Scientific Article

The effect of midazolam premedication on discharge time in pediatric patients undergoing general anesthesia for dental restorations

Jason J. Horgesheimer, DDS Charles G. Pribble, MD Ralph A. Lugo, PharmD

Dr. Horgesheimer is pediatric dental resident, Department of Pediatric Dentistry, and Dr. Pribble is associate professor, Department of Pediatrics, and clinical assistant professor, Department of Anesthesiology, University of Utah School of Medicine, Primary Children's Medical Center, Salt Lake City, Utah; Dr. Lugo is associate professor, Department of Pharmacy Practice, and adjunct assistant professor, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah. Correspond with Dr. Pribble at chuck.pribble@hsc.utah.edu

Abstract

Purpose: *The purpose of this study was to evaluate the effect of oral premedication with midazolam on recovery times of children undergoing dental restorations under general anesthesia.*

Methods: *The records of 106 children (1.2-11.3 years, ASA I or II) undergoing ambulatory dental restorations were randomly selected and retrospectively reviewed: 50 subjects received midazolam (M) 0.5 mg/kg orally approximately 30 minutes prior to their procedure and 56 control subjects received no premedication (C). General anesthesia consisted primarily of inhalational anesthesia. Time in the operating room (OR), post-anesthesia care unit (PACU) and same day surgery (SDS) were determined and compared between groups.*

Results: *Both groups were similar with respect to age and weight. There were no significant differences between groups in time spent in the OR, PACU or SDS ($p>0.05$). In a subset of children having shorter dental procedures (OR time ≤75 minutes, n=29), there remained no significant difference in discharge times between groups.*

Conclusions: *Preoperative administration of oral midazolam does not delay discharge of children undergoing general anesthesia for dental rehabilitation. (Pediatr Dent 23:491-494, 2001)*

Oral midazolam has become one of the most common premedications used in pediatric anesthesia practice.[1] It can effectively decrease anxiety,[2] reliably produce amnesia[3] and facilitate anesthetic induction.[4] In addition, it may also decrease agitation on emergence from general anesthesia,[5] increase the quality of sleep the night of day surgery,[6] and result in fewer adverse behavior changes one week postoperatively.[7] Furthermore, preoperatively administered midazolam has an excellent safety and side effect profile with no adverse effects on cardiorespiratory parameters.[2,8]

Midazolam premedication has the theoretical potential to cause postoperative sedation and delay recovery from general anesthesia. However, there is no clear consensus in the literature about this issue despite numerous studies conducted during the past decade. Furthermore, some studies conducted in children who received midazolam have demonstrated increased recovery room stays, yet no clinically or statistically significant delay in discharge from the hospital.[5,9] Currently, there are no published studies evaluating the effects of preoperative midazolam use in children undergoing general anesthesia for dental restorations.

The purpose of this study was to determine if the administration of preoperative midazolam affects the recovery or discharge time of pediatric dental patients undergoing general anesthesia.

Methods

This was a retrospective analysis of the medical records of patients undergoing dental restorations at Primary Children's Medical Center in Salt Lake City, Utah, between April 1998 and January 2000. This study was approved by the Institutional Review Board of Primary Children's Medical Center. All patients underwent dental restorations under general anesthesia in the operating room. American Society of Anesthesiologists (ASA) class I or II patients were randomly selected from the 1,317 children who underwent dental restorations during this time period. Patients were retrospectively assigned to either the midazolam study group if they were premedicated with oral midazolam or the control group if they received no premedication. Approximately 50 records of patients in each group were initially selected.

Patients received midazolam preoperatively based on the practice of the anesthesiologist and/or request of the patient or parent(s). Patients in the midazolam group received 0.5 mg/kg midazolam syrup (2 mg/mL, Roche Pharmaceuticals, Nutley, NJ) orally,[1,2] approximately 30 minutes prior to entering the operating room for complete dental restorations. Patients in the control group received no sedative premedication prior to their dental surgery.

All children underwent mask inhalational induction with nitrous oxide and either sevoflurane or halothane, depending on the preference of the attending anesthesiologist. All patients were nasotracheally intubated and general anesthesia was maintained primarily with inhalational anesthesia.

