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Pre-Anesthetic Midazolam: A Randomized Trial with Three Different Routes of Administration

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Abstract

Aim: We aimed to determine the most effective route of midazolam administration in children prior to surgery to produce a cooperative patient.

Background: Pediatric patients often experience preoperative anxiety and uncooperativeness which has been associated with postoperative behavioral problems.

Methods/Materials: Ninety-nine children one to six years old with ASA status 1 or 2 requiring minor outpatient surgical procedures were enrolled in the study. Patients were randomized to receive preoperative midazolam rectally, nasally, or orally. Patients were graded on a three point cooperativeness scale at baseline, during midazolam administration, 20 minutes after administration, at parent separation, and at induction.

Results: Children receiving midazolam by the rectal route were more cooperative than the nasal or oral groups during administration of midazolam, at separation and at induction. The rectal group had similar cooperativeness to baseline at administration, while the nasal and oral groups were less cooperative at administration than at baseline.

Conclusions: In children undergoing surgical procedures under general anesthesia, rectal administration of midazolam, compared to oral or nasal routes, is better tolerated and more effective at alleviating perioperative uncooperativeness.

Keywords: Midazolam; Rectal; Nasal; Oral; Cooperativeness; Perioperative

Introduction

Children having surgery are often uncooperative due to anticipation of pain, an unfamiliar environment, parental separation, or a previous unpleasant experience [1,2]. This lack of cooperation may be the result of anxiety that has been shown to be associated with an increased level of postoperative pain and the release of stress hormones which may lead to negative outcomes [3,4]. In addition, approximately half of children undergoing surgery demonstrate negative behaviors postoperatively, which are partially predicted by the patient's anxiety at induction and previous bad hospital experiences [1,5].

Midazolam is a commonly used premedicant in children and has been demonstrated to have a protective effect against these negative postoperative behaviors [6]. This short-acting benzodiazepine produces anterograde amnesia, provides sedation, decreases separation anxiety, and facilitates induction of anesthesia [7-10]. It does not delay recovery [11] and can be readily antagonized by flumazenil [12].

Midazolam's efficacy has been well established when administered intramuscularly [13], orally [7], rectally [14], or intranasally [15]. There are advantages and disadvantages to each method of administration. Intramuscular administration is rarely utilized because although it produces rapid onset, the needle injection causes pain. Oral administration is the most common and least invasive, but requires patient cooperation. Although oral preparations are available, midazolam has a bitter taste which is not easily disguised. Rectal administration of midazolam, though effective, is not accepted in some cultures and by older children. As with oral midazolam, larger doses are required for the rectal route, onset times are slower, and absorption may be erratic [14]. Nasal midazolam has faster peak concentrations than oral and rectal routes [15] but causes burning and discomfort [16].

The main goal of administering preoperative midazolam is to provide for a calmer and more cooperative child who will undergo a smooth induction. We designed this randomized, observer blinded study to determine the most effective route of midazolam administration to produce a cooperative patient undergoing surgery.

Materials and Methods

After institutional review board approval 103 families were approached and following written parental consent, ninety-nine children one to six years old with ASA status 1 or 2 requiring minor outpatient surgical procedures were sequentially enrolled in the study as convenient. Any child with a significant cardiac, pulmonary or airway problem, or an active or recent upper respiratory infection was excluded from the study. Patients were also excluded if they or their parents expressed a preference for a particular route of midazolam administration. No preoperative tours were offered to any of the participants.

Children were randomly assigned to one of three groups according to a computer generated table of random numbers, after the parents consented. Equipotent doses of midazolam were determined as detailed

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in the discussion section. The "Nasal Group" received 0.2 mg/kg of intranasal midazolam as nose drops (maximum dose 5 mg). The "Oral Group" received 0.5 mg/kg (maximum dose 10 mg) orally. The "Rectal Group" received 0.7 mg/kg of midazolam (maximum dose of 15 mg) diluted in 10 mls of normal saline via the rectal route. Midazolam was administered by the anesthesiologist, approximately 25 to 30 minutes prior to induction, in the pre-anesthesia area, with the parent(s) present.

Behavioral observations of the subjects were made on a 3 point cooperativeness scale (Table 1) that has face validity for the desired endpoint. This scale is related to scales validated from measuring preoperative anxiety, such as [11]. One trained observer blinded to the route of administration scored all the patients before premedication was given (baseline), 20 minutes after premedication was administered, at the time of separation from the parent(s), and on induction of anesthesia. The anesthesiologist scored the patient at the time premedication was administered. All patients were taken to the operating room in their beds without their parents. The four anesthesiologists participating in this study and the blinded observer received thorough, standardized instructions of the study scale used. Each subject's sex, age, weight, and time to parental separation, time to induction and time in PACU were recorded. General anesthesia was induced in each subject using a standard inhalation induction technique. After surgery and emergence from anesthesia, patients were taken to the PACU.

