Original Article

Assessing the sedative effect of oral vs submucosal meperidine in pediatric dental patients

Lida Toomarian[1], Katayoun Salem[1], Ghassem Ansari[1]

[1]Department of Pedodontics, Dental School, Shahid Beheshti Medical University, Tehran, Iran

ABSTRACT

Background: The goal of this investigation was to compare the behavioral and physiological effects of three sedative drug regimens: oral meperidine (OM), submucosal meperidine (SM) and oral midazolam (M) in healthy pediatric patients.

Materials and Methods: This study sample consisted of thirty children aged 24-72 months (mean = 41.1) exhibiting definitely negative behavior. Three sedative regimens including: Oral meperidine/hydroxyzine, oral midazolam/hydroxyzine and submucosal meperidine/oral hydroxyzine were administered randomly during three consecutive appointments with a crossover design. Houpt behavioral scale was employed for evaluating the sedation effect of each regimen by a calibrated independent Pediatric dentist. Physiologic parameters were also recorded including blood oxygen saturation and pulse rate. Data was analyzed using Wilcoxon-signed ranked test, Mc-Nemar, GEE Logistic regression, Friedman, Fisher exact and Cochran tests for significance.

Results: Overall success rates were 50%, 46.7% and 26.7% for submucosal meperidine, oral meperidine and oral midazolam, respectively ($P = 0.03$). The probability of achieving a success in behavior control was more in 48-72 month olds. Child's age and drug type were the two main predictors of altered behavior. Evaluating the differences between the effects of three tested regimens on recorded physiological parameters showed no significant differences.

Conclusion: All three regimens were proved safe within the limits of the current study. Meperidine sedation in both routes was considered to be more effective. Although there was less sleep and more head/oral resistance in midazolam group, the difference between groups was not significant.

Key Words: Dental anxiety, meperidine, midazolam, oral, pediatric sedation, submucosal

INTRODUCTION

A successful behavior management strategy requires the use of a variety of behavioral and sometimes pharmacological techniques in pediatric dental practice.[1,2] Pharmacological strategies are valuable adjuncts to daily practice; however, despite a large body of information, pediatric dentistry still seeks for safe and effective sedative regimens. Meperidine, an opioid agonist, in combination with hydroxyzine is assumed to be an effective sedative regimen for its euphoric and analgesic properties.[3-6] Compared to adults, higher sedative values are registered in children.[3] The medication is usually administrated via several routes including oral and submucosal means. Submucosal meperidine is exclusively administered in the field of dentistry and allows a rapid rise in drug's serum level;[6] a property that makes it suitable for pediatric dental patients. However, oral administration, in spite of its longer waiting time and bitter taste, may be more preferred by many children.[3] A high success rate has been reported for oral and submucous meperidine in children with a mean age of 51 and 54 months.[4-7]

Hydroxyzine has been shown to have an analgesic as well as antiemetic and euphoric effects in addition to

its sedative potential with fewer hazards.[8] Midazolam, a relatively short-acting benzodiazepine, has received considerable attention as a safe and effective agent mainly beside nitrous oxide.[8-18] Midazolam has gained high popularity over the recent years based on its margin of safety, half-life, amnestic potential and availability of antagonist. However the effectiveness of these drugs is not fully understood in children younger than 4 years of age.[14,19] The purpose of this study was to compare the efficacy and safety of three sedative regimens of oral midazolam, oral meperidine and submucosal meperidine; in 2-6-year-old uncooperative pediatric dental patients.

MATERIALS AND METHODS

Study design
Ethical approval was obtained from the Ethic Committee of Shahid Beheshti University of Medical Sciences along with a written, informed consent being signed and agreed by parents. This randomized crossover clinical trial was conducted on a group of uncooperative young children. Case selection was in a random blocking manner. Sequentially numbered containers were used for randomization by operating Pediatric dentist. Blinding was carried out on the rater and operator, as none had any role in the drug administration process. However, behavioral rating was performed after the administration of different regimens; operators were calibrated in advance through the course of treatment. Drug administration was performed along with monitoring physiological parameters by an anesthesiology technician to ensure proper drug administration. A hypothesis was drawn as meperidine to be a superior sedative medication to midazolam in children.

