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Oral Midazolam Preanesthetic Medication in Pediatric Outpatients

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A need exists for a safe and effective oral preanesthetic medication for use in children undergoing elective surgical procedures. We evaluated the effectiveness of three different doses of oral midazolam when administered in combination with atropine prior to ambulatory surgery. In this randomized, double-blind, placebo-controlled study, 124 children, ages 1–10 yr, received midazolam, 0.25, 0.50, or 0.75 mg · kg^{-1} po, and atropine, 0.03 mg · kg^{-1} po, mixed with apple juice, or a placebo (containing the midazolam vehicle, atropine, and apple juice). A blinded observer noted the child's level of sedation, the quality of separation from parents, and the degree of cooperation with an inhalation induction of anesthesia. Picture-recall was used to assess the amnesic effect of midazolam in children over 5 yr of age. Midazolam 0.75 mg · kg^{-1} produced significant sedation at 30 min. After procedures lasting an average of 106–113 min, recovery was not prolonged by the oral midazolam–atropine combination. We concluded that oral midazolam 0.5–0.75 mg · kg^{-1} is an effective preanesthetic medication for pediatric outpatients. (Key words: Anesthesia: outpatient; pediatric. Anesthetics, hypnotics: midazolam. Premedication, oral: midazolam, atropine.)

EFFECTIVE PREANESTHETIC MEDICATION for use in children undergoing operations in the outpatient setting should allay apprehension regarding anesthesia and surgery, lessen the trauma of separation from family, and facilitate induction of general anesthesia without prolonging the postanesthetic recovery period.[1] Midazolam (Versed®), a water-soluble benzodiazepine, has been shown to be an effective intramuscular preanesthetic medication in both adults[2,3] and children[4,5] that does not prolong the recovery room stay. Furthermore, oral midazolam was reported to provide rapid sedation and amnesia when administered to adults undergoing outpatient dental[6] and ophthalmologic surgery.[7]

A recent study suggested that oral preanesthetic medication may be as efficacious as intramuscular preanesthetic medication in pediatric patients.[8] In a preliminary study,[9] we reported that midazolam 0.5 mg · kg^{-1} po was as effective as midazolam 0.2 mg · kg^{-1} im for preanesthetic medication in children. However, concerns have been raised regarding the potential of effective oral doses of midazolam to prolong recovery times.[10,11] The current investigation was designed to determine the optimal oral dose of midazolam when used as preanesthetic medication in children. In this prospective, randomized, placebo-controlled, double-blind study, we evaluated the perioperative effects of midazolam 0.25–0.75 mg · kg^{-1} po in pediatric outpatients presenting for elective surgery.

Materials and Methods

One hundred twenty-four children, ages 1–10 yr, were randomly assigned to one of four treatment groups (n = 31 each) according to a double-blind protocol design. Patients assigned to group 1 received the midazolam vehicle; group 2, midazolam 0.25 mg · kg^{-1} po; group 3, midazolam 0.5 mg · kg^{-1} po; and group 4, midazolam 0.75 mg · kg^{-1} po. All patients received atropine 0.03 mg · kg^{-1} po in 5 ml apple juice. The study was approved by the Institutional Review Board at Stanford University and was performed at Stanford University Hospital. Written informed consent was obtained from the child's parents or legal guardians.

The level of sedation was assessed with a 3-point sedation scale (1 = tearful/combative; 2 = alert/aware; and 3 = drowsy/sleeping) at the time of preanesthetic medication and every 15 min thereafter until entry into the operating room. Just prior to separation from their parents, children greater than 5 yr of age were shown a picture of either a house, cat, or fish. At the time of separation from their parents, the child's behavior was evaluated with a different 3-point rating scale (1 = poor [anxious/combative]; 2 = good [anxious/easily reassured]; 3 = excellent [calm/drowsy]). A minimum of 30 min were allowed from the time of oral preanesthetic medication until entering the operating room. After the patient had entered the operating room, induction of anesthesia *via* mask was initiated with nitrous oxide 70% in oxygen and halothane 1–3%.

