

Randomized clinical trial of sedation with oral midazolam for voiding cystourethrography in children

Hadi Sorkhi¹, Mohammad-Kazem Bakhshandeh-Bali², Haji-Ghorbann Nooredini³

Non-Communicable Pediatric Disease Research Center, Babol University of Medical Sciences, Babol, Iran.

Received: 29 January 2010

Revised: 6 May 2010

Accepted: 13 May 2010

Abstract

Background: Voiding Cystourethrography (VCUG) is a distressing procedure for children. Conscious sedation with any drug that its dose would not influences the procedure is preferred. The aim of this study was to assess the effectiveness of conscious sedation using oral midazolam in children undergoing VCUG.

Methods: From November 2008 to October 2009 period, 93 Patients (68 girls and 25 boys), age ranging from 24 months to 11 years old (mean, 5.8 years) were double blindly randomized to receive a placebo (water) or oral midazolam before the examination. The primary outcome measures were patients' cooperation, facility of the procedure, 48 hours post procedure memory of children, bladder urine residue and detection of Vesocoureteral reflex. The data were analysed by SPSS and categorical variables compared using t-test and continuous variables compared using Chi. Square and Fisher's exact tests.

Results: 93 children were randomizly divided in two groups. In midazolam group, 44(93.6%) patients had good cooperation but in the control group 26(56.5%) had bad cooperation and 19 patients (41.3%) very bad cooperation ($P=0.000$). In midazolam group, 36 children (76.6%) had easy separation from their parents but in control group 20 children (43.5%) had moderate resistant and 21(45.7%) severe resistant. ($P=0.000$). Eighteen (38 %) patients of the study group and twenty patients (43 %) of control group had VUR respectively ($P=0.65$).

Conclusion: According to this study, midazolam is a useful sedation in children undergoing VCUG.

Keywords: conscious sedation, midazolam, pediatric radiology, urinary tract infection, voiding cystourethrography (VCUG).

Introduction

The Vesicoureteral reflux(VUR) is a congenital anomaly and a predisposing factor for urinary tract infection (UTI) that is a risk factor for rennin mediated hypertension and renal failure[1-2]. The Voiding cystourethrography (VCUG) is a method of choice for detecting the

VUR and other anomaly of lower urinary tract system. But this procedure is an invasive and unpleasant method for the children and their parents [3]. Consequently, other methods or agents such as hypnosis or lidocaine lubricant have been recommended to decrease anxiety or increase painful threshold to maintain the child, s cooperation and consciousness [4-5]. Non-

1. Pediatric Nephrologists, Associate Professor, Non-Communicable Pediatric Disease Research Center, Babol University of Medical Sciences, Babol, Iran. Email: dr.sorkhe@yahoo.com

2. **Corresponding author**, Pediatric Resident, Amirkola Children Hospital, Babol University of Medical Sciences, Babol, Iran. Tel: +98 9118036330. Email: mkbakhshandeh@yahoo.com

3. Radiologist, Babol Medical University, Iran. Email: noredinkm@yahoo.com

Table 1. Characteristics of children in midazolam and control groups.

Children	Number	Mean age	Girl	Boy
Midazolam group	47	5.8	34(73.9%)	13(27.7%)
Control group	46	5.3	34(72.3%)	12(26.1%)
Total	93	5.6	68(73.1%)	25(26.9%)

painful route of administration, short acting and quick onset, with no serious side effects and less effect on child cooperation and consciousness during voiding are desirable characteristics of sedative agents used for the VCUG. Although oral chloral hydrate and diphenhydramin are used for noninvasive radiological procedures, but only few reports are available regarding the use of midazolam before the VCUG [6-8]. The Midazolam is a water soluble and short-acting benzodiazepine with sedative, amnesic, anxiolytic, muscle relaxant and anti-convulsant properties. It also has a faster onset and shorter duration of action than the other benzodiazepines such as diazepam and lorazepam. The onset of sedation occurs typically within 3 to 5 minutes after IV injection and 15 to 20 minutes after oral administration. The duration of action is 2 to 6 hours and recovery of sedation usually begins within 5 to 30 minutes. [9-11]. The plasma half life of midazolam is 2 hours with anxiolytic effect of less than 15 minutes after oral use and the child stays conscious and cooperative during the VCUG procedure [12]. Therefore, the use of midazolam may be preferred to than others.