Sample
This study included 30 uncooperative children (23 boys and 7 girls scored as Frankl 1, definitely negative) aged 2-6 years, who were referred to the Pediatric Hospital Dentistry Clinic at Shahid Beheshti Dental School with a history of previous unsuccessful dental appointment by a Pediatric Dentist (Frankle 1). Only subjects in ASA I and those in need of at least three teeth for pulp treatments in separate sedation appointments were included. Subjects were excluded if there was any evidence of tonsillar enlargement (Brodsky >+2), weight more than 25 kg,[4] any mental disabilities, or any reported history of allergy to these applied drugs.

Sample size was estimated according to earlier similar studies,[8,17,18] with a power of 90%, $\alpha = 0.05$, and $\varepsilon = 0.2$. Thirty samples were then used to evaluate cross over effect.

Sedation appointment
Cases were instructed to maintain a 6 hours period NPO time for solid foods and 2 hours for clear liquid. Physiological parameters were monitored including systolic and diastolic blood pressure, SPO_2, heart rate and respiratory rate. Data was recorded in baseline (when the patient was calm) followed by the same records during and at the end of each treatment section. Scheduled sedative drugs were administered under the supervision of an anesthesiologist. Liquid drugs were administered by cup and in the case of unwillingness to drink, 2 mL needleless syringe was used to deliver the drug at the retromolar area. Behavioral alteration was assessed throughout each treatment section using the recorded video films according to Houpt[10] and modified Houpt scales.[5]

An initial Child Fear Survey Schedule Dental subscale questionnaire (CFSS-DS) was requested to be filled in by child's mother before the start of sedation appointment as well as the end of third sedation appointment.[20] Attempts were made to complete all dental procedures within a time limit of 15-20 minutes. Adverse effects of the drugs were recorded including nausea, vomiting, restlessness, or aggressiveness both during the study and the next day, by phone. Each patient was recalled for the 2nd or 3rd visits in a week interval pattern.

Sedative regimens
Children in all groups received hydroxyzine hydrochloride syrup 1 mg/kg from a 10 mg/5 mL syrup (Kharazmi Pharmaceuticals ®Tehran, Iran) as base one hour prior to the dental treatment commencement.

Group I (Submucosal Meperidine) patients received meperidine 1 mg/kg from 50 mg/mL vial (Gerot, Austria®) by injection using Insulin syringe after a topical 5% lidocaine hydrochloride application in the opposing area of the treating side.

Group II (Oral Midazolam) cases received a dose of 0.5 mg/kg midazolam prepared from vials of 5 mg/mL (Midamax, ®Abou Reyhan Pharmaceuticals, Tehran, Iran) mixed with 50% aqueous sucrose solution. This mixture was administered 30 minutes after the initial hydroxizine intake and 30 minutes before starting the dental treatment.[5]

Group III (Oral Meperidine) cases received 2 mg/kg meperidine (50 mg/mL, Vial, Gerot, Austria®) 1 hour before dental treatment commencement along with hydroxyzine.[5,6]

During the course of treatment oxygen was available via central supply using a nose mask, to compensate any possible desaturation; in cases of any decline in blood oxygen saturation from 93%. Cases were dealt with appropriately while excluded from study.

Dental procedures

All participants received a local anesthetic injection (Lidocaine 2% - Epinephrine 1/80.000, max. dose of 4 mg/kg, Daroupakhsh®, Iran) before receiving pulp treatment and restoration of primary molar in each visit. Behavior rating was conducted by reviewing the recorded films of each section by two independent clinicians, according to Houpt behavioral rating scale [Table 1]. To improve evaluation of child's behavior alterations, authors recorded head and oral resistance as Modified Houpt[8] behavioral rating scale [Table 2]. The inter-examiner reliability test was conducted in order to calibrate them. The Interclass Correlation Coefficient (ICC) was 0.811 for first examiner and 0.899 for the second examiner and the inter-examiner reliability was 0.965. The Kappa coefficient was 1 when the subjects were divided into two broad groups acceptable (scores 4, 5, 6) and unacceptable (scores 1, 2, 3) Houpt rating scale. Papoose board or other types of physical restraint were abandoned for this clinical investigation. Disruptive movements were only controlled passively, when needed by the aid of one assistant under the supervision of principle pediatric dentist.

Physiological parameters including heart rate, respiratory rate, blood pressure and oxygen saturation were recorded using operating room design monitors (Masimo Set, Alborz B5 Saadat, Iran) throughout the course of treatment and at discharge with records every 15 minutes.

Data analysis was performed using Wilcoxon-signed ranked test, Mc-Nemar, generalized estimate equitation (GEE) logistic regression, Friedman and Fisher exact and Cochran test with SPSS18 and 95% confidence level.