It was determined that with approximately 33 patients per group, a difference of 35% in cooperativeness could be found with a statistical power of 80% and a significance of 0.05. Statistical analysis was performed using chi-square techniques to compare the cooperativeness scores of the three routes of administration (3x3) at each of the five times. If significant at P<0.05, chi-square was performed between each of the pairs of routes at that time (3x2). Chi-square was also used to compare the cooperativeness scores for each group versus the five time points. Continuous data (weight, age, time to separation and induction, and PACU time) were compared between groups with one way analysis of variance. All significance was at P < 0.05. Statistical calculations were performed with Sigma Plot 11.0.

Results

Ninety-nine patients were enrolled in the study. 3.9% families refused to participate in the study. Thirty-five were randomized to the nasal group, 31 patients to the oral group, and 33 to the rectal group. There were no differences in sex, age, and weight in the three groups (Table 2). There were also no significant differences in drug administration to parental separation times, drug administration to induction times, and PACU stay times (Table 3). The types of procedures were equally distributed in the three groups.

Observations		Score
Excellent	Fully cooperative, unafraid, or asleep	1
Good	Mild to moderate fear and/or crying which ceases and child becomes cooperative with reassurance	2
Poor	Uncooperative, crying, inconsolable	3

Table 1: Cooperativeness Scale.

	Nasal	Oral	Rectal	P
Number	35	31	33	
sex(M:F)	22:13	19:12	21:12	0.98
age(mo)*	34.0±20.4	42.3±23.5	40.0±21.3	0.28
weight(kg)*	14.0±5.2	15.3±5.6	15.5±4.7	0.45

*Data are mean ± standard deviation

Table 2: Demographic Data.

	Nasal	Oral	Rectal	P
Time to parental separation (min)	26.1 ± 10.1	27.0 ± 12.3	24.2 ± 5.9	0.51
Time to induction (min)	29.5 ± 9.9	30.1 ± 12.0	27.2 ± 6.4	0.45
PACU stay (min)	21.6 ± 14.7	24.1 ± 13.9	21.9 ± 12.7	0.73

Data are mean ± standard deviation

Table 3: Time from administration to Parental Separation and Induction, and time of PACU stay.

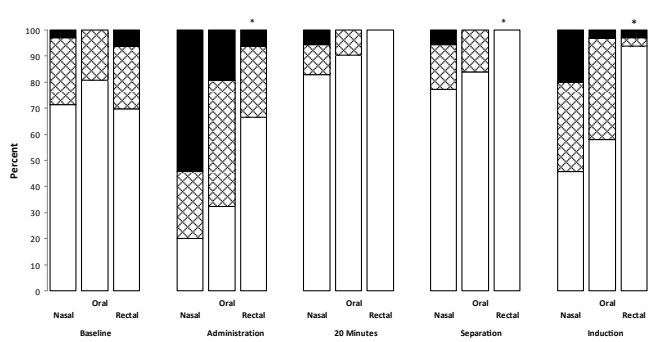

Figure 1: Patient cooperativeness. Comparison of the three groups (nasal, oral, and rectal) at the five measured time points (baseline, midazolam administration, 20 minutes after midazolam administration, separation from parent, and mask induction of anesthesia). White = 1 (excellent, fully cooperative), checkered = 2 (good, cooperative with reassurance), and black = 3 (poor, uncooperative). * Rectal > oral and nasal (P<0.05).

There was no difference in cooperativeness scores among the groups prior to administration or 20 minutes after administration of midazolam (Figure 1). However, cooperativeness scores among the three groups differed significantly at the time of drug administration (P < 0.001), parental separation (P = 0.037), and induction (P < 0.001). At these three times, rectal administration resulted in more cooperativeness than the nasal route (P<0.001, = 0.014, < 0.001, respectively) and oral route (P = 0.019, 0.022, and 0.002, respectively). All of theses were significant at P<0.05, however this does not take into account a lower P value due to multiple testing.

The oral and nasal groups each had lower cooperativeness at midazolam administration than at baseline (P<0.001) while there was no statistical difference between those times for the rectal group (P = 0.96).

There was no difference in cooperativeness based on age of patient (< 36 months vs. > 36 months, n = 48 and 41 respectively) for any of the time points (P > 0.05). The only difference between males and females occurred 20 minutes after administration, where the percentage of excellent cooperativeness was 98% for males and 78% for females (P = 0.002).

There were no serious adverse events, although one patient in the nasal group had a nose bleed. No patient received flumazenil to reverse sedation.

Discussion

This study was designed to determine the most effective method of administration of midazolam when used for premedication of young children undergoing outpatient surgical procedures. The results demonstrate that the rectal administration of midazolam is well accepted and provides better cooperativeness than via the nasal and oral routes (Figure 1). Rectal administration of midazolam resulted in 100% of patients being fully cooperative 20 minutes after administration and 93% fully cooperative at induction.

