Evaluation of two dosages of oral midazolam as a conscious sedation for physically and neurologically compromised pediatric dental patients

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Abstract

Physically and neurologically handicapped pediatric dental patients are often a challenge to treat and may require the use of pharmacological agents for behavior modification. The purpose of this study was to investigate the safety, in terms of vital sign changes and complications, and the effectiveness, in terms of behavioral changes, of two dosages of oral midazolam as a conscious sedative agent for this unique population. Participating in this study were 31 patients of Texas Scottish Rite Hospital for Children, who were uncooperative (as rated on the Frankl scale) at a previous dental appointment. The patients, 3–18 years old, were randomly selected to receive one of the two dosage regimens; Group A received 0.3 mg/kg oral midazolam and Group B received 0.5 mg/kg. Physiologic parameters and behavior were recorded throughout the appointment and overall safety and success were determined. Although clinically insignificant, Group A's pulse rates 20 min into treatment were significantly higher than at baseline or treatment start, and oxygen saturations were lower during treatment than at baseline and start of treatment. Intratreatment systolic and diastolic blood pressures and pulse rates of Group B were significantly higher than the baseline figures; however, these changes were not clinically significant. No clinical or postoperative complications were noted for either dosage. The regimen of 0.3 mg/kg of oral midazolam was successful 75% of the time, and the regimen of 0.5 mg/kg of oral midazolam was successful 60% of the time in providing adequate sedation to allow operative treatment to be safely and efficiently performed. There was no statistically significant difference in the effectiveness of the two regimens when overall success rates were analyzed. (Pediatr Dent 16:350–59, 1994)

Introduction

Providing dental care to patients with neurological disorders can be very challenging because they are often noncommunicative, negating the effectiveness of many age-appropriate behavior-modifying or behavior-shaping techniques. For many physically, neurologically, or developmentally compromised children a sedative agent is effective and indicated to reduce fear and improve the child's ability to cooperate, and thereby improve the quality of care delivered.

For the "well" child, meperidine is one of the most commonly used sedatives. However, concerns have recently been expressed regarding meperidine use in patients with a history of seizure activity/disorders because of the possible risk of inducing seizure activity. Precautions should be taken because meperidine may aggravate pre-existing convulsions in patients with seizure disorders.[1] Also, animal studies have indicated that narcotics can reduce the convulsive threshold of local anesthetics and increase their CNS depressant effects.[2-4] The reported success and widespread use of oral midazolam as a preoperative sedative agent for pediatric patients has brought this medication to the forefront as a prospective replacement. Most documented studies have reported favorable results for its effectiveness as a preoperative agent for general anesthesia cases. However, the use and effectiveness of midazolam in providing modified behavior for procedures lasting longer than 20 min needs to be evaluated. There are no documented studies reporting the effectiveness of oral midazolam in pediatric dentistry.

Midazolam is a potent imidazobenzodiazepine used as a premedicant and as an anesthetic induction agent. The pharmacokinetics are similar to other benzodiazepines in possessing hypnotic, anticonvulsant, muscle relaxant, antegrade amnesic, and anxiolytic activity. It is rapidly absorbed from the gastrointestinal tract and short acting.[5] The hypnotic potency of midazolam compared with diazepam is 1.5–2.1 times more potent. However, recovery characteristics are comparable for the two agents. Midazolam has a high affinity, approximately twice that of diazepam, for the benzodiazepine receptors, which occur mainly in the CNS and account for its increased potency and hypnotic effects compared with that of diazepam.[6] The anxiolytic and muscle relaxant properties of midazolam are attributed to its ability to increase glycine-inhibitory neurotransmitters in the brain stem and spinal cord.[7] The half-life activity of midazolam — both in distribution (6–15 min) and in elimination (1–4 hr) — is the most favorable of the benzodiazepines.[5,8]

Midazolam is the most lipid-soluble member of the benzodiazepines. The lipophilic nature of midazolam accounts for its rapid absorption and metabolism by the gastrointestinal tract, as well as its efficient entry into brain tissue. This property produces rapid onset and recovery.

Midazolam acts to protect against cerebral hypoxia — useful for patients who have decreased intracranial compliance.[9] Data investigating cerebral effects of various induction agents have shown a decrease in cerebral blood flow, cerebral perfusion pressure, cerebral metabolic rate of oxygen, intracranial pressure, and intraocular pressure with midazolam.[10] These actions help to prevent episodes of cerebral hypoxia and also protect the brain against episodes of ischemic insult. Midazolam doses of 10 and 15 mg, compared with diazepam in similar doses, produced significant pharmacological effects in preventing seizure activity as measured by an EEG.[11] The cerebral effects of most sedative agents are of concern in a patient with a history of seizure disorder and/or developmental delay because many cause increased intracranial pressure and decrease oxygen to the brain.

Benzodiazepines' depression of respiration has concerned dental professionals. A comparison of the respiratory effects of diazepam and midazolam demonstrated that intravenous (IV) administration of 0.15 mg/kg of midazolam and 0.3 mg/kg of diazepam produced comparable and significant respiratory depression.[12] The results also indicated that these effects are due to direct depression of the central respiratory drive. Although midazolam does not appear to produce less respiratory depression than diazepam, it does have the advantage of a shorter duration of action.

