat acute seizure episodes [23]. It should be considered that when the drug is administrated to control seizure an upper respiratory tract infection is often present. Although the infection should facilitate the mucosal absorption due to increased blood flow but the presence of mucosal secretion might dilute the drug and also limit its contact with mucosa[24]. The widespread usage of intranasal midazolam is partly limited due to the limitations of the drug form available which is designed for intravenous injection not nasal administration (a practice due to specially prepared intranasal solution not being readily available) and causes irritation in patients. This irritation is caused by the low pH and the high volume of the drug needed to be used. This problem can be redeemed by using the solution of midazolam in cyclodextrin which then can be delivered by a spray method and has less acidity and higher drug concentration[25].

This study was performed to measure the time needed to control seizure attacks using intranasal midazolam compared to the common treatment (intravenous diazepam) and to evaluate its probable side effects.

Subjects and Methods

Patients

This study was conducted as non blind randomized clinical trial among patients coming to Imam Ali Hospital, Zahedan, Iran from October 2008 to June 2009. We acquired verbal consent from parents before entering patients into our study. After the seizure was controlled written consent was completed by parents. The study was approved by Zahedan University of Medical Sciences ethics committee. The patients were 2 months to 15 years old and came to our

emergency department suffering from an acute seizure episode. All types of seizure including new onset seizures were included in our study as long as they fulfilled our inclusion and exclusion criteria. The patients were selected using easy selection method (all patients coming to hospital with seizure who fulfilled inclusion and exclusion criteria, determined by the physician, entered the study) and were randomly divided into two groups of 30 each, receiving intranasal midazolam or intravenous diazepam based on block randomization method (block size: 6). Block randomization was done by the statistician before the start of study.

The sample size was calculated based on 5% first error and 90% power. To calculate the standard deviation for treatment using intravenous diazepam (time needed for securing IV line+time needed for drug to stop seizure attack) a pilot study on five patients was performed. The standard deviation in this pilot study was 2.4 minutes. The standard deviation for the time needed to stop seizure using intranasal midazolam was considered to be 2.2 minutes based on the study by Lahat et al^[25]. Finally we considered two minutes difference to be statistically significant. Based on these assumptions the sample size needed for each group of case and control was calculated to be 28. We entered 30 patients in each group to cover for probable drops. A participant flow diagram is presented in appendix 1.

Inclusion criteria

Inclusion criteria were age between 2 months and 15 years, suffering from acute seizure episode and presence of parents (in order to acquire consent).

Exclusion criteria

Those patients who had an IV line before coming to our center or had been administered with any kind of anticonvulsant drug were excluded from our study. We also excluded patients who had any sign of upper respiratory tract infection.

Methods

A questionnaire was used by the practitioner to gather all the required data from each patient consisting of demographics and findings sections. The time from the start of seizure attack was determined by questioning the parents which was

more than 5 minutes in all our cases. The choice of drug for patients was based on block randomization and sealed in opaque envelopes.

For all patients an IV line was established on their arrival and the time needed was registered. The treatment was performed immediately after the practitioner confirmed the diagnosis based on the treatment method inside the envelope. If intranasal midazolam was the treatment method it was administered 0.2 mg/kg equally dropped in both nostrils. If intravenous diazepam was the treatment choice 0.3mg/kg was administered via IV line. After both treatments the time needed to control the seizure was registered by the practitioner. The control of seizure was based on practitioner's clinical judgment. If the seizure was controlled in less than 10 minutes it was considered a treatment success and if control was not achieved in 10 minutes it was deemed to be a failure and other methods were used to control the seizure.

In failure cases if the preliminary treatment was intranasal midazolam, diazepam was added and if the preliminary treatment was intravenous diazepam, phenobarbital was administered. Pulse rate and O₂ saturation using pulse oximetry was recorded at patient's entrance and in minutes 5 and 10 after drug administration. In both treatment methods respiratory aid was performed using oxygen mask.

Data analyzing methods

Means and standard deviations for the time needed to control the seizure, O₂ saturation and pulse rate were calculated in both case and control groups and paired t-test was performed to compare the results. SPSS software version 13 was utilized to perform statistical analysis. We considered *P* values less than 0.05 to be statistically significant.