The data were gathered and recorded by one examiner (JH) from the patients' medical records using the following information: preoperative Same Day Surgery (SDS) assessment form, anesthesia intraoperative record, Post Anesthesia Care

Received May 22, 2001 Revision Accepted October 15, 2001

Table 1. Demographic Characteristics (Mean ±SD)

	Midazolam (n=50)	Control (n=56)	*P* value
Age (years)	3.8 ± 1.7	3.7 ± 1.5	0.83
Weight (kg)	15.6 ± 3.3	15.4 ± 3.8	0.82
Sex (M/F)	26/24	28/28	

Unit (PACU) assessment form, post operative same day surgery recovery form, the perioperative nursing record and the perioperative medication list. Demographic data included the age, weight and sex of each child. The operating room (OR) time was defined as the time elapsed between entering the OR and leaving the OR for the PACU. The PACU time was the total time spent in the Post Anesthesia Care Unit upon admission from the operating room to the time of discharge to the SDS outpatient unit. The SDS time was the period of time between admission to same day surgery and discharge home. The total postoperative time was the sum of the times in the PACU and SDS. All times were recorded in minutes. Patients were discharged from the PACU and SDS after meeting discharge criteria according to a written institutional protocol, which is a modification of the Aldrete scoring system.[10]

Descriptive statistics were used to represent the data. Data are presented as mean ± SD and the two groups were compared by Student's t-test. For data that failed the test of normality, groups were compared using the Mann-Whitney Rank Sum Test. Proportions were compared between groups using chi square analysis. Multiple linear regression analysis was used to determine whether OR, PACU, SDS or total postoperative time could be predicted from dependent variables, including preoperative midazolam use, intraoperative opioid use and whether an extraction procedure was performed. Statistical significance was set a priori at P≤0.05. Statistical analysis was performed using SigmaStat software version 2.03 (SPSS, Inc., Chicago, Illinois).

Results

There was a total of 106 patients included in the final analysis: 56 patients in the control group and 50 patients in the midazolam study group. The mean age and weight for the entire group of 106 patients was 3.8 ± 1.6 years and 15.5 ± 3.6 kg, respectively. The mean OR time for the entire group of patients was 94.7 ± 27.9 minutes, while PACU and SDS times were 34.9 ± 13.3 and 109.3 ± 44.7 minutes, respectively. The total postoperative time was 144.2 ± 44.5 minutes.

There were no significant differences in the age, weight or sex distribution between the two groups (Table 1). Outcome results are presented in Tables 2 and 3. There were no significant differences in time spent in the OR, PACU or SDS between the patients who received preoperative midazolam and those in the control group.

Potentially confounding variables included extraction procedure during surgery and administration of opioids. Statistical analysis demonstrated no significant difference between the two groups in the percentage of patients requiring extraction; however, a greater percentage of patients in the midazolam group received an opioid postoperatively (82%) as compared to the control group (54%; P=0.004). Analysis by multiple linear regression indicated that neither opioid administration nor preoperative midazolam administration significantly contributed to predicting the time in the OR, PACU, SDS or the total postoperative time (P>0.34).

To study the effect of midazolam premedication on children having shorter OR procedures, a subset of patients with OR times ≤75 minutes was analyzed (n=29). There were 16 patients in the midazolam group and 13 in the control group, and the mean OR time for this subset of children was 65.0 ± 9.1 minutes. Mean time in the PACU and SDS was 33.3 ± 11.3 and 103.6 ± 38.5 minutes, respectively. There was no significant difference between the midazolam and control group with respect to OR time (65.6 ± 11.9 vs. 64.6 ± 6.5 min, respectively; p=0.76) when the two groups of this subset were compared. Similarly, there was no difference between the midazolam and control group in the time that patients remained in the PACU (35.9 ± 11.4 vs. 30.0 ± 10.7 minutes, respectively), SDS (99.1 ± 40.9 vs. 109.2 ± 36.2 min, respectively) and the total postoperative time (135 ± 39.8 vs. 139.2 ± 39.4 min, respectively) (P>0.13).