Oral administration is a beneficial and atraumatic means of consciously sedating patients in a private practice setting. As opposed to intramuscular (IM) and IV administration, this route alleviates a child's fear of an injection and does not sensitize the patient to injections prior to beginning the proposed dental treatment. Rectal and nasal administration are invasive and may also have long-term negative effects on the child. The efficacy of orally administered sedatives has been studied in comparison to IM administration.[13] The results of this study indicate that oral preanesthetic dosages may be just as effective as IM administration. Another investigation found that the rapidly acting benzodiazepines, such as midazolam, produced a safe and effective alternative to IV diazepam for minor dental surgical procedures in adults.[14]

The use of oral midazolam as a premedication involves different pharmacokinetics than all other routes of administration. Following oral administration, peak plasma concentrations generally are achieved within 1 hr of ingestion, and the clinical onset is correspondingly rapid. There is an extensive first-pass hepatic extraction of oral midazolam. In reported cases, 30–41% of the unmetabolized form of an oral dose reaches the systemic circulation.[5, 15] This high rate of hepatic extraction makes the need for an oral dose two times greater than the IV dose to obtain similar clinical effects. Interestingly, the elimination half-life is independent of the administration route.

The majority of studies on pediatric patients have been performed utilizing rectal, nasal, IV, or IM administration. In pediatric patients, peak serum concentrations for the IM, rectal, and oral routes are 15, 30, and 53 min, respectively. Bioavailability was 87, 18, and 27%, respectively, at a dosage of 0.15 mg/kg.[16]

Oral preanesthetic medication with midazolam in the pediatric population has shown favorable results, although the data on effectiveness have been sketchy and inconclusive. Three different dosages of oral midazolam were evaluated in combination with atropine prior to surgery.[17] Results in children 1–10 years old, indicated that 0.75 mg/kg of midazolam produced more significant sedation at 30 min compared with dosages of 0.25 and 0.50 mg/kg. In children 1–6 years old undergoing elective cardiac surgery, 0.75 mg/kg of oral midazolam was more effective in reducing anxiety and increasing sedation at separation from the parent and at application of the face mask than 2.0 mg/kg pentobarbitone or 0.2 mg/kg each morphine and atropine.[18] However, in children 0.5–4 years old undergoing day surgery, 0.3 mg/kg oral midazolam produced the same anxiolytic effect as the placebo.[19] The effect of oral midazolam on anxiety levels of preschool children during emergency laceration repair was evaluated in another study;[20] 70% of the children in the midazolam group had at least a 2-point decrease in anxiety level compared with 12% of the placebo group.

The clinical implications in pediatric dentistry are favorable. Antegrade amnesia, muscular relaxant capabilities, and anxiolytic properties provide the patient and parent with a more pleasant dental experience. Rapid absorption and onset, short duration of action, and potency have given this agent further credibility as a sedative agent. However, studies on oral midazolam have failed to address the safety and efficacy of this agent for prolonged time periods and postoperative complications.

The purpose of this study was to investigate the use of oral midazolam to sedate the emotionally, neurologically, and physically compromised pediatric dental patients in two parameters. The first was to evaluate and compare two dosages, 0.3 and 0.5 mg/kg, of orally administered midazolam in terms of safety by evaluating their effects on vital signs and clinical and postoperative complications. The second purpose was to evaluate patient cooperation at specific intervals during the appointment and as an overall rating to determine and compare effectiveness of the two dosages.

Methods and materials

All 32 subjects selected were patients of record at the Texas Scottish Rite Hospital for Children in Dallas, Texas, a facility limited to treatment of orthopedically and/or neurologically involved pediatric patients. One patient was eliminated from the study when it was discovered that the child had been inappropriately

Table 1. Comparison of Frankl Scale and Modified Behavior Scale

	Frankl Scale	*Modified Behavior Scale*
Category #1	Definitely negative. Child refuses treatment, cries forcefully, fearfully, or displays any overt evidence of extreme negativism.	Combative, thrashing, agitated, verbal, unable to be restrained, need to terminate procedure.
Category #2	Negative. Reluctant to accept treatment and some evidence of negative attitude (not pronounced).	Slightly combative, verbal, slightly agitated, able to be restrained and procedure safely completed.
Category #3	Positive. The child accepts treatment but may be cautious. The child is willing to comply with the dentist, but may have some reservations.	Quiet, not combative, cooperative, nonverbal.
Category #4	Definitely positive. This child has a good rapport with the dentist and is interested in the dental procedures.	N/A

stimulated during the onset of sedation. The remaining 31 patients, ranging in age from 3 to 18 years, had exhibited uncooperative behavior at a previous dental appointment. One of the primary investigators, a faculty member previously calibrated for participation in numerous sedation studies, selected patients based on a score of 1 or 2 on the Frankl Scale (Table 1).[21] Acceptance into the study required that patients need treatment involving local anesthesia. Most patients were selected for this study at either a recall or new patient exam appointment. However, some patients' behaviors did not become negative until a subsequent operative appointment.

Due to the unique patient population and their multiple medical diagnoses, medical charts were reviewed and consultations with the neurologist and/or anesthesiologist were obtained prior to acceptance into the study. Contraindications for acceptance into the study included patients who were presently taking monoamine oxidase inhibitors, benzodiazepines, or other drugs that could change or exaggerate the therapeutic response to benzodiazepines.