The difference in cooperativeness scores at the time of midazolam administration was caused by the drug administration procedure itself. Rectal administration was well tolerated; cooperativeness at this time was no different from the baseline cooperativeness. Contrarily, oral and nasal administration each caused less cooperativeness, probably because of the unpleasant taste and irritation of nasal mucosa. Oral administration may have been better tolerated if we had attempted to disguise the taste of the medication, although in a study using commercially supplied syrup, only approximately half of patients accepted the medication readily without grimace or verbal complaint [17]. Nasal administration was poorly accepted causing pain and irritation, and resulted in a nose bleed in one patient. This was consistent with study by [16]. who observed that although intranasal midazolam administration reduced pre-procedural negative behaviors exhibited during separation from parents, this method of drug delivery resulted in increased negative behavior during the administration of the drug [16]. It has been suggested that using a nasal spray instead of drops may reduce the negative behaviors of the child upon administration because it decreases the amount of undiluted midazolam that comes in contact with the nares [18], although one study refutes this [19]. In contrast to our observation, Malinovsky et al. [15] found that intranasal midazolam is an excellent method for premedication compared to the oral and rectal routes [15]. However, they did not assess the patients' initial anxiety scores or how the route of administration affected anxiety and negative behavior at the time of administration of midazolam. Their observation was based on the most rapid onset of sedation for patients receiving intranasal midazolam.

In addition to better acceptance, rectal midazolam administration provided better cooperativeness at the time of parental separation and at induction of anesthesia. This may have been due to a lingering effect from the trauma from oral and nasal administration; although there was no statistical difference 20 minutes after administration, the data trended to favor the rectal group. All three groups had similar times between administration and separation as well as administration and induction (Table 3). These times are well within the limits that midazolam has been shown to be effective [8,20]. Nasal midazolam has a slightly faster onset time than the oral or rectal routes but at 20 minutes after administration, plasma levels in all the three groups attain peak plasma levels [15]. The increased cooperativeness at induction may also have been due to higher plasma levels of midazolam in the rectal group, although the doses were calculated as below in an attempt to achieve a uniform level.

We did not develop a dose response curve for each route of administration because significant work has already been done to establish effective doses. The doses of midazolam that we used in this study were approximately equipotent and within the ranges that have been shown to be effective in producing sedation [9,14,16]. Oral midazolam given as 0.5 mg/kg is the most effective with the fewest side effects [9]. The bioavailability of rectal, nasal and oral midazolam are approximately 18%, 64% and 26% (range 15-36%) respectively [20,21,22]. Therefore total effective dose (bioavailability x dose) was approximately 0.13 mg/kg for each route. Children in our study were administered the intravenous form of midazolam via all three routes. The oral preparation of midazolam was not reliably available in our pharmacy at the time of this study.

Our results differ from a study by Kogan et al. [23] which showed no difference in patient anxiety level between four different modes of midazolam administration (oral, rectal, nasal, and sublingual) at the time of induction [23]. There are several possible reasons for this. In Kogan's study, a parent was present throughout, including at the time of induction, which has been demonstrated to decrease anxiety. Kogan et al. [23] used a smaller dose for rectal midazolam and larger dose for intranasal midazolam than used in our study. Our doses were calculated to give an approximately equal blood level. The beta for their study allowed for an 80% chance of showing no difference when a true difference was present. In addition, there is no mention of formal training or the number of anesthesiologists that did the rating.

The higher cooperativeness in males versus females 20 minutes after midazolam administration is not easily explained, but the proportion of males was not statistically different in the three groups so this should not influence the prior results. Time in the PACU was similar in each of the groups, and although the patients were not compared with unmedicated controls, the time in PACU was reasonable for ambulatory procedures.

A criticism of our study is that it was not possible to blind the anesthesiologists who administered the midazolam, although this is unlikely to have biased the results.

Oral administration is currently the preferred method in greater than 90% of pediatric patients that are premedicated [24]. Patient and parent preference for oral administration may partly explain this as some patients who were approached to participate in this study refused to do so because they had a strong preference for oral midazolam as opposed to intranasal or rectal administration. Although it would have been interesting, we did not collect data on those patients or parents who refused to participate. It was a small group of subjects and was a parental decision due to acceptable previous experiences with oral midazolam in all four children. In some cases it could be due to parental or children's aversion to rectal administration of drugs. In such circumstances they should be given alternative routes of administration of midazolam agreeable to them.

In summary, this is the first study to demonstrate in children up to age six years undergoing surgical procedures under general anesthesia, rectal administration of midazolam, compared to oral or nasal routes, is better tolerated and more effective at alleviating perioperative uncooperativeness.

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