The quality of induction was evaluated with a 4-point rating scale: 1 = poor (afraid, combative, crying); 2 = fair (moderate fear of mask; not easily calmed); 3 = good (slight fear of mask; easily calmed); and 4 = excellent (unafraid, cooperative; accepts mask readily). The times

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TABLE 1. Demographic and Time Interval Data for the Four Midazolam Treatment Groups

Treatment Group	Number (n)	Age (months)	Weight (kg)	Premedication Time (min)	Anesthesia Time (min)	Eye Opening Time (min)	Discharge Time (min)
1) Placebo	31	58 ± 33	20 ± 10	39 ± 11	113 ± 73	12 ± 15	152 ± 74
2) 0.25 mg·kg^{-1}	31	47 ± 29	17 ± 7	49 ± 31	107 ± 81	15 ± 16	144 ± 80
3) 0.5 mg·kg^{-1}	31	47 ± 24	16 ± 4	44 ± 21	106 ± 55	16 ± 15	137 ± 58
4) 0.75 mg·kg^{-1}	31	45 ± 34	17 ± 9	40 ± 9	107 ± 76	13 ± 13	142 ± 59

Data shown are mean values ± SD.

from administration of the preanesthetic medication to induction of anesthesia, from discontinuation of anesthesia until spontaneous eye opening, from induction of anesthesia until extubation of the trachea, and from admission to the postanesthesia care unit (PACU) until discharge were recorded. Immediately prior to discharge from the PACU, the older children were asked to recall the picture shown to them prior to induction of anesthesia. Upon discharge from the recovery room, the child's level of sedation was assessed with the same 3-point scale used to assess their preoperative (baseline) level of sedation. All adverse reactions and side effects during the perioperative period were recorded.

Twenty-four hours after the surgical procedure, the child's parents were asked to complete a follow-up questionnaire. As part of the questionnaire, they were asked to assess their child's preoperative experience (1 = pleasant; 2 = acceptable; and 3 = unpleasant), and where applicable (children over the age of 4 yr), the parents asked the child to assess the surgical experience (1 = pleasant; 2 = acceptable; and 3 = unpleasant). The child was also asked if he or she remembered "going to sleep" before the operation or remembered the application of the face mask. Follow-up questionnaires were obtained from 83% of the participants. Data analysis included analysis of variance (ANOVA) (for continuous variable) with appropriate *post hoc* testing, and chi-squared tests (for discrete variables). Values of $P < 0.05$ were considered statistically significant.

Results

There were no statistically significant differences between treatment groups with respect to age, weight, time from preanesthetic medication to separation from parents, duration of anesthesia, time from discontinuation of the anesthetic until eye opening occurred, or discharge from the PACU (table 1).

At the time of the baseline (pretreatment) evaluation, there were no differences in sedation scores among the four treatment groups. Despite the somewhat bitter taste of the midazolam-containing solution, all children willingly accepted the oral mixture. The group receiving 0.75 mg·kg^{-1} po showed increased sedation at the 30-min time interval, as well as at the time of separation from their parents, when compared to the placebo-treatment group (table 2). At the time of separation from their family, only 9% of children in the high-dose midazolam group were tearful and combative (*vs.* 21–22% in the midazolam 0.25–0.5 mg·kg^{-1} dosage groups and 42% in the placebo group). There were no significant changes over time in the level of sedation after the lowest dose of midazolam, 0.25 mg·kg^{-1}, or after placebo (table 2).

Apprehension upon entering the operating room was decreased and the quality of induction was significantly improved in both the midazolam 0.5 and 0.75 mg·kg^{-1} groups compared to the placebo-treatment group (table 3). Patients who received midazolam 0.75 mg·kg^{-1} had significantly less recall of the picture shown immediately

TABLE 2. Distribution of Sedation and Separation Scores for the Four Midazolam Treatment Groups During the Perioperative Period