Upon identifying a candidate for the study, the procedures, possible discomforts or risks, as well as possible benefits were explained fully to the parents and their informed consent was obtained prior to the investigation. At the time of selection, the patients were divided randomly into two groups. Group A received 0.3 mg/kg midazolam HCl (Versed®, Roche Laboratories, Nutley, NJ) and Group B received 0.5 mg/kg midazolam. The selection of the dosages used in this investigation was determined in part by the recommendation and personal experiences of two pediatric anesthesiologists at Texas Scottish Rite Hospital[22,23] and dosages used in previous studies.[17,20] Anecdotal success was high with oral dosages of 0.3–0.8 mg/kg prior to induction of general anesthesia. Pilot studies were performed using various dosages to determine which produced adequate conscious sedation while maintaining the patient's protective reflexes. From these communications and pilot studies, the two dosages — 0.3 mg/kg and 0.5 mg/kg — were selected and incorporated into the protocol. At the direction of the anesthesiologists, all doses administered were based on an estimated lean body weight of the child. Lean body weight was calculated as follows: weight in kg x dosage x 0.8 for a lean child or 0.7 for an obese child.

Acceptable patients were scheduled for an appointment and given preoperative instructions regarding NPO orders prior to the appointment. The patients were not to have any solid food after midnight the day before the appointment and no liquids 4 hr prior to treatment. An exception was made for regular medications to be taken on schedule with minimal liquid. The parents were told to cancel the sedation appointment if the child had a cold or any other acute illness.

Study conduct

Prior to drug administration, vital signs including hemoglobin oxygen saturation, pulse rate, respiratory rate, and blood pressure were taken to establish a baseline reading, and cooperation was noted. A pulse oximeter (Nellcor N-200®, Nell Corp, Hayward, CA; or Invivo 4500™, Invivo Research Inc., Broken Arrow, OK) and automatic blood pressure monitor (Dinamap™ — Critikon, Tampa, FL) were attached to the child's upper limbs. Either oral or axillary temperature was taken by an electronic thermometer (Survalent® — Patient Technology Inc, Hauppauge, NY). A stethoscope was used to assess breath sounds for any signs of congestion.

The randomly selected dosage was administered in the following manner. The midazolam, as prepared by the manufacturer for IM or IV use, was drawn from the vial by syringe and mixed in a medication cup with approximately 5 cc of a grape-flavored suspension (Syrpalta®, Emerson Laboratories, Texarkana, TX) to provide a more palatable oral administration. Behavior, dose, and administration time all were recorded. The patient was allowed to return to the waiting area under close supervision until onset of sedation. The

clinical signs of onset included a glazed look or delayed eye movements, lack of muscle coordination, slurred speech, or sleep. Upon initial signs of sedation, the child was brought to the operatory and the time was noted. Appropriate vital sign monitors were placed, and recordings made every 10 min, in accordance with the sedation/anesthesia policy of the hospital, until the patient was dismissed. Behavior was recorded upon placement of monitors and every 10 min thereafter until dismissal.

Topical mucosal anesthetic was applied prior to injecting local anesthesia. After achieving adequate anesthesia, a rubber dam was placed whenever possible and operative treatment was performed. A bite block was used (with parental permission) if the patient was unable to keep his or her mouth open. If a child was athetotic or unable to remain still for treatment, a restraining device was used (with parental permission). A combative child was not placed in a restraining device. In those patients in which the sedation was considered unsuccessful, treatment was terminated, temporary restorations placed if appropriate, and the treatment was completed at another appointment through other means, either in the operating room or under an alternative sedation. Following treatment, the patient was allowed to return to the waiting area with the parents until responsive to verbal stimulation, awake, exhibited no sign of compromised respiration and, according to the accompanying adult, appeared to behave in the usual manner. All patients in the study were required to remain in the clinic or waiting area for at least 90 min after drug administration. Postoperative instructions were discussed with the parents regarding the after-effects of the conscious sedative, local anesthesia, or any other precautionary measures concerning the actual dental treatment. An emergency phone number was made available for questions or problems. A post-treatment follow-up phone call was made the next day to obtain additional information regarding the overall well-being and conscious state of the child.

Behavior evaluation

Due to many of the patients' severe neurological handicaps, developmental delays, and inability to communicate, a modified scale was devised to more accurately describe the level of cooperation (Table 1). The cooperation scale used to evaluate behavior during midazolam sedation was independent of the Frankl scale. A behavior rating of 1 indicated a total lack of cooperation, combative nature, and ineffectiveness of the medication. A rating of 2 was indicative of a somewhat cooperative patient exhibiting periods of anxiety or crying in a noncombative manner. A rating of 3 was considered very favorable cooperation for dental treatment. Clinical assessments of cooperation, measured at 10-min intervals during the appointment, were recorded by one of two faculty members standardized in the use of the behavior scale developed for this study. These faculty members were familiarized with the modified scale by an oral and written review of the three categories and by viewing a taped example of each category. They then viewed multiple taped scenarios depicting a variety of patient behaviors and made ratings separately and independently. Ratings were coincident for 18 of the 19 scenarios for an inter-rater reliability of 95%. The scenario in which there was disagreement received ratings of 2 and 3, both of which were considered to be successful ratings for the purposes of this study. In addition to the ratings, comments were written regarding procedures and behaviors during various intervals.