Findings

Baseline characteristics of our patients and the distribution of different kinds of seizures treated in each group are illustrated in Table 1. There was no statistically significant difference between case and control groups regarding the age, sex, O₂

Table 1: Baseline characteristics of intervention and the types of seizure in each group

Characteristic	Group *	
	Intranasal Midazolam (n=30)	Intravenous Diazepam (n=30)
Median age (Inter quartile range), yrs	2.3 (1,5)	2.5 (1.2,6)
Sex M/F, (M %)	16/14 (53)	17/13 (57)
Mean (SD) O ₂ Saturation (%)	98.13 (5.54)	97.16 (3.56)
Mean (SD) pulse rate/Min	147.83 (34.70)	146.56 (26.14)
Type of seizure	Simple FS	19
	Complex FS	3
	GTC Epilepsy	4
	PS with 2 nd generalization	1
	Lennox Gestaut Syndrome	2
	Infantile Spasms	1
	Undetermined	0

SD: Standard Deviation / FS: Febrile Seizure / GTC: Generalized Tonic Clonic / PS: Partial Seizure

* There was no statistically significant difference between two groups ($P>0.05$)

saturation at entrance, pulse rate and the distribution of different kinds of seizures.

Statistical data representing the time needed to control seizure using intranasal midazolam and diazepam is presented in Table 2. In this comparison diazepam shows a statistically significant advantage if the time needed to take IV line is not taken into account ($P=0.001$), but intranasal midazolam has a statistically significant advantage over intravenous diazepam if the time needed to establish IV line is taken into account ($P<0.001$).

Findings considering O₂ saturation and heart rate at entrance (minute 0) and at 5 and 10 minutes after administration of intranasal midazolam and intravenous diazepam are represented in Table 3 and Fig 1 and 2.

The readings for O₂ saturation or pulse rate do not indicate a statistically significant difference between two groups of patients either at entrance or 5 and 10 minutes after drug administration.

During the treatment with both intranasal midazolam and intravenous diazepam there was

no case of treatment failure and we did not encounter any serious side effects necessitating the use of mechanical ventilation.

Discussion

Intranasal administration of drugs has been the center of much interest in recent years. This interest comes from the upper respiratory mucosal ability to readily absorb molecules which makes it a prime route for fast and easy drug delivery. This route of administration seems to be the best choice when rapid drug delivery is crucial but drug injection is problematic.

A prime example of such a combination is the control of acute seizure at home when the fast delivery of anticonvulsant is of foremost importance but injection by parents is often a limited practice. Although diazepam has widely served as the first line drug to control the seizure

Table 2: Comparison of the time needed to control seizure using diazepam and intranasal midazolam

Time needed to control seizure	Variable	Group		Difference (^{95%} CI)	P-value
		Intranasal Midazolam	Intravenous Diazepam		
Not considering the time needed to take IV line	Mean Time (SD), min	3.16 (1.24)	2.16 (1.02)	1.00 (0.41,1.59)	0.001
	Range	1.08 - 5.00	1.00 - 5.63		
Considering the time needed to take IV line	Mean Time (SD), min	3.16 (1.24)	6.42 (2.59)	3.26 (3.20,4.32)	<0.001
	Range	1.08 - 5.00	3.08 - 15.63		

CI: Confidence Interval / SD: Standard Deviation

Table 3: Comparison of O₂ saturation level between two groups of patients receiving midazolam or diazepam

Parameter	Time (minutes)	Group		Diff (95% CI)	P value
		Intranasal Midazolam	Intravenous Diazepam		
O₂ Saturation†	Mean (SD)	98.13 (5.54)	97.16 (3.56)	0.97 (-1.43_3.38)	0.4
	Range	71 - 98	85 - 99		
	Mean (SD)	93.83 (2.99)	94.66 (2.70)	0.83 (-0.64_2.30)	0.3
	Range	87 - 100	88 - 100		
	Mean (SD)	96.13 (2.40)	96.96 (2.04)	0.83 (-0.32_1.98)	0.1
	Range				
Pulse rate‡	Mean (SD)	147.83 (34.70)	146.56 (26.14)	1.27 (-14.61_17.15)	0.9
	Range	60 - 210	88 - 20		
	Mean (SD)	139.53 (26.49)	137.46 (21.08)	2.07 (-10.30_14.44)	0.7
	Range	75 - 208	90 - 189		
	Mean (SD)	140.53 (21.99)	135.70 (20.22)	4.83 (-6.09_15.75)	0.4
	Range	100 - 200	90 - 186		