In this study, we evaluated the effect and side effect of the midazolam on sedation of children during VCUG and it was compared with placebo.

Methods

From November 2008 to October 2009 period in Amirkola hospital Babol medical university, 93 children who met the American Society of Anesthesiologists (ASA) classes I and II and without any systemic disease and no history of narcotic usage, were enrolled in this study and double blindly randomized into two groups.

The study group consists of 47 patients, 34 girls, 13 boys, with age ranging from 24 months to 11 years old (mean, 5.8 years) (Table.1) underwent VCUG after receiving oral midazolam. The indications for VCUG were urinary tract infection, urinary incontinence and hydronephrosis.

The control group was 46 children, 34 girls, 12 boys, 24 months to 11 years old (mean, 5.3 years) (Table.1) underwent VCUG after receiving oral water (0.5 cc/kg) as placebo. The indications for VCUG in this group were urinary tract infection and, urinary incontinence. There were no statistically significant differences between the two groups ($p>0.05$).

The Midazolam (5 mg/ml) was added to a concentrated artificially sweetened Kool-Aid mixture with a total dose of 0.6 mg/kg and administered to the child in the radiology unit. The maximum prescribed dose was 15 mg.

The parents of children were contacted via phone in pediatric sedation a few days before the sedation was scheduled. Vital signs were obtained before the administration of the midazolam at every 5 minutes for a 45 minutes period. In addition, pulse oximetry was recorded every 5 minutes for 15 minutes and then every 10 minutes for an additional 30 minutes.

The significant decrease in oxygen saturation was defined as a drop in PO_2 by more than 10%. Approximately 20-30 minutes after receiving oral midazolam, the child underwent the VCUG, and their Parents were allowed to be present in the room with them during the study. The children were kept in the radiology unit until they could drink clear liquids, at least 30 minutes after completing the examination.

Patient cooperation along with facility of

Table 2. Vital signs of children in midazolam and control groups.

Children	Before vcug		During vcug		After vcug	
	PR	O2 sat	PR	O2 sat	PR	O2 sat
Midazolam group	79 / min	96%	82/min	93%	81/min	95%
Control group	85/min	97%	99/min	98%	96/min	98%
Mean	81/min	96.4%	90/min	95.4%	88/min	96.4%

parent separation were measured during the VCUG and recorded by a trained nurse when conducting and monitoring the sedation procedure according to Table 3. 48 hours after the procedure, the children memory about the VCUG was obtained by telephone call from their parents.

The data were analysed by SPSS and categorical variables compared using t-test and then continuous variables compared by Chi-Square and Fisher's exact test.

Results

The children's behavior began to change 15 minutes after taking the midazolam. Typically, they had slurred speech, ataxia, and anxiolytic, yet were able to communicate with their parents and the radiology staff. There were not any significant changes in the vital signs and pulse oximetry in midazolam group (Table.2).

In midazolam group 44(93.6%) patients had good cooperation, and 3 children (6.4%) bad cooperation, but in the control group 1(2.2%) had good cooperation, 26(56.5%) had bad co-

operation and 19(41.3%) very bad cooperation ($P=0.000$) (table.1). To evaluate the facility of parent separation in midazolam group, 36 (76.6%), 10(21.3%), 1 (2.1%) children had easy separation, mild resistance, moderate resistance from their parents respectively, and there was not severe resistance (table.3).

In the control group, 1(2.1%), 4(8.7%), 20(43.5%) and 21(45.7%) children had easy separation, mild resistance, moderate resistance and severe resistance from their parents respectively ($P=0.000$) (table.3).