Data interpretation

Behavior scores were evaluated using descriptive statistics due to the nature of the behavior rating scale. To aid in analysis, ratings taken during local anesthesia administration were eliminated from the criteria to evaluate success. The operative phase of treatment was considered the most critical as it is usually the longest phase and the most technique sensitive with regard to the quality of dentistry performed. That is, the quality of the dentistry performed may suffer if the patient's struggling or movement leads to inadvertent movement of the handpiece and/or contamination of the preparations and dental materials. Therefore, if the patient's behavior dropped to a rating of 1 after local anesthesia administration, the sedation was considered a failure due the need for restraint or other aggressive behavior management techniques required to render treatment during this time period. Behavior ratings of 2 or 3 on the modified scale during operative treatment were considered successful since treatment was rendered with minimal patient trauma. The success:failure ratios were considered as the overall success of the two regimens and were used to compare the effectiveness of the two different dosages.

Vital signs, including systolic and diastolic blood pressures and pulse rates, were examined at various time intervals using the ANOVA for repeated measures to determine if significant changes were observed during the sedation appointment. Respiration rate data were evaluated using descriptive statistics.

Results

Of the 31 patients available for data analyses, 16 received a midazolam dosage regimen of 0.3 mg/kg (Group A) and the other 15 received a dosage regimen of 0.5 mg/kg (Group B). There were no statistically significant demographic differences between the two groups. Demographics are shown in Table 2.

All patients' vital signs were measured and behavior rated (using the modified scale) at the following times:

Table 2. Patient data for groups A and B

Demographics	*Group A*	*Group B*
Sex		
Male	8	7
Female	8	8
Ages in years	4–17 (Mean 9)	3–18 (Mean 9)
Diagnosis		
Static encephalopathy	6	5
Developmental delay	3	2
Spina bifida	1	1
Left hemiparesis	1	1
Hypothyroidism	1	1
Chomosome deletion	1	1
Status post-meningitis	1	0
Hydrocephalus	0	1
Multiple congenital anomalies	1	0
Sturge-Weber syndrome	1	0
Tuberous sclerosis	0	1
Leukodystrophy	0	1
Status post-skull trauma	0	1
An above diagnosis with seizure disorder	7	6

1. Presedation for baseline values (B)
2. Immediately before treatment (T) for the effect of the drug alone on these parameters
3. Every 10 min intratreatment for effect of the drug while undergoing treatment
4. At the end of treatment prior to the child exiting the operatory (E).

Group A: 0.3 mg/kg midazolam

Sixteen patients were evaluated for cooperation during medication administration, clinical onset, cooperation during injection of local anesthetic, complications, overall clinical success, and postoperative problems (Table 3). In Group A, 13 of 16 patients (81%) were cooperative when taking the oral medication. The remaining three patients required coaxing and/or more forceful actions with the concurrent use of a head and/or body restraint to get the child to take the oral sedation.

Average time for clinical onset of sedation after administering the 0.3 mg/kg dosage of midazolam was 30 min. One child exhibited clinical signs after 20 min.

Good behavior (rating of 3) was exhibited by seven of 16 patients (44%) during the local anesthetic injection phase of treatment while the other nine patients were uncooperative. Of these uncooperative patients, six cried forcefully throughout the injection and the remaining three patients were unable to remain still or were combative.

Table 3. Behavioral data for groups A and B

Results	*Group A* N = 16	*Group B* N = 15
No. of patients cooperative in taking medication	13	10
Average clinical onset of sedation in min	30	25–30
No. of patients cooperative for local anesthesia	7	4
No. of successful sedations for operative treatment	12	9
No. of patients who slept during treatment	1	2
Postoperative complications	1•	0

• Prolonged sedation

In Group A, 12 of 16 patients (75%) cooperated sufficiently during operative treatment to be considered successful sedations and four patients were considered failed sedations. Of the 12 successful sedations, six were cooperative during a major portion of the appointment with a favorable experience and outcome of clinical treatment. These patients, receiving ratings of 3, had no episodes of poor behavior and would be considered successes in any study population. During the treatment phase, the other six successful patients exhibited short periods of lack of cooperation that either prolonged or complicated treatment. These patients received a combination of ratings of 2 and 3. The remaining four patients, receiving ratings of 1, were evaluated as failed sedations either due to a total lack of cooperation or loss of cooperation during the treatment phase, causing an increased risk of patient injury. In one failed case, the operator was unable to administer local anesthetic. In the second failed sedation, the patient became so combative after treatment had begun that temporary restorations had to be placed and the patient was rescheduled for completion of treatment under general anesthesia. The remaining two patients in whom sedations failed became so combative and aggressive that restraining techniques were required to complete treatment.

One child of 16 in the 0.3 mg/kg group slept but was easily arousable by verbal stimulation throughout the appointment; the others remained awake and fully conscious for the duration of the appointment.