	Preoperative*			15 min*			30 min*			Separation†			Discharge*		
Treatment Group	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1) Placebo	42	58	0	13	87	0	30	70	0	42	55	3	87	10	3
2) 0.25 mg·kg^{-1}	47	53	0	9	91	0	7	93	0	22	75	3	88	6	6
3) 0.50 mg·kg^{-1}	34	66	0	3	93	4	11	89	0	21	72	7	90	7	3
4) 0.75 mg·kg^{-1}	59	41	0	3	84	13	3	90‡	7	9	88‡	3	94	0	6

Data reported as percentage of patients in each treatment group.
* Sedation scale: 1 = tearful/combative; 2 = alert/aware; and 3 = drowsy/sleeping.
† Rating scale: 1 = poor; 2 = good; and 3 = excellent.
‡ Significantly different from placebo group, $P < 0.05$.

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TABLE 3. Distribution of Induction Scores for the Four Midazolam Treatment Groups

Treatment Group	Induction Score†			
	1	2	3	4
1) Placebo	40	10	23	27
2) 0.25 mg·kg^{-1}	18	22	16	44
3) 0.50 mg·kg^{-1}	17	14	7	62*
4) 0.75 mg·kg^{-1}	13	9	28	50*

Data reported as percentage of patients in each treatment group.
* Significantly different from placebo group, $P < 0.05$.
† Scores range from 1 = poor to 4 = excellent.

prior to entering the operating room (30%) compared to those in groups 1, 2, and 3 (76, 75, and 88%, respectively). However, the discharge sedation scores were similar in all four treatment groups (table 2).

There were no statistically significant differences among groups with respect to the parents' or child's response when asked to assess the child's experience on the day of surgery (table 4). Nevertheless, 50% of the parents of children in the high-dose midazolam group reported that their child's experience was pleasant (*vs.* 21% in the placebo group). While 46% of the children in the placebo group felt that their experience was unpleasant, only 20% of the children receiving midazolam, 0.5–0.75 mg·kg^{-1}, felt that the operation was an unpleasant experience. Finally, fewer midazolam-treated children (*vs.* placebo) recalled "going to sleep" and recalled the application of the face mask ($P < 0.05$).

Discussion

Several studies have reported that preanesthetic medication in children can allay anxiety and facilitate separation of children from their parents as they enter the surgical suite.[4,8,12] Preliminary studies have suggested that midazolam is an effective preanesthetic medication for children when administered either intramuscularly,[2–5] rectally,[13] intranasally,[14] or orally.[6,9]

Sjovall *et al.*[15] compared the effects of oral midazolam with those of intramuscular meperidine and atropine in children. They concluded that midazolam 0.2 mg·kg^{-1} po was as effective with respect to anxiolysis as a combination of meperidine 1 mg·kg^{-1} and atropine 0.01 mg·kg^{-1} im; however, increased secretions were noted in the midazolam group. More recently, Saarnivarra *et al.*[16] reported a comparative study involving children (1–9 yr of age) receiving midazolam or chloral hydrate po (in combination with atropine) 65 ± 12 min before induction of general anesthesia. These investigators concluded that midazolam 0.4–0.6 mg·kg^{-1} po provided only "fair" anxiolysis in children younger than 5 yr of age. In contrast, midazolam 0.4–0.6 mg·kg^{-1} po produced good anxiolysis in older children (>5 yr of age). In the younger children, these investigators noted restlessness with both the lowest and highest doses of midazolam. Although recovery room times were not reported by Saarnivarra *et al.*,[16] all patients reportedly had acceptable "recovery scores" at 70 min after tracheal extubation. However, amnesia was reported in 7–20% of their midazolam-treated children 2 h after their brief outpatient procedures.

