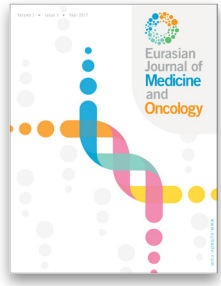
EJMO

DOI: 10.14744/ejmo.2017.18480
EJMO 2017;1(4):207-211



Research Article

A Randomized, Prospective, Double-Blind Clinical Trial on the Optimal Dose of Oral Midazolam Premedication in Pediatric Day Case Surgery

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Abstract

Objectives: Anxiolysis and sedation with oral midazolam are common practice in pediatric anesthesia. The aim of the present study was to evaluate the efficacy and safety of 3 different doses of midazolam as a premedication agent in day case pediatric surgery patients.

Methods: This prospective, randomized, double-blind clinical investigation was designed at Medeniyet University Göztepe Education and Training Hospital Department of Anesthesiology and Reanimation. In all, 90 children aged 6 months to 6 years with American Society of Anesthesiologists physical status of class I or II, who were scheduled for inguinal hernia repair or hydrocele operation were included in the study. Patients were randomly allocated into 3 groups to receive midazolam premedication 0.3 mg kg-1 (Group I), 0.5 mg kg-1 (Group II), or 0.75 mg kg-1 (Group III). Psychological, behavioral, and physiological parameters (heart rate, mean arterial pressure, arterial oxygen saturation, respiratory rate, sedation, anxiolysis score and mask toleration score) were recorded at particular time intervals and special stressful events (separation from parents, induction of anesthesia). Adverse events were also noted.

Results: Satisfactory sedation was achieved in all groups. At the end of the operation, the sedation score was higher in Group III. The anxiety rating of face mask application was satisfactory in Group II. There were significant differences between groups in hemodynamic variables, oxygen saturation, and respiratory rate. However, they were accepted as clinically insignificant. There was no significant difference in separation scores between the 3 groups. Postoperative vomiting occurred in 3 patients in Group II and in 2 patients in Group III. Also in Group III, recovery was late in 2 patients and agitation was seen in 2 patients.

Conclusion: A dose of 0.3-0.75 mg kg-1 oral midazolam can be used safely for the premedication of pediatric patients to provide sufficient sedation, a pleasant separation from the parents, and fair tolerance of face mask application.

Keywords: Children, midazolam, premedication, sedation

Cite This Article: *Ordu S, Orhon Z, Celik M. A Randomized, Prospective, Double-Blind Clinical Trial on the Optimal Dose of Oral Midazolam Premedication in Pediatric Day Case Surgery. EJMO. 2017; 1(4): 207-211*

In recent years, an increasing amount of pediatric surgery has been performed on an outpatient basis. Children are excellent candidates for day case surgery because they are usually healthy, free of systemic disease, and require only minor or intermediate surgical procedures. Undoubtedly, a primary reason is cost effectiveness. Also, waiting lists can be reduced and inpatient resources can be used for children requiring more complex surgical procedures. The preoperative period can be a stressful time for children and their parents. Effective premedication minimizes

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Submitted Date: June 29, 2017 **Accepted Date:** October 10, 2017 **Available Online Date:** November 01, 2017

the emotional trauma. An ideal preanesthetic medication should have the features of easy application, rapid onset, short duration, and a lack of significant side effects. Preanesthetic medication with benzodiazepines reduces anxiety and produces sedation and anterograde amnesia. Oral premedication with midazolam is common practice in pediatric anesthesia.[1]

The aim of this study was to investigate the efficacy and safety of 3 different doses of midazolam used in premedication in day case pediatric surgery patients.

Methods

After receiving our institutional Ethics Committee approval and parental written, informed consent, 90 healthy children between the ages of 6 months and 6 years, who were American Society of Anesthesiologists physical status I or II outpatients undergoing inguinal hernia repairing or a hydrocele operation, were enrolled in this double-blinded study. Exclusion criteria were central nervous system disorders; obesity; hepatic, renal, or gastrointestinal dysfunction; anticipated difficult airway; refusal of the whole dose of the study drug; or any medical status that could compromise the safety of the patient or interfere with the interpretation of the results. The study drug was injectable midazolam (5 mg mL $^{-1}$ or 15 mg mL $^{-1}$) prepared in cherry juice at a total volume of 0.4 mL kg $^{-1}$ by an anesthesiologist who was not one of the observers. The study drugs were marked only with a coded label to maintain the double-blinding. The children were allocated to 1 of 3 study groups using random, computer-generated numbers (Microsoft Excel software; Microsoft Corp., Redmond, WA, USA). Midazolam was administered orally 30 minutes before surgery as follows: Group I (n=30) was given 0.3 mg kg -1, Group II (n=30) received 0.5 mg kg $^{-1}$, and Group III (n=30) was given 0.75 mg kg^{-1}. An observer blinded to the group assignment recorded baseline heart rate (HR) and respiratory rate (RR), and an anxiety score before the administration of preanesthetic medication. A parental separation score (at the time of separation from parents) was assessed using a 4-point scale shown in Table 1.[2] When the children were taken into the operating room, the degree of sedation was assessed using a 5-point sedation scale provided in Table 2.[3] Mean arterial pressure (MAP), HR, RR, and peripheral oxygen saturation (SaO_2) were recorded 30 minutes after administration of the drug, before induction of anesthesia, at the end of the operation, and in the recovery period.