Table 2. Comparison of Postoperative Times (Mean ±SD)

	Midazolam (n=50)	Control (n=56)	*P* value
OR time (min)	94.4 ± 28.7	94.9 ± 26.7	0.68
PACU time (min)	36.1 ± 15.4	34.2 ± 10.8	0.87
SDS time (min)	112.2 ± 45.0	106.9 ± 43.9	0.48
Total post-op time (min)	148.2 ± 46.7	141.1 ± 42.0	0.41

Discussion

It is well established that benzodiazepines potentiate the sedative and hypnotic effects of opioids[10] and volatile anesthetics.[11] Accordingly, preoperative administration of midazolam has the potential to augment postoperative sedation, thus delaying recovery from general anesthesia and increasing costs. While numerous studies have addressed the effectiveness of preoperative midazolam in patients receiving general anesthesia, there are no published studies evaluating its effect on duration of recovery and hospital stay in pediatric patients undergoing outpatient dental restorations. Studies evaluating other patient populations have revealed conflicting results. Cray et al[12] reported that midazolam decreased anxiety scores in children presenting for day case surgery; however, the median time to hospital discharge was delayed by 30 minutes in the midazolam group. In two recently published studies,[5,9] children undergoing same day ear, nose, and throat surgery were prospectively assigned to midazolam premedication or placebo. Both studies found that emergence from anesthesia was slightly longer (less than 10 minutes) in the midazolam groups, although discharge to home was not delayed compared to the placebo group.

Table 3. Number of Patients Who Had Extractions and Who Received Opioids Postoperatively

	Midazolam (n=50)	Control (n=56)	*P* value
Extractions	14 (28%)	20 (36%)	0.52
Opioids	41 (82%)	30 (54%)	0.004

Other investigators have found that premedication with midazolam does not delay discharge. McMillan et al[2] evaluated the use of midazolam premedication in children undergoing same day surgery in a randomized, placebo-controlled study. Sedation and anxiolysis scores were greater in the midazolam-treated groups, and anxiolysis at the time of separation from parents was rated excellent in 80%-90% of the children. They found that mean times to hospital discharge were similar in the midazolam-treated group and placebo group. In the only other study of children undergoing dental surgery, Alderson and Lerman[14] randomly assigned 40 children to either midazolam or ketamine premedication in a blinded manner. Patients given midazolam were ready for discharge from the hospital approximately 20 minutes earlier than the children who received ketamine.

The results of this study provide additional evidence that preoperative sedation with midazolam does not prolong recovery time or hospital stay in children. The time spent in the OR, PACU and SDS was strikingly similar between the two groups. In this study, two potentially confounding variables, dental extractions and opioid administration, and their effect on discharge times were evaluated. Performing dental extractions could potentially contribute to longer recovery times. The latter may be a result of greater levels of pain and the subsequent need for additional opioids. Performing dental extractions did not affect the outcomes of this study, primarily since there were equal numbers of patients in each group that required extractions. Consequently, the total postoperative times for the midazolam and control groups were almost identical, 148.2 min vs. 141.1 min, respectively.

Administration of opioids with benzodiazepines may prolong sedation and therefore must also be analyzed as a covariate in determining discharge times. In this study, a greater percentage of patients in the midazolam group received postoperative opioids (82% vs. 54% in the control group), thus increasing the likelihood of prolonged postoperative times and hospital stays in the benzodiazepine group. Nevertheless, no such trend in the data was found. It is not certain why the midazolam group required more frequent opioid administration. There have been reports that midazolam may have a mild anti-analgesic effect.[15,16] This appears to be due to an interaction with the central GABA receptors, as the benzodiazepine antagonist, flumazenil, eliminates this effect.[16] Although we did not specifically compare pain scores in the two groups, both groups had approximately the same number of patients undergoing potentially painful extraction procedures. Thus, the results of these studies do not appear to be confounded by a greater magnitude of pain in either one of the study groups.