† The difference between groups through the study was not significant ($P=0.1$, based on Repeated measure analysis)

‡ The difference between groups through the study was not significant ($P=0.2$, based on Repeated measure analysis)

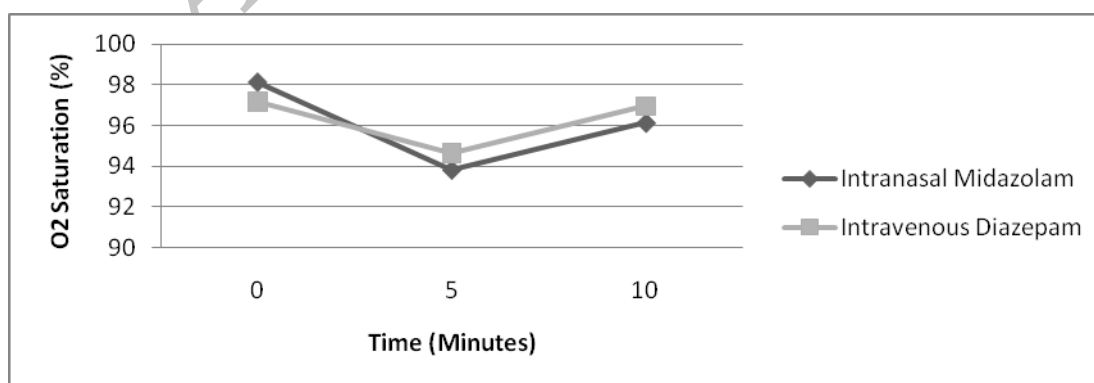
for a long time its administration needs injection to be rapidly effective, a method limited at home setting. The other method of drug delivery by rectal administration has not been as reliable or fast as injection. Some authors consider rectal diazepam to be an inferior treatment method for adolescents and adults due to its adverse personal and social effects and advocate the use of intranasal midazolam as a substitute^[25,26].

Our study has demonstrated that intranasal midazolam is an effective anticonvulsant for acute seizure treatment in an emergency setting with comparable safety and less administration time compared to intravenous diazepam.

There is a considerable volume of literature on the use of intranasal midazolam to treat

seizures^[5,14-16,24-33]. Lahat et al^[25] compared the safety and efficiency of intranasal midazolam with IV diazepam in children presenting to the emergency department. They concluded that both intranasal midazolam and intravenous diazepam were equally effective, but the mean time to control the seizures was shorter in the midazolam group, because there was no time needed to establish an IV line in this group before administering the drug.

Lahat et al^[25] and Mahmoodian et al^[28] reported the mean time to control seizure using intranasal midazolam to be 3.5 ± 1.8 and 3.58 ± 1.68 respectively. In our study this time was 3.16 ± 1.24 showing a comparable outcome. Our study also indicates that if the time needed to secure an IV

**Fig. 1:** Comparison of O₂ saturation level between two groups of patients receiving intranasal midazolam or intravenous diazepam

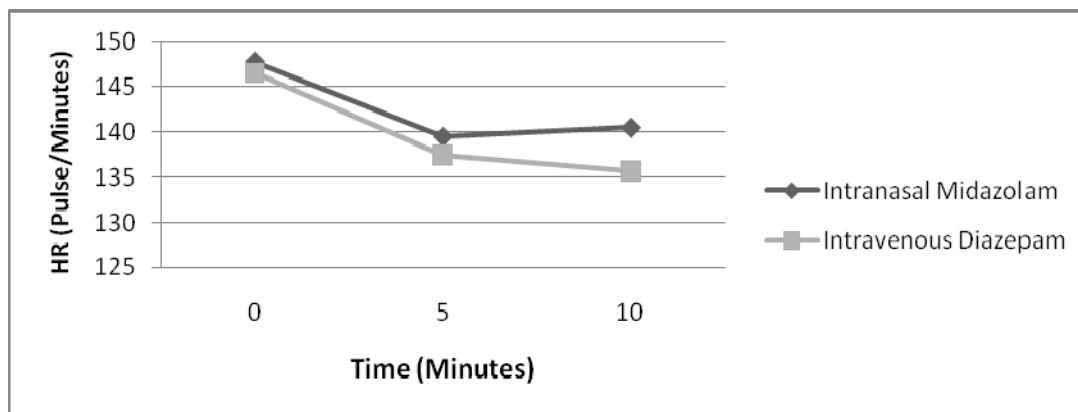


Fig. 2: Comparison of pulse rate between two groups of patients receiving intranasal midazolam or intravenous diazepam