Intravenous access was attempted when the patients were taken into the operating room. If it was successful, general anesthesia was induced with thiopental sodium 5 mg kg^{-1}. If intravenous access couldn't be established, anesthesia was induced with sevoflurane 8% and 50% nitrous oxide and 50% oxygen, and afterwards venipuncture was performed. At the time of face mask application, cooperation (mask tolerance) was assessed with a 4-point scale (4: poor, strongly refuses intervention; 3: fair, considerable effort required to achieve compliance with intervention; 2: good, accepts intervention reluctantly; 1: excellent, accepts intervention readily). A score of 1 to 3 was considered satisfactory. Rocuronium 0.6 mg kg $^{-1}$ was administered for muscle relaxation, and then laryngeal mask or endotracheal tube was inserted. Paracetamol 15 mg kg^{-1} was given for postoperative analgesia intravenously at the time of wound closure. At the end of the surgical procedure, residual neuromuscular blockade was antagonized with atropine and neostigmine. After extubation, complications such as agitation or postoperative nausea and vomiting (PONV) were recorded.

Statistical Analysis

Demographic data (age, weight, sex, duration of operation), HR, MAP, RR, SaO_2, and sedation score were compared using one-way analysis of variance with posthoc analysis (t-test) and chi-square test. The Tukey test was also used in comparisons within groups. Results were expressed as mean and standard deviation. Values of $p<0.05$ were considered statistically significant.

Results

The patients demographic variables are provided in Table 3. There was no statistically significant difference between

Table 1. Separation scale

Criteria	Grade	Score
Patient unafraid, cooperative, asleep	Excellent	1
Slight fear or crying, quiet with reassurance	Good	2
Moderate fear, crying, not quiet with reassurance	Fair	3
Crying, need for restraint	Poor	4

A score of 1 or 2 was considered satisfactory, and a score of 3 or 4 was judged unsatisfactory.

Table 2. Sedation scale

Level of sedation	Score
Agitated, clinging to the parent, crying	1
Alert but anxious, not clinging to parent, may whimper, but not cry	2
Calm, sitting or lying comfortably with eyes open	3
Drowsy, eyes closed, but responds to verbal/tactile stimulation	4
Asleep, not responding to minor stimulation	5

A sedation score of 3 or above was considered satisfactory, and a scoreof 1 or 2 was deemed unsatisfactory.

Table 3. Demographic variables

	Group 1	Group 2	Group 3	p
Age (years)	4.75±2.74	4.64±2.86	4.18±2.40	0.106
Sex				
Male	29	24	24	0.685
Female	1	6	6	
Weight (kg)	16.65±5.87	17.25±6.02	17.21±7.15	0.920
Duration of surgery (min)	35.23±7.08	38.40±6.63	36.26±4.56	0.136

Data were expressede as mean (SD or range) or number.

Table 4. Method of induction and technique of controling airway

	Group 1	Group 2	Group 3
Technique of controling airway			
LMA	13	11	10
ETT	17	19	20
Method of induction			
Intravenous	7	13	7
Inhalation	23	17	23

ETT: Endotracheal tube; LMA: Laryngeal mask airway.

Table 5. Sedation score of the groups

Level of sedation	Group 1	Group 2	Group 3	p
Basal	1.45±0.40	1.40±0.49	1.43±0.50	>0.05
Before induction	3.16±0.98	3.90±0.80	4.83±0.69	<0.01
	***, ##	***, ##	***, ##	
End of operation	3.30±1.08	3.93±0.78	4.80±0.84	<0.01
	***, ##	***, ##	***, ##	
Recovery	3.06±0.86	3.70±0.65	4.03±0.66	<0.01
	***, ##	***, ##	***, ##	

Significant differences p<0.01 between groups.