In only one case did parents describe any form of postoperative, sedation-related complication. This was prolonged sedation for approximately 20 hr and then resumption of normal behavior and activity. There were no cases of postoperative nausea, seizure activity, or

Table 4. Scheffe F-test for vital signs

Comparison	Group A Significance				Group B Significance			
	Dias BP	*Syst BP*	*Pulse*	*O^2 sat*	*Dias BP*	*Syst BP*	*Pulse*	*O^2 sat*
B vs. T	NS	NS	NS	NS	NS	NS	NS	NS
B vs. 20	NS	NS	Sig.*	Sig.*	Sig.*	Sig.*	Sig.*	NS
B vs. E	NS	NS	NS	NS	NS	Sig.*	Sig.*	NS
T vs. 20	NS	NS	Sig.*	Sig.*	Sig.*	Sig.*	Sig.*	NS
T vs. E	NS	NS	NS	Sig.*	NS	NS	Sig.*	NS
20 vs. E	NS	NS	NS	Sig.*	NS	NS	NS	NS

B = Baseline
T = Start of treatment
E = Exit reading
20 = 20 min into treatment
NS = Nonsignificant
Dias BP = Diastolic blood pressure
Syst BP = Systolic blood pressure
Pulse = Pulse rate
O_2 sat = Oxygen saturation
Sig.* = $P < 0.05$

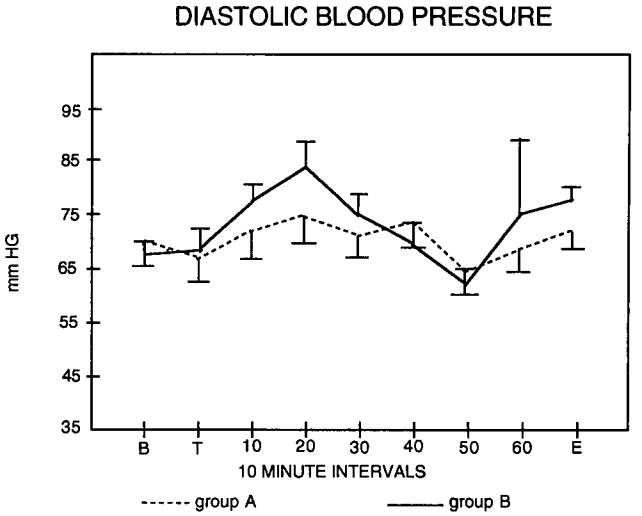

Fig 1. Diastolic blood pressure of Group A (0.3 mg/kg) and Group B (0.5 mg/kg) along with means and standard deviations. (B = Baseline Reading; T = Start of Treatment; E = Exit)

other postoperative complications at the time of the follow-up phone call.

Vital signs changes were evaluated and statistically analyzed at four different time periods: baseline reading (B), start of treatment (T), 20 min into treatment (20) and the exit reading (E). The 20-min time period was chosen to be representative of the intratreatment phase of the study.

Vital sign measurements recorded during the sedation appointments showed that respiration rate varied only slightly in all patients at all recorded intervals. An ANOVA for repeated measures revealed that there were no significant differences among the various measurements for the diastolic blood pressures (Fig 1; Table 4). Similar results were obtained for the measurements of systolic blood pressure, showing no significant differences (Fig 2; Table 4). Pulse rates differed significantly (ANOVA; $P < 0.05$). Further analysis by a Scheffe F-test showed that the mean pulse rate at 20 min differed significantly from those at baseline (B) or treatment start (T)(Table 4; Fig 3). Oxygen saturation measurements were most significant when statistically analyzed (ANOVA; $P < 0.05$). Further analysis by a Scheffe F-test revealed significantly lower O_2 readings intratreatment when comparing different time periods (Table 4). Differences existed between (B) and (20), (T) and (20), (T) and (E), and (20) and (E). Oxygen saturation readings showed fluctuations during treatment with one patient dropping to 92% oxygen saturation, another to 93%, and seven patients dropping to 94% for a short period of time (Fig 4). Head repositioning resulted in return of oxygen saturations to acceptable levels. All patients registered acceptable (95%) oxygen saturation levels for the majority of treatment and were discharged without complications or delays.

Group B: 0.5 mg/kg midazolam

Fifteen patients were evaluated for cooperation during medication administration, clinical onset of effect, cooperation during injection of local anesthetic, complications, overall clinical success, and postoperative problems (Table 3). In Group B, 10 of 15 patients (67%) were cooperative when taking the oral midazolam. The remaining five patients were not cooperative and required restraint and more forceful actions to get the child to take the medication. The average time period for clinical signs of sedation for the majority of Group B children was 25–30 min. Onset of clinical signs for three children was 15 min, while one child did not show signs of sedation until almost 40 min.

Good behavior (3 rating) was exhibited by four of 15 patients during the injection phase of treatment, while 11 patients (73%) were uncooperative. Of these patients, five cried forcefully during the procedure and the remaining six were unable to remain still or were combative.