48 hours later in the study group, 30 (63.8%) children could not remember the procedure, 11 (23.4%) had a good memory, and 6 (12.8%) cases had a "negative" experience. In the control group 1 (2.2 %) child could not remember the study, 6 (13%) cases had a good memory, and 39 (84.8%) patients had a "negative" experience ($P=0.000$) (Table 3).

Most patients within the two groups had no residual urine but mean residual urine of the others were 5 cc in midazolam group and 2 cc in control group ($p>0.05$). Eighteen (38%) pa-

Table 3. Parent separation facility, children cooperation and memory during the voiding cystourethrography.

<i>Children cooperation score *</i>	<i>Midazolam group</i>	<i>Control group</i>
good (mild irritability)	44(93.6%)	1(2.2%)
bad (moderate irritability)	3 (6.4%)	26(56.5%)
very bad (severe irritability)	-	19(41.3%)
<i>Parent separation facility score *</i>	<i>Midazolam group</i>	<i>Control group</i>
easy (no movement and crying)	36 (76.6%)	1(2.1%),
mild resistant (a little crying)	10(21.3%),	4(8.7%),
moderate resistant (more crying and movement)	1 (2.1%)	20(43.5%)
severe resistant (very crying and movement)	-	21(45.7%)
<i>Children memory after 48 hr *</i>	<i>Midazolam group</i>	<i>Control group</i>
no memory	30 (63.8%)	1 (2.2 %)
good memory	11 (23.4%)	6 (13%)
negative" experience	6 (12.8%)	39 (84.8%)

* $P\text{-value}<0.05$

tients of the study group and 20(43%) children in the control group had vesicoureteral reflux ($P>0.05$).

The side effects were basically one episode of vomiting and one episode of lethargy after the procedure in the study group that improved after 30 minutes. No remarkable cardiopulmonary, respiratory or over sedation events were noted.

The patients and their parents gave their informed consent in accordance with the Declaration of Helsinki and the consent forms were signed by their parents. This study was approved by the Ethics Committee of Babol University of Medical Science as final residency thesis number 276.

Discussion

This study showed that oral midazolam can be used for sedation of children before the VCUG. Oral midazolam was used instead of the VCUG procedure. Heden et al, reported reducing fear and distress for needle procedures in oncology patients, especially in children under 7 years old when oral midazolam was used [12]. Also, Cengiz et al, showed the safety and effective sedation in children undergoing MRI with oral midazolam and diphenhydramin [13]. Consequently, the midazolam is considered safe drug not only for VCUG but also it may be used for other invasive and non invasive procedures.

In our study, there was not significant difference between the detection of VUR in midazolam and the control group ($p>0.05$). The Propofol was used for sedation of children before VCUG and patient could not void the urine completely [14]. Keidan and et al, used oral midazolam and continuous flow 50% nitrous oxide and reported the safety and decreased anxiety and distress for VCUG, but sedation effect is more rapid with nitrous oxide and the recovery time is shorter than the midazolam [15].

Wheesler et al compared oral chloral hydrate and the midazolam for sedation of children un-

dergoing echocardiography, and reported deeper sedation with chloral hydrate than midazolam [16].

In this study the change of behavior initiated 15 minutes after taking the drug and 93.6% of had good cooperation in midazolam group, but 98% of the control group patients did not have good cooperation ($p<0.05$). Moreover the residual urine was not different in both groups ($p>0.05$). Although in the Merguerian et al study, voiding was not completed with sedation included by propofol, and they suggested that sedation might interfere with diagnosis of the VUR, but in our study there were no differences between residual urine and detection of VUR in the midazolam group. Nonetheless significant side effects were present in midazolam group and there were only one episode of vomiting and a case with lethargy which improved within 30 minutes. The negative experience after 48 hours of procedure in patients and their parents was 6 (12.8%) and 39 (84.8%) cases for midazolam and control group, respectively. Anterograde amnesia after 48 hours of procedure in patients was 1(2.2%) and 30 (63.8%) patients in midazolam and control group, respectively.