*** Significant differences p<0.001 in the group compared with baseline.

Table 6. Mask tolerance and separation score of the groups (mean±SD)

	Group 1	Group 2	Group 3	p
Mask tolerance	2.33±1.24 ##	1.46±0.68 ##	1.86±1.19 ##	=0.009
Separation score	1.76±0.77	1.50±0.50	1.86±0.77	=0.095

Significant differences p<0.01 between groups.

the groups in patient characteristics (age and weight) or duration of surgery (Table 3).

There were no significant differences between the groups in the method of induction or technique of controlling the airway (Table 4).

There was no significant difference in HR between the groups. In the comparison within groups, in Group I and Group II, HR values were significantly higher before induction, at the end of the operation, and in the recovery period, compared with the baseline HR values. There was no significant difference in Group III HR at any period.

MAP values were significantly lower in Group III than in the other 2 groups in the recovery period. There was no significant difference between Groups I and II.

There was a statistically significant difference in the SaO_2 level between groups, but it was not clinically significant.

The RR level was significantly lower in Group II and Group III before induction. In comparison within the groups, RR levels were significantly lower than baseline levels in Groups II and III before induction, at the end of the operation, and in the recovery period.

A sedation score of 3 to 5 was considered satisfactory, and this target level was achieved in all groups. The sedation score evaluated before induction was lower in Group I than that seen in Group II and Group III. The score was also lower in Group II than in Group III (p<0.01). At the end of the operation, the sedation score in Group III was higher than in the other 2 groups and it was also higher in Group II than in Group I (p<0.01). In the recovery period, it was similar in Group II and Group III, and higher than in Group I (Table 5).

Group sedation scores, before induction, the end of the operation and recovery period scores were significantly higher (p<0.001) (Table 5).

There was no significant difference in parental separation score between groups. A score of 1 or 2 was accepted as satisfactory and was observed in all groups. The best mask tolerance was observed in Group II (Table 6).

PONV was seen in 3 patients in Group II and 2 patients in Group III. Recovery was longer in 2 patients in Group III and postoperative agitation was also observed in 2 patients in Group III.

Discussion

In recent years, there has been a trend toward performing pediatric surgery on a day care basis. More than 60% of pediatric surgery in the United States of America is performed in outpatient clinics.[4]

Anesthesia and surgery may cause a great deal of anxiety in both the parents and the child. Fear of painful or unpleasant procedures and separation from parents may result in psychological consequences in children.[5] Therefore, effective preanesthetic medication is important to alleviate the stress and fear of surgery as well as to ease child-parent separation and promote a smooth induction.

In the past, due to excessive postoperative sedation and the emetic side effects of opioids,

sedative premedication was not routinely used in pediatric day care practice.

Today, anxiolysis and sedation using preoperative medication is common practice in pediatric anesthesia. Key features of good premedication are easy application, rapid onset, short duration, and a lack of significant side effects. These criteria are met by midazolam, which offers multiple routes of administration (oral, rectal, nasal), a rapid onset (10-20 minutes), approximately 30-minute duration, and no interference with vital signs in doses less than 0.5 mg kg^{-1}. Benzodiazepines reduce anxiety and produce sedation and anterograde amnesia.[6, 7] In this study, the oral route was preferred for the ease of application.

Midazolam is a known substrate of the cytochrome P450 3A4 enzyme system,[8, 9] so patients taking known cytochrome P450 3A4 inhibitors (e.g., grapefruit juice, imidazole derivatives, erythromycin, clarithromycin, or cimetidine)[10] or cytochrome P450 3A4 inducers (e.g., phenobarbital, phenytoin, rifampin, or corticosteroids) were excluded.[11-13] Mishra evaluated the efficacy of saline solution and 3 doses of oral midazolam, 0.5, 0.75, and 1 mg kg^{-1}, as premedication for pediatric neurosurgery patients. He reported that the patients in the midazolam groups had better separation scores and that the patients who were given 1 mg kg^{-1} midazolam had higher sedation scores and a later recovery than the other groups. A dose of 0.75 mg kg^{-1} midazolam was found to be effective and safe for patients undergoing neurosurgical operations.[14] McMillan studied the effects of oral midazolam doses of 0.5, 0.75, 1 mg kg^{-1}, and a placebo on sedation, anxiolysis, and separation scores in pediatric surgery patients. HR, systolic blood pressure, SaO^2, and RR were unchanged during the study. He concluded that sedation and anxiolysis was better in the midazolam groups and that 80% to 90% of the patients in the midazolam groups demonstrated excellent separation scores and that there was no significant difference between the midazolam groups. He reported some side effects (loss of balance and head control, blurred vision, and dysphoric reactions) with 0.75 and 1 mg kg^{-1} midazolam, and recommended 0.5 mg kg-1 midazolam as an effective and safe means of anxiolysis.[7]