The conflicting results between published studies may be partially explained by differences in study methodologies, duration of surgery, and administration of opioids intraoperatively and in the postanesthesia care unit. Thus, one must be cautious in extrapolating the findings of one study to another population. Similarly, the fact that midazolam did not delay discharge in the entire cohort of patients in this study may not apply to shorter procedures. To investigate the effect of midazolam premedication on shorter dental procedures, a subset of patients with operative times less than 75 minutes (mean 65 minutes) was selected. Shorter OR times led to similar results (ie, patients who received midazolam premedication did not experience longer times in the OR, PACU or SDS as compared to the children who received no premedication). One should be careful, however, not to overinterpret these results since the number of patients in this subgroup was small and the power was likely insufficient to determine small differences. Additional data are needed to determine whether premedication with midazolam affects discharge time after short OR procedures.

The limitations of this study include its retrospective design and the possibility that PACU and SDS discharge times may have been influenced by nurses' interpretation of discharge readiness. However, this potential discharge bias was minimized by the presence of a written institutional protocol[10,17] with predetermined PACU and SDS end points for discharge. While the discharge protocol is still dependent upon nurses' assessments and judgment, the discharge criteria utilize objective physical measures of discharge readiness (eg, blood pressure compared to preoperative values, duration of capillary refill time, etc), thus minimizing the potential for bias. Another potential limitation was the fact that this study did not control for the use of different maintenance inhalational anesthetics. The influence of halothane vs. sevoflurane on discharge times is somewhat controversial in the literature. Some studies suggest that sevoflurane produces more rapid recovery, ie, time spent in the PACU. However, for relatively brief outpatient procedures similar to dental restorations, several studies suggest that there are no significant differences in time to discharge between the two inhalational agents.[18-21]

Our preoperative practice is to administer oral midazolam 0.5 mg/kg at least 30 minutes prior to the start of the procedure. Although the onset of action occurs in 10 minutes,[8] peak sedative effects do not occur until approximately 30 minutes, which corresponds to the time at which we separate the child from his/her parents and begin induction of anesthesia. Peak serum concentrations of midazolam after oral administration occur at about 60 minutes.[22] Since midazolam's half-life is approximately 60 to 70 minutes[22] and the average dental OR time in this study was approximately 90 minutes, one would expect midazolam's serum concentrations at the time of emergence to be approximately 50% of the peak concentration. As indicated by the results of this study, this estimated concentration of midazolam apparently does not prolong PACU or SDS discharge.

In summary, the results of this study indicate that premedication with oral midazolam prior to outpatient dental restoration does not prolong recovery time and/or hospital stay. By administering midazolam approximately 30 minutes prior to induction of anesthesia, the child receives the maximum preoperative benefit of anxiolysis and amnesia while not delaying discharge. Furthermore, the use of preoperative midazolam will contribute to the additional benefits of smoother emergence, increased quality of sleep the night of surgery and less night waking and nightmares as compared to children who do not receive midazolam premedication.

Conclusions

Oral midazolam 0.5 mg/kg administered to children 30 minutes prior to induction of anesthesia and dental restoration does not prolong time in the operating room, postanesthesia care unit or same day surgery outpatient unit.