Oral pentobarbital was recommended by some authors for oral sedation in the radiographic procedures. Other studies were done in infants with a small population. Therefore studies with higher patient population are needed in all pediatric ages' group, in order to assess the midazolam effects [17-18].

Conclusion

In conclusion, we recommend using the midazolam to decrease anxiety in patients undergoing the VCUG with bearing few but not significant side effects.

Acknowledgments

We are grateful to the Research Council and Non communicable Pediatric Research Center of Babol Medical University, for supporting this study.

References

1. Weiss R, Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). The International Reflux Study in Children. *J Urol* Nov 1992; 148(5 Pt 2): 1667-73.
2. Walter F, Heale B. Hereditary Vesicoureteral reflux; Phenotype variation and family screening. *Pediatr Nephrol* 1997; 11: 504-507.
3. Stashinko EE, Goldberger J. Test or trauma: The voiding cystourethrogram experience of young children. *Issues Compr Pediatr Nurs* 1998; 21(2): 85-96.
4. Gerard LL, Cooper CS, Duethman KS, et al. Effectiveness of lidocaine lubricant for discomfort during pediatric urethral catheterization. *J Urol* Aug 2003. 170(2 Pt 1):564-7.
5. Butler LD, Symons BK, Henderson SL, et al. Hypnosis reduces distress and duration of an invasive medical procedure for children. *Pediatrics* Jan 2005; 115(1): 77-85.
6. Stokland E, Andréasson S, Jacobsson B, et al. Sedation with midazolam for voiding cystourethrography in children: a randomised double-blind study. *Pediatr Radiol* 2003; 33(4): 247-9.
7. Elder JS, Longenecker R. Premedication with oral midazolam for voiding cystourethrography in children: safety and efficacy. *AJR Am J Roentgenol* 1995; 164(5): 1229-32.
8. Herd DW, McAnulty KA, Keene NA, et al. Conscious sedation reduces distress in children undergoing voiding cystourethrography and does not interfere with the diagnosis of vesicoureteric reflux: a randomized controlled study. *AJR Am J Roentgenol* 2006; 187(6): 1621-6.
9. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998; 35: 37-47.
10. Rey E, Delaunay L, Pons G, et al. Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *Eur J Clin Pharmacol* 1991; 41(4): 355-7.
11. Malinovsky JM, Populaire C, Cozian A, et al. Premedication with midazolam in children. Effect of intranasal, rectal and oral routes on plasma midazolam concentrations. *Anaesthesia* 1995; 50(4): 351-4.
12. Hedén L, von Essen L, Frykholm P, et al. Low-dose oral midazolam reduces fear and distress during needle procedures in children with cancer. *Pediatr Blood Cancer* 2009; 15;53(7): 1200-4.
13. Cengiz M, Baysal Z, Ganidagli S. Oral sedation with midazolam and diphenhydramine compared with midazolam alone in children undergoing magnetic resonance imaging. *Paediatr Anaesth* 2006; 16(6): 621-6.
14. Merguerian PA, Corbett ST, Cravero J. Voiding ability using propofol sedation in children undergoing voiding cystourethrograms: a retrospective analysis. *J Urol* 2006; 176(1): 299-302.
15. Keidan I, Zaslansky R, Weinberg M, et al. Sedation during voiding cystourethrography: comparison of the efficacy and safety of using oral midazolam and continuous flow nitrous oxide. *J Urol* 2005; 174(4 Pt 2): 1598-600;
16. Wheeler DS, Jensen RA, Poss WB. A randomized, blinded comparison of chloral hydrate and midazolam sedation in children undergoing echocardiography. *Clin Pediatr Phila* 2001; 40(7): 381-7.
17. Mason KP, Sanborn P, Zurakowski D, et al. Superiority of pentobarbital versus chloral hydrate for sedation in infants during imaging. *Radiology* 2004; 230(2): 537-42.
18. Chung T, Hoffer FA, Connor L, et al. The use of oral pentobarbital sodium (Nembutal) versus oral chloral hydrate in infants undergoing CT and MR imaging a pilot study. *Pediatr Radiol* 2000; 30(5): 332-5.