In our preliminary study,[9] we compared the effects of oral midazolam 0.25 or 0.5 mg·kg^{-1} po and midazolam 0.1 or 0.2 mg·kg^{-1} im. We concluded that midazolam 0.5 mg·kg^{-1} po was an effective alternative to im injections for pediatric outpatients requiring preanesthetic medication. Our current dose-ranging study was designed to define the most appropriate dose of po midazolam in children. Midazolam 0.75 mg·kg^{-1} po produced an increased level of sedation in children 1–10 yr of age within 30 min after oral administration. Furthermore, midazolam 0.75 mg·kg^{-1} facilitated separation of the child from parents and provided a better quality of induction. No untoward effects attributable to the midazolam–atropine preanesthetic medication regimen were noted during the perioperative period. A recent study suggested that administration of small amounts of fluid (*e.g.*, 5–10 ml) to children prior to induction of general anesthesia does not pose a significant risk with respect to aspiration of abdominal contents.[17]

TABLE 4. Results of Parental Postoperative Questionnaire

Treatment Group	Parental Response*				Child's Response				Going to Sleep†		Face Mask†	
	n	1	2	3	n	1	2	3	Yes	No	Yes	No
1) Placebo	26	21	79	0	11	0	54	46	67	33	83	17
2) 0.25 mg·kg^{-1}	27	32	68	0	9	0	68	32	17‡	83	40	60
3) 0.50 mg·kg^{-1}	24	29	71	0	8	13	67	20	33	67	40	60
4) 0.75 mg·kg^{-1}	26	50	50	0	8	13	67	20	22‡	78	36‡	64

Data reported as percentage of patients in each midazolam treatment group.
n = number of responses in each group.
* Response scores refer to: 1 = pleasant; 2 = acceptable; and 3 = unpleasant.
† Refers to child's ability to recall going to sleep or to recall application of the face mask.
‡ Significantly different from placebo group, $P < 0.05$.

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Midazolam has a bitter taste that is not easily disguised in apple juice or other clear fluid vehicles. Although our patients accepted the oral drug mixture without difficulty, some of the children stated that the mixture was bitter (or made a facial expression which suggested that the taste was unpleasant). It has been suggested that the sweet taste of a partially melted commercially available popsicle is highly effective in disguising midazolam's bitter taste.§

The limited bioavailability of oral midazolam may explain the high-dose requirement for sedation and anxiolysis after the oral route of administration. Payne *et al.*[18] determined that the bioavailability of midazolam was only 27% after a dose of 0.15 $mg \cdot kg^{-1}$ and 15% after 0.45 and 1.0 $mg \cdot kg^{-1}$, as a result of incomplete absorption and extensive first-pass metabolism. In a few cases where surgery was unexpectedly delayed longer than 60 min, we found that the effects of midazolam appeared to rapidly dissipate and the child's behavior appeared to return to their baseline state. If an excessive period of time elapsed prior to induction of anesthesia, this would explain why Saarnivarra *et al.*[16] found only "fair" anxiolysis after midazolam, 0.4–0.6 $mg \cdot kg^{-1}$ in their younger age group (2–5 yr). In our experience, it is this younger age group that appears to benefit most from oral preanesthetic medication because of their fear of injections and heightened separation anxiety. We therefore recommend that these patients receive midazolam 0.5–0.75 $mg \cdot kg^{-1}$ po preanesthetic medication approximately 30 min prior to entering the operating room. The concomitant use of atropine decreases secretions during induction and may have contributed to the absence of respiratory complications (*e.g.*, laryngospasm).

A deficiency of the study design was that we did not quantify the effects of the preanesthetic medication on ventilatory, cardiovascular, or gastrointestinal function. Future studies should examine the effects of oral midazolam on oxyhemoglobin saturation and carbon dioxide levels, as well as residual gastric volume, during the immediate preinduction period. Despite the administration of large doses of midazolam to some children (3–18 mg po), the midazolam–atropine combination did not delay their time to emergence from anesthesia or prolong their stay in the recovery room. However, it will be important to determine the emergence and recovery times when oral midazolam is administered prior to shorter (<60-min) outpatient surgical procedures.

In conclusion, midazolam 0.5–0.75 $mg \cdot kg^{-1}$ po in combination with atropine 0.03 $mg \cdot kg^{-1}$ po increased sedation, decreased separation anxiety, and improved the quality of induction of anesthesia in children 1–10 yr of age. However, 9–17% of the children who received this dose of midazolam were still afraid, combative, or crying at the time of anesthetic induction. After elective surgical procedures lasting 1–3 h, there were no clinically significant side effects, and the recovery room stay was not prolonged by the preanesthetic medication.

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