References

1. Liu LM, Ryan JF. Premedication and Induction of Anesthesia. In*: A Practice of Anesthesia for Infants and Chidlren*, 2nd ed. Cote CJ, Ryan JF, Todres ID, Goudsouzian NG. Philadelphia: W.B. Saunders Co; 1993:140.
2. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. *Can J Anaesth* 39(6):545-550, 1992.
3. Feld L, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. *Anesthesiology* 73:831-834, 1990.
4. Holm-Knudsen RJ, Carlin JB, McKenzie IM. Distress at induction of anaesthesia in children. A survey of incidence, associated factors and recovery characteristics. *Paediatr Anaesth* 8(5):383-392, 1998.
5. Lapin SL, Auden SM, Goldsmith LJ, Reynolds AM. Effects of sevoflurane anaesthesia on recovery in children: a comparison with halothane. *Paediatr Anaesth* 9(4):299-304, 1999.
6. Viitanen H, Annila P, Viitanen M, Tarkkila P. Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. *Anesth Analg* 89(1):75-79, 1999.
7. McCluskey A, Meakin G. Oral administration of midazolam as a premedicant for paediatric day-case anaesthesia. *Anaesthesia* 49:782-785, 1994.
8. Spear RM, Yaster M, Berkowitz ID, Maxwell LG, Bender KS, Naclerio R, Manolio TA, Nicholds DG. Preinduction of anesthesia in children with rectally administered midazolam. *Anesthesiology* 74(4):670-674, 1991.
9. Viitanen H, Annila P, Viitanen M, Yli-Hankala A. Midazolam premedication delays recovery from propofol-induced sevoflurane anesthesia in children 1-3 years. *Can J Anaesth* 46(8):766-771, 1999.
10. Aldrete JA. Modifications to the postanesthesia score for use in ambulatory surgery. *J Perianesth Nurs* 13(3):148-155, 1998.
11. Kissin I, Brown PT, Bradley EL. Sedative and hypnotic midazolam-morphine interactions in rats. *Anesth Analg* 71:37-43, 1990.
12. Melvin MA, Johnson BH, Quasha AL, Eger EI II. Induction of anesthesia with midazolam decreases halothane MAC in humans. *Anesthesiology* 57:238-241, 1982.
13. Cray SH, Dixon JL, Heard CM, Selsby DS. Oral midazolam premedication for paediatric day case patients. *Paediatr Anaesth* 6(4):65-70, 1996.
14. Alderson PJ, Lerman J. Oral premediction for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. *Can J Anaesth* 41(3):221-226, 1994.
15. Oxorn DC, Ferris EF, Harrington E, Orser BA. The effects of midazolam on propofol-induces anesthesia: propofol dose requirements, mood profiles, and perioperative dreams. *Anesth Analg* 85:553-559, 1997.
16. Daghero AM, Bradley EL, Kissin I. Midazolam antagonizes the analgesic effect of morphine in rats. *Anesth Analg* 66:944-947, 1987.
17. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 49(6):924-934, 1970.
18. Hallen J, Rawal N, Gupta A. Postoperative recovery following outpatient pediatric myringotomy: a comparison between sevoflurane and halothane. *J Clin Anesth* 13(3):161-166, 2001.
19. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. *Pediatr Anaesth* 10(4):419-424, 2000.
20. Viitanen H, Baer G, Annila P. Recovery characteristics of sevoflurane or halothane for day-case anaesthesia in children aged 1-3 years. *Acta Anaesthesiol Scand* 44(1):101-106, 2000.
21. Beskow A, Westrin P. Sevoflurane causes more postoperative agitation in children than does halothane. *Acta Anaesthesiol Scand* 43(5):536-541, 1999.
22. Payne K, Mattheyse FJ, Liebenberg D, Dawes T. The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 37:267-272, 1989.

Abstract of the Scientific Literature

Are Antibiotics Being Used Appropriately for Emergency Dental Treatment?

The purpose of this prospective study was to determine if antibiotics were being prescribed appropriately for emergency dental treatment. All patients presented to any of five emergency dental clinics during an 11-week period were included in this study. A questionnaire was completed for each patient which contained the patient's complaint, the dentist's clinical diagnosis, the treatment provided, and the type of antibiotic used, if any. For all patients, 879 out of 1011 presented due to pain, 35% of these (311/879) had pulpitis, and 74% of these (230/311) were given a prescription for antibiotics without any additional treatment. Of the children who presented, 95% were in pain (94/99) with 76% (76/99) receiving antibiotics as the sole treatment. The most frequently prescribed antibiotic was amoxicillin. The authors concluded that antibiotics are being inappropriately prescribed by the dental profession.

Comments: The authors recognize that these results may not be representative of the entire U.K., let alone the U.S., but using antibiotics appropriately is something all of us need to be aware of. **MM**

Address correspondence to Y.M. Dailey, Department of Clinical Dental Services, University of Liverpool, Liverpool L69 3BX, U.K.

Are antibiotics being used appropriately for emergency dental treatment? Dailey YM, Martin MV. *Brit Dent J* 191:391-393, 2001.

19 references