According to our results, there was no difference in HR between groups. MAP values were significantly lower in the recovery period with midazolam 0.75 mg kg^{-1}. There was a statistically significant difference in SaO_2 level between groups; however, it was not clinically significant. RR levels were significantly lower with doses of 0.5 and 0.75 mg kg^{-1}.

Cote compared 3 doses, 0.25, 0.5, and 1 mg kg-1, of a commercially prepared oral midazolam syrup in children. He concluded that oral midazolam syrup was effective to produce sedation and anxiolysis at a dose of 0.25 mg kg^{-1}, with minimal effects on respiration and oxygen saturation even when administered at doses as large as 1.0 mg kg^{-1}. With all doses, 97% of the patients demonstrated satisfactory sedation, and 86% demonstrated satisfactory anxiolysis when the face mask was applied.[15]

Ko et al. investigated the effect of premedication with low-dose (0.2 $mgkg^{-1}$) oral midazolam on the incidence and severity of emergence agitation in pediatric patients following sevoflurane anesthesia. A significantly lower incidence and less severe emergence agitation were noted in patients given midazolam. The duration of the post anesthetic care unit stay was not significantly different from that of saline-treated patients; however, both parents and the post anesthetic care unit nurses were more satisfied with midazolam.[16]

Brosius compared 2 oral dosage formulations of midazolam on sedation score and plasma midazolam level using either 0.5 mg kg^{-1} of commercial syrup or a prepared mixture as an anesthetic premedication. He concluded that a prepared mixture with intravenous midazolam produced a greater sedative effect and higher plasma midazolam levels.[17]

Levine et al. investigated the minimum time interval between 0.5 mg kg^{-1} oral midazolam premedication and separation from parents that ensures a smooth separation. They concluded that children may be separated from their parents as early as 10 minutes after receiving oral midazolam 0.5 mg kg^{-1}.[18]

Parnis et al. studied the effects of oral premedication with midazolam 0.25 and 0.5 mg kg^{-1}, diazepam 0.5 mg kg^{-1}, or a placebo in 200 children undergoing day-stay anesthesia. The results showed that a high proportion of unsedated children are calm at induction of anesthesia and that oral midazolam is an effective premedication in children for day-stay anesthesia.[19]

Feld et al. evaluated the effectiveness of 3 different doses of oral midazolam, 0.25, 0.50, and 0.75 mg kg^{-1}, on children's sedation level, the quality of separation from parents, and the degree of cooperation with inhalation anesthesia. They concluded that oral midazolam at a dose of 0.5 to 0.75 mg kg^{-1} was an effective preanesthetic medication for pediatric outpatients.[20]

In the present study, a sedation score 3 to 5 was considered satisfactory and was achieved in all groups. The patients who were given 0.75 mg kg^{-1} midazolam had higher sedation scores and their recovery was later than in the other groups. There was no significant difference in parental separation scores between the groups. Satisfactory parental separation scores were observed in all groups. Our results are similar to those of McMillan, Keith, and Levine.

Arai et al. and Kazak et al. investigated whether the combination of low-dose (0.25 mg kg^{-1}) midazolam premedication with parental presence can effectively reduce anxiety at induction, as well as provide a smoother emergence. Children were randomized to receive either 0.5 mg kg^{-1} or 0.25 mg kg^{-1} midazolam with parental presence or parental presence alone. These studies demonstrated that preoperative administration of midazolam 0.5 mg kg^{-1} and low-dose midazolam 0.25 mg kg^{-1} with parental presence at induction were both equally effective at reducing separation anxiety and providing a smooth emergence. Parental presence during induction of anesthesia enhanced the effect of oral midazolam. However, parental presence alone, without midazolam for premedication, was not an adequate approach for this outcome.[21, 22]

Conclusion

We concluded that premedication with 0.3 to 0.75 mg kg^{-1} oral injectable midazolam in pediatric patients scheduled for inguinal hernia repair or hydrocele operation was acceptable, effective, and safe. A dose of 0.75 mg kg^{-1} does not offer any additional benefit over a dose of 0.3 or 0.5 mg kg^{-1}, but does delay recovery and may compromise safety. If the environment is convenient for parental presence, the dose of midazolam may be reduced.