In Group B, nine of 15 patients (60%) were considered successful sedations, and six had failed sedations. During the operative phase, five patients were cooperative with virtually no episodes of combativeness or undesirable vocal behavior, resulting in a successful sedation rating of 3. During isolated periods of treatment four patients received ratings of 2; however, the overall clinical assessment of behavior was favorable. These patients were evaluated as successful sedations because treatment was completed with minimal behavioral complications. The remaining six patients were so uncooperative, receiving ratings of 1, that treatment was difficult or impossible to complete. In the unsuccessful sedations, half were characterized by a total

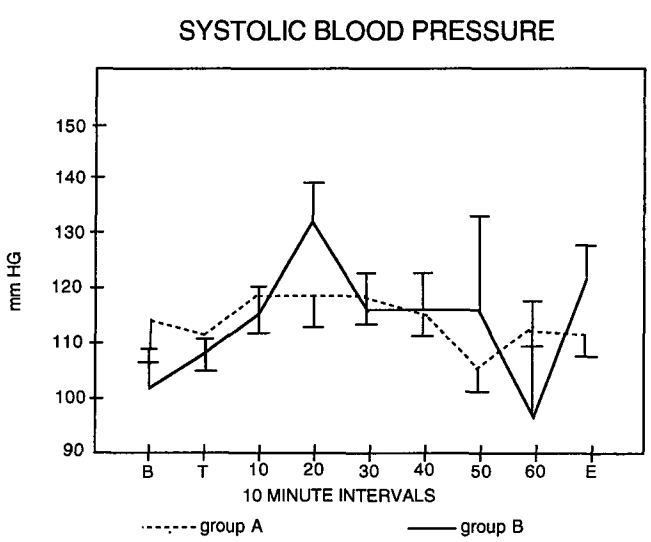

Fig 2. Systolic blood pressure of Group A (0.3 mg/kg) and Group B (0.5 mg/kg) along with means and standard errors. (B = Baseline Reading; T = Start of Treatment; E = Exit)

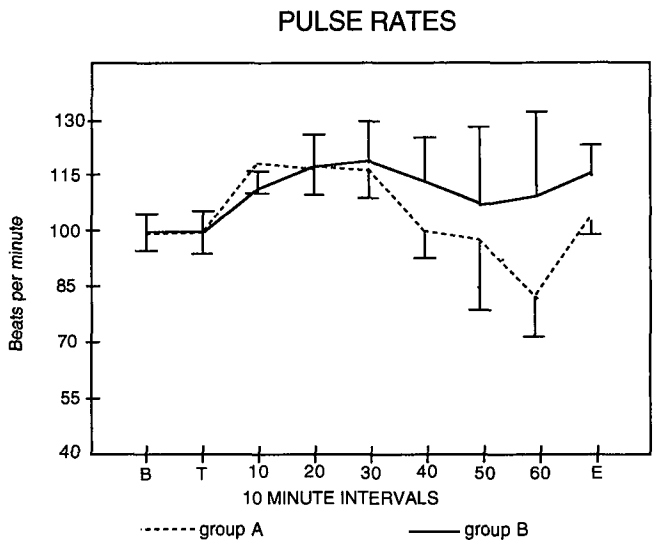

Fig 3. Pulse rate of Group A (0.3 mg/kg) and Group B (0.5 mg/kg) along with means and standard errors. (B = Baseline Reading; T = Start of Treatment; E = Exit)

lack of cooperation. Treatment was aborted and temporaries were placed until an alternative treatment method was scheduled. The three unsuccessfully sedated patients required aggressive restraining to complete treatment.

Two children slept during a major part of the treatment period, yet both were easily arousable with verbal stimulation; the other 13 patients remained awake and fully conscious. None of the children in Group B had prolonged sedation. There were no reports of postoperative nausea, seizure activity, or other postoperative complications at the time of the follow-up phone calls.

Vital sign measurements recorded during the sedation appointment revealed that respiration rates varied only slightly in all patients. Slight decreases in respirations were seen in five patients when compared with the presedation rate; however, it was not clinically evident that the children were in any form of compromised respiratory status.

Diastolic blood pressure readings revealed significant changes (ANOVA; $P < 0.05$) when time periods were compared (Fig 1; Table 4). Further analysis by a Scheffe F-test showed that diastolic blood pressures differed significantly when comparing (B) and (20), and (T) and (20). Systolic blood pressure statistical analysis using the ANOVA also revealed significant differences ($P < 0.05$; Fig. 2; Table 4). The Scheffe F-test showed these differences to be statistically higher during treatment ($P < 0.05$) than readings at (B) or (E). Significance was seen between (B) and (20), (B) and (E), and (T) and (20). Pulse rates revealed significant differences (ANOVA; $P < 0.05$; Fig. 3; Table 4). Using a Scheffe F-test, pulse rates were significantly lower at (B) than at (20), or at (E). Pulse rates were also significantly lower at (T) than at (20) and at (E). Oxygen saturation revealed no significant differences (ANOVA; $P < 0.05$; Fig 4; Table 4). Vital sign measurements recorded during the sedation appointments showed that oxygen saturation momentarily dropped to 92% in one child and to 93% in another. In both instances, the patient quickly returned to an acceptable oxygen saturation with head repositioning. All patients recorded an acceptable oxygen saturation level (95%) during a majority of the appointment and were discharged without complications or delays.

Comparing Group A with Group B

Overall success, as determined by the ability to complete treatment, was 75% for Group A (0.3 mg/kg), and 60% for Group B (0.5 mg/kg). Chi-square analysis revealed no significant difference in these success rates.