line is calculated the time needed for intravenous diazepam to control the seizure is statistically longer than the time needed by intranasal midazolam (6.42 ± 2.59 minutes vs 3.16 ± 1.24 minutes, $P < 0.001$) which is mostly due to the time needed to establish IV line needed in intravenous diazepam administration. This finding is also supported by other studies [25,32,34].

In several studies midazolam has been reported to be a safe drug in controlling seizure episodes [27-29]. Although midazolam usage has been reported to cause hypertension, bradycardia and hypoxia but these effects have been minimal and self limited [20,23].

Kutlu et al [27] reported intranasal midazolam to be 100% effective in controlling prolonged seizure attacks in children. Only in one patient from their study there was a need for re-administration of drug to control the seizure episode and they did not find any serious side effects or respiratory depression except for one case, who had seizure secondary to serious CNS infection [27].

In another study conducted by Fisgin et al on 16 children between 2 months and 14 years suffering from acute seizure episode, intranasal midazolam was administered and the respiratory rate, heart rate, and O_2 saturation was recorded. They concluded the drug to be effective, safe, and easy to administer with less side effects than diazepam [29]. In none of these studies a need for mechanical ventilation after drug administration has been reported.

Similarly to these findings we had no case of treatment failure in our study and the heart rate and O_2 saturation findings indicated no difference between patients treated with intranasal midazolam compared to patients controlled by intravenous diazepam. We also did not encounter any case necessitating the use of mechanical ventilation in line with other studies regarding the safety of intranasal midazolam compared to diazepam.

This study has some limitations namely not being carried out as a double blind study. We did not envision our study as a double blind study due to our limitations regarding the need for rapid control of seizures in emergency department and also the different routes of drug administration. Better designed prospective double blind studies, using a double dummy double blind method, are recommended to further evaluate the effectiveness and safety record of intranasal midazolam in controlling acute seizure.

Conclusion

Considering the shorter time needed to control acute seizure episodes compared to intravenous diazepam and its safety record, intranasal midazolam seems to be a good candidate to replace diazepam, as the drug of choice, in controlling this condition.

Acknowledgment

We would like to thank the personnel of clinical research and development center, Imam Hossein Medical Center, Tehran and Imam Ali Hospital, Zahedan, for their valuable help in conducting this research. This study was registered in Iranian Registry of Clinical Trials with code: IRCT201012105358N1.

Conflict of Interest:

References

- Koren G. Intranasal midazolam for febrile seizures. A step forward in treating a common and distressing condition. *BMJ* 2000;321(7253): 64-5.
- van Stuijvenberg M, deVos S, Tjiang GC, et al. Parents fear regarding fever and febrile seizures. *Acta Paediatr* 1999; 88: 618-22.
- Abend NS, Huh JW, Helfaer MA, Dlugos DJ. Anticonvulsant medications in the pediatric emergency room and intensive care unit. *Pediatr Emerg Care* 2008;24(10):705-21.
- Wermeling DP. Intranasal delivery of antiepileptic medications for treatment of seizures. *Neurotherapeutics* 2009;6(2):352-8.
- Harbord MG, Kyrkou NE, Kyrkou MR, Kay D, Coulthard KP. Use of intranasal midazolam to treat acute seizures in paediatric community settings. *J Paediatr Child Health* 2004;40(9-10): 556-8.
- Somerville ER, Antony JH. Position statement on the use of rectal diazepam in epilepsy. Epilepsy Society of Australia, the Child Neurology Study Group, the Australian Association of Neurologists, and the National Epilepsy Association of Australia. *Med J Aust* 1995; 163(5):268-9.
- Holmes GL. Buccal route for benzodiazepines in treatment of seizures? *Lancet* 1999;353(9153): 608-9.
- Sirsi D. Is intranasal midazolam better than rectal diazepam for home management of acute seizures? *Arch Neurol* 2011;68(1):120-1.
- Johnston MV. Seizures in childhood. In: Kliegman, Behram, Jenson, Stanton, editors. *Nelson Textbook of Pediatrics*, 18th ed. Philadelphia, Saunders, 2007; Pp:2457-75.
- Dundee JW, Halliday NJ, Harper KW, Brogden RN. Midazolam. A review of its pharmacological properties and therapeutic use. *Drugs* 1984; 28(6):519-43.
- Malinovsky JM, Lejus C, Servin F, et al. Plasma concentrations of midazolam after i.v., nasal or rectal administration in children. *Br J Anaesth* 1993;70(6):617-20.
- Knoester PD, Jonker DM, van der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. *Br J Clin Pharmacol* 2002;53(5):501-7.
- de Haan GJ, van der Geest P, Doelman G, et al. A comparison of midazolam nasal spray and diazepam rectal solution for the residential treatment of seizure exacerbations. *Epilepsia* 2010;51(3):478-82.
- Wolfe TR, Macfarlane TC. Intranasal midazolam therapy for pediatric status epilepticus. *Am J Emerg Med* 2006;24(3):343-6.
- Holsti M, Dudley N, Schunk J, et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med* 2010; 164(8):747-53.
- Jeannet PY, Roulet E, Maeder-Ingvar M, et al. Home and hospital treatment of acute seizures in children with nasal midazolam. *Eur J Paediatr Neurol* 1999;3(2):73-7.
- Holsti M, Sill BL, Firth SD, et al. Prehospital intranasal midazolam for the treatment of pediatric seizures. *Pediatr Emerg Care* 2007; 23(3):148-53.
- de Haan GJ, van der Geest P, Doelman G, Bertram E, Edelbroek P. A comparison of midazolam nasal spray and diazepam rectal solution for the residential treatment of seizure exacerbations. *Epilepsia* 2010;51(3):478-82.
- Sharvon S.D. Emergency treatment of status epilepticus: midazolam. In: Sharvon S.D, editor. *Status epilepticus: its clinical features and treatment in children and adults*. Cambridge University Press, Cambridge, 1994; Pp: 213-8.
- Kendall JL, Reynolds M, Goldberg R. Intranasal midazolam in patients with status epilepticus. *Ann Emerg Med* 1997;29(3):415-7.
- Warden CR, Frederick C. Midazolam and diazepam for pediatric seizures in the prehospital setting. *Prehosp Emerg Care* 2006;10(4):463-7.
- Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. *Pediatr Neurol* 2006;34(5):355-9.
- O'Regan ME, Brown JK, Clarke M. Nasal rather than rectal benzodiazepines in the management of acute childhood seizures? *Dev Med Child Neurol* 1996;38(11):1037-45.
- Wallace SJ. Nasal benzodiazepines for management of acute childhood seizures? *Lancet* 1997;349(9047):222.

25. Lahat E, Goldman M, Barr J, Eshel G, Berkovitch M. Intranasal midazolam for childhood seizures. *Lancet*. 1998;352(9128):620.
26. Fişgin T, Güreş Y, Senbil N, et al. Nasal midazolam effects on childhood acute seizures. *J Child Neurol* 2000;15(12):833-5.
27. Kutlu NO, Yakinci C, Doğrul M, Durmaz Y. Intranasal midazolam for prolonged convulsive seizures. *Brain Dev* 2000;22(6):359-61.
28. Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav* 2004;5(2):253-5.
29. Fişgin T, Güreş Y, Senbil N, et al. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. *J Child Neurol* 2002;17(2): 123-6.
30. Scheepers M, Scheepers B, Clarke M, et al. Is intranasal midazolam an effective rescue medication in adolescents and adults with severe epilepsy? *Seizure* 2000;9(6):417-22.
31. Wilson MT, Macleod S, O'Regan ME. Nasal/buccal midazolam use in the community. *Arch Dis Child* 2004;89(1):50-1.
32. Mittal P, Manohar R, Rawat AK. Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures. *Indian J Pediatr* 2006;73(11):975-8.
33. McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. *Acad Emerg Med* 2010;17(6):575-82.
34. Millikan D, Rice B, Silbergleit R. Emergency treatment of status epilepticus: current thinking. *Emerg Med Clin North Am* 2009;27(1):101-13.

Archive of SID