Disclosures

Ethics Committee Approval: The study was approved by the local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – S.O., Z.N.O.; Design – Z.N.O., S.O.; Supervision – Z.N.O.; Materials – S.O., Z.N.O.; Data collection &/or processing – S.O.; Analysis and/or interpretation – S.O., Z.N.O.; Literature search – Z.N.O., S.O.; Writing – Z.N.O.; Critical review – M.C., Z.N.O.

References

1. Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S. Premedication in the United States: a status report. Anesth Analg 1997;84:427–32.
2. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Br J Clin Pharmacol 1998;46:101–10.
3. Naqash I, Nisa W, Zargar J, Farooqi A. Midazolam premedication in children: comparison of nasal and sublingual routes. J Anaesth Clin Pharmacol 2004;20:141–5.
4. Hannallah RS, Epstein BS. The paediatric patient. In: Wetchler VV, editor. Anesthesia for ambulatory surgery. 2nd ed. Philadelphia: JB Lippincott; 1997. p. 131–95.
5. Karl HW, Keifer AT, Rosenberger JL, Larach MG, Ruffle JM. Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients. Anesthesiology 1992;76:209–15. [CrossRef]
6. Geldner G, Hubmann M, Knoll R, Jacobi K. Comparison between three transmucosal routes of administration of midazolam in children. Paediatr Anaesth 1997;7:103–9. [CrossRef]
7. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. Can J Anaesth 1992;39:545–50. [CrossRef]
8. Thummel KE, O'Shea D, Paine MF, Shen DD, Kunze KL, Perkins JD, et al. Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. Clin Pharmacol Ther 1996;59:491–502. [CrossRef]
9. Wandel C, Böcker R, Böhrer H, Browne A, Rügheimer E, Martin E. Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaesth 1994;73:658–61. [CrossRef]
10. Hiller A, Olkkola KT, Isohanni P, Saarnivaara L. Unconsciousness associated with midazolam and erythromycin. Br J Anaesth 1990;65:826–8. [CrossRef]
11. Yuan R, Flockhart DA, Balian JD. Pharmacokinetic and pharmacodynamic consequences of metabolism-based drug interactions with alprazolam, midazolam, and triazolam. J Clin Pharmacol 1999;39:1109–25.
12. Pelkonen O, Mäenpää J, Taavitsainen P, Rautio A, Raunio H. Inhibition and induction of human cytochrome P450 (CYP) enzymes. Xenobiotica 1998;28:1203–53. [CrossRef]
13. Watanabe M, Tateishi T, Asoh M, Nakura H, Tanaka M, Kumai T, et al. Effects of glucocorticoids on pharmacokinetics and pharmacodynamics of midazolam in rats. Life Sci 1998;63:1685–92.
14. Mishra LD, Sinha GK, Bhaskar Rao P, Sharma V, Satya K, Gairola R. Injectable midazolam as oral premedicant in pediatric neurosurgery. J Neurosurg Anesthesiol 2005;17:193–8. [CrossRef]
15. Coté CJ, Cohen IT, Suresh S, Rabb M, Rose JB, Weldon BC, et al. A comparison of three doses of a commercially prepared oral midazolam syrup in children. Anesth Analg 2002;94:37–43.
16. Ko YP, Huang CJ, Hung YC, Su NY, Tsai PS, Chen CC, et al. Premedication with low-dose oral midazolam reduces the incidence and severity of emergence agitation in pediatric patients following sevoflurane anesthesia. Acta Anaesthesiol Sin 2001;39:169–77.
17. Brosius KK, Bannister CF. Midazolam premedication in children: a comparison of two oral dosage formulations on sedation score and plasma midazolam levels. Anesth Analg 2003;96:392–5. [CrossRef]
18. Levine MF, Spahr-Schopfer IA, Hartley E, Lerman J, MacPherson B. Oral midazolam premedication in children: the minimum time interval for separation from parents. Can J Anaesth 1993;40:726–9. [CrossRef]
19. Parnis SJ, Foate JA, van der Walt JH, Short T, Crowe CE. Oral midazolam is an effective premedication for children having day-stay anaesthesia. Anaesth Intensive Care 1992;20:9–14.
20. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 1990;73:831–4. [CrossRef]
21. Arai YC, 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.
22. Kazak Z, Sezer GB, Yilmaz AA, Ates Y. Premedication with oral midazolam with or without parental presence. Eur J Anaesthesiol 2010;27:347–52. [CrossRef]