Discussion

The widespread and successful use of oral midazolam as a preoperative sedative in pediatric hospitals indicates that it is a favorable choice for pediatric dentists. The initial question posed was which dosages of midazolam would be ideal to study. The fact that this study population consisted of children of various ages, weights, and degrees of mental compromise made the decision on an appropriate dosage more difficult. The dosages selected for this study were based on both recommendations by pediatric anesthesiologists who used 0.3–0.8 mg/kg of the agent for preanesthetic sedation[22,23] and reports from the literature using 0.25–0.75 mg/kg dosages of oral midazolam.[17,20] It was unknown whether these dosages would modify the behavior of uncooperative mentally or physically compromised patients sufficiently and for a duration long enough to

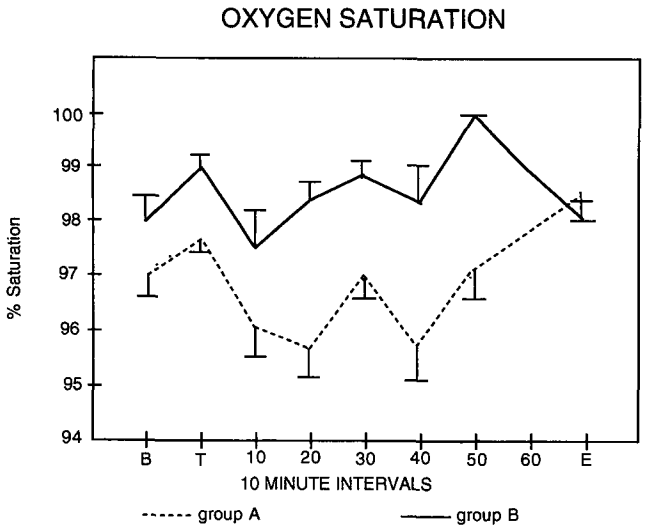

Fig 4. Oxygen saturation of Group A (0.3 mg/kg) and Group B (0.5 mg/kg) along with means and standard errors. (B = Baseline Reading; T = Start of Treatment; E = Exit)

allow dental care to be performed safely. Several pilot studies were performed using various dosages to determine which produced adequate sedation while maintaining the patient's protective reflexes. It was found that dosages > 0.5 mg/kg did not always produce conscious sedation and these patients had to be recovered and monitored for extended periods of time. Thus, 0.3 mg/kg and 0.5 mg/kg were chosen for this study. The results of this study indicate that both of the selected dosages provided adequate sedation and working time for the majority of patients.

An obstacle to overcome in evaluating the success of a conscious sedation is the use and development of an assessment tool for behavior and cooperation. The study population was not typical of those seen routinely in private practice. Many of these children were moderately to severely neurologically handicapped with ages ranging from 3–18 years. In addition, many of the children were nonverbal, making behavior assessment even more difficult. The scale used in this study had to be standardized and provide specific criteria for each rating from good to very unfavorable behavior.

The most commonly used behavior scale in pediatric dentistry is the Frankl Behavioral Rating Scale,[21] which assigns four levels of patient cooperation emphasizing patient rapport. It tends to disregard patient personality and other factors that play an important part in assessing the handicapped child patient's behavior. For this reason a modified scale was developed to enable more accurate cooperation ratings by focusing on the patient's verbal intensity and physical actions rather than on verbal communication. The modified scale was simplified so that a clear distinction could be made as to when treatment was accomplished safely, effectively, and without psychological or physical trauma to the patient. In the opinion of the investigators, this modified scale was not only successful in its purpose, but provided an easy method to quickly and accurately rate cooperation during the course of the appointment.

The investigators determined behavioral success of the sedation by rating the patient's cooperation at set time intervals during treatment. Overall success was determined if behavior during operative treatment did not drop to a rating of 1 and the procedure was completed safely and without excessive physical restraint and harsh management techniques. Behavior did not tend to deteriorate over time to a rating of 1 — rather, the patients considered to be failed sedations had multiple ratings of 1. The results indicate a slight difference in the effectiveness of the two dosages. In general, the patients were more cooperative and less combative with the lower dosage, yielding a success rates of 75% for Group A and a 60% for Group B. The higher dosage did not result in a greater rate of success, possibly due to the small population size. With an increased sample population, a larger dosage may prove to be equally or more effective. However, the findings of this investigation support use of the lower dosage of 0.3 mg/kg since the increased dosage did not offer sufficient advantages.

Oral drug administration is considered the route of choice in pediatric dentistry. There were no episodes of nausea or vomiting and most children found the medication acceptable. The midazoalm-Syrpalta mixture was considered less than palatable by 35% of the patients; the remaining 22 patients took the medication without complaints. Although the oral route has a slower onset of action than other routes and extensive first-pass hepatic extraction, it is least traumatic for the child and produces acceptable results for in-office conscious sedation.

The length of time between administering the oral medication and starting treatment — varying from 15 to 40 min — was an important finding. It appeared that the children with the more rapid onset received less distraction and stimulation, eliminating factors that might produce apprehension and allowing the child to relax. In future studies, placing the child in a quiet room after oral sedation may produce more rapid sedation and lead to better cooperation.

Monitoring vital signs to determine the safety of oral midazolam was the second objective of this investigation. It was unknown what the clinical effect of oral midazolam would be after the initial 15–30 min reported in the preoperative studies.[17, 22, 23] Analysis of vital signs was performed to provide a comprehensive assessment of physiological parameters during the appointment. These readings were taken preoperatively upon arriving at the clinic for a baseline (B), and following clinical onset of the medication prior to the

actual start of treatment (T), to provide an accurate assessment of the effects of the oral midazolam without interference from clinical treatment factors.

The statistical results indicated that there were no significant differences in the vital sign measurements in either Group A or B when comparisons were made between (B) and (T), showing little influence of the orally administered midazolam. In Group A, intratreatment (20) pulse rates were significantly elevated and oxygen saturation significantly decreased compared with (B) and (T) readings. In Group B, significant elevations were noted in all the vital sign parameters except oxygen saturation when similar comparisons were made. These comparisons indicate that the oral midazolam itself was not a major factor in altering vital signs, but that anxiety-related factors and stimulation were more influential in elevating blood pressure and pulse. Vital signs were, however, monitored to the completion of treatment to assure that there were no significant long-term changes from baseline readings or delayed effects of midazolam over time. For the majority of patients, treatment lasted only 30 min and therefore, the decreased number of patients in the extended periods resulted in larger standard deviations (Figs 1–4).

A relationship was found between changes in cardiovascular vital signs and success of the midazolam dosage. The higher dosage (0.5 mg/kg) used in Group B was clinically less successful and had statistically significant increases in all three of these parameters — pulse and diastolic and systolic blood pressures — when comparing (B) with (20). Similar comparisons for the more successful Group A (0.3 mg/kg) showed only significantly increased pulse rates.

The respiratory effects of oral midazolam, as measured by oxygen saturation and respiratory rate showed the only significant change to be a decrease in oxygen saturation for Group A. This may be explained in several ways. First, the oxygen probe is sensitive to movement and the muscle relaxant properties may not have been as effective at the lower dosage, causing the oxygen readings to be inaccurately low due to artifact, especially in patients with uncontrolled movement associated with their diagnoses. Second, one of the unsuccessful patients in Group A, with a low saturation, was breath-holding as well as struggling during a reading. Also, because Group B tended to be less cooperative and cry more, their respiratory effort was greater, causing increased oxygen saturation in this group. Restraints used on the more combative patients in this group may have eliminated some of the effect of movement artifact expected in the more uncooperative group. Although some vital sign changes were statistically significant, no patients showed any signs of physiologic compromise clinically.

The questions and concerns over postoperative complications were answered favorably. There were no reported cases of nausea, seizure activity, or any other unfavorable reactions at a 24-hr follow-up phone conversation with the parent. Since the elimination half-life is from 1 to 4 hr, this followup would allow for any adverse reaction to occur. Only one case of residual sedation effects was seen — a child in Group A who was overweight. Because midazolam may be stored in adipose tissue and slowly time-released, this may explain the prolonged sedation and secondary sedative effects.

Personality factors and age also may play an role in assessing candidates for conscious sedation with oral midazolam. Though not an official part of the project design, patients' personalities, and the nature of their interpersonal interactions were noted prior to sedation. Children who were extroverted tended to be more successful than those individuals who were timid and introverted or did not relate well with others. These children were difficult to sedate and even more difficult to make cooperate. Interestingly, age did not seem to be related to the success or failure of oral midazolam sedation. The average age of the uncooperative patients in both groups was 9 years as was the average age for the groups as a whole.

Although it was never the intent of the study to measure parent desire or satisfaction, there were some anecdotal observations worth noting. Many parents of children with muscle spasticity commented that they had never seen their child so relaxed. Parents whose children had been previously sedated with oral meperidine and promethazine generally considered oral midazolam to be more effective. The vast majority of parents were pleased that their child returned to their normal behavior so rapidly. And last, many parents expressed the desire for their child to be sedated or relaxed with midazolam for future appointments including routine examinations and oral prophylaxis. Future studies should be designed to include collection of parental attitudes concerning the drug's effect.

This investigation's primary purpose was to initiate research on using oral midazolam on the pediatric dental patient. The scarcity of information on this topic has made many pediatric dentists reluctant to incorporate it into their private practices. This study involved some of the most challenging dental patients to treat and the results indicate an acceptable success rate. Future evaluation of oral midazolam on the "normal child" would perhaps yield even more favorable results. Dosage modification and concurrent use of nitrous oxide with oral sedation are areas of research that could expand knowledge of midazolam and its effectiveness and practicality in the pediatric dental office. Concerns over some changes in vital signs in this study could also be addressed in future investigations. Measurement of end tidal carbon dioxide is considered an accurate analysis of respiratory alteration and could be incorporated into a study to further evaluate any respiratory depres-

sion from oral midazolam. Pulse oximetry also could be improved to eliminate some distortion from patient movement through the use of EKG leads wired into the pulse oximeter.

Conclusions

1. Orally administered midazolam was successful 75% of the time at a dosage of 0.3 mg/kg and 60% of the time at a dosage of 0.5 mg/kg in providing adequate sedation to allow operative treatment to be safely and efficiently performed for the moderately to severely physically and neurologically compromised pediatric patient.
2. There was no statistically significant difference in the effectiveness of the two oral regimens when either overall success rates or intratreatment ratings were analyzed.
3. Although clinically insignificant, Group A (0.3 mg/kg) showed a statistically significant increase in pulse rate and decrease in oxygen saturation and Group B (0.5 mg/kg) showed statistically significant increases in pulse rate and diastolic and systolic blood pressures during treatment compared with readings at baseline and the start of treatment.
4. No clinical signs of a compromised respiratory rate were noted with use of either dosage of the oral midazolam.
5. Neither sedation regimen caused any postoperative complications.

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