RESULTS

This study was conducted from May 2010 to January 2011 at the Hospital Dentistry Unit, Department of Pediatrics Dentistry, Shahid Beheshti

Table 1: Original Houpt behavioral rating scale

Rating scale for sleep
  Fully awake, alert
  Drowsy, disoriented
  Asleep
Rating scale for movement
  Violent movement that interrupts treatment
  Continuous movement that makes treatment difficult
  Controllable movement that does not interferes with treatment
Rating for crying
  Hysterical crying that interrupts treatment
  Continuous persistent crying that makes treatment difficult
  Intermittent, mild crying that does not interfere with treatment
  No crying
Rating for overall behavior
  Aborted no treatment rendered
  Poor treatment interrupted, only partial treatment completed
Fair treatment interrupted, but eventually all completed
Fair treatment interrupted, but eventually all completed
  Very good some limited crying or movement, e.g., during anesthesia or mouth prop insertion
  Excellent, treatment completed

Table 2: Head and oral status according to modified Houpt behavioral rating scale[8]

Head/oral resistance
Turns head, refuse to open mouth
Mouth closing, must request to open
Choking, gagging, spitting
No crying present

University of Medical Sciences, Tehran, Iran. Thirty subjects including 7 girls (23.3%) and 23 boys (76.7%) included in this study. The mean age was 13.9 ± 41.6 months with 14 subjects being under the age of 3 years, with the mean weight 2.5 ± 14.5 kg. Calculating the data from dental fear questionnaires revealed a pretreatment CFSS-DS of 14.4 ± 45.2 which showed an increase to 49 ± 10.8 throughout the course of treatment; however, the difference was not significant using *Wilcoxon-signed rank* test ($P = 0.06$). A non-significant change was also achieved in pretreatment status of dental fear following this approach when Mc-Nemar test was used ($P = 0.219$).

To assess the impact of sequence of sedation appointments on overall behavior, a carryover analysis was used with GEE logistic regression. Evaluation of the overall behavior was carried out through the following classification: 1. Successful (Houpt score 4, 5, 6) and 2. Unsuccessful (Houpt 1, 2, 3). No significant relationship was found between overall behavior and sequence of sedation regimens using GEE test ($P = 0.28$).

It was noted that older children (4-6 years of age) show six times more success for overall behavior than younger children (2-3 years of age). No significant difference was observed between the mean subscales (sleep, movement, crying and overall) of the groups [Table 3]. Head and oral resistance according to modified houpt is presented in Table 4. When overall behavior was classified to successful and unsuccessful, the differences were significant, $P = 0.037$ [Table 5].

The mean recovery time from the administration of drugs was 83.50 ± 9.57 minutes for midazolam followed by 85.33 ± 4.32 min for submucosal meperidine, and 97.50 ± 10.72 minutes for oral meperidine. Significant difference was found between the recovery time of oral meperidine and two other groups, Friedman test ($P < 0.005$).

Nervousness was reported at home in the following 48 h in 11 cases of midazolam and one case of severe agitation immediately after completion of

Table 3: Mean sedation scores according to Houpt behavioral rating scale

	Sleep	Movement	Crying	Overall
Submucosal meperidine	1.57±0.56	2.20±0.88	2.30±1.02	3.40±1.63
Oral midazolam	1.67±0.47	2.27±0.82	2.40±0.81	2.97±1.37
Oral meperidine	1.57±0.67	2.30±0.95	2.47±0.67	3.63±1.73
P value	0.41	0.9	0.58	0.2

Friedman test. *P*>0.05

Table 4: Head and oral resistance in addition to verbal behavior according to modified Houpt

	Body movement	Head and oral resistance	Verbal behavior	Overall assessment
Submucosal meperidine	2.00±0.83	2.17±1.14	2.6±1.13	2.9±1.43
Midazolam	1.97±0.68	1.76±0.87	2.52±1.09	2.93±1.30
Oral meperidine	2.03±0.89	2.04±1.03	2.53±1.00	2.93±1.43
P value	0.41	0.9	0.58	0.2

Friedman test. *P*>0. 05

Table 5: Overall assessment of Houpt divided into successful and unsuccessful behavior

Overall behavior	Successful (Houpt 4, 5, 6) (%)	Unsuccessful (Houpt 1, 2, 3) (%)	Total (%)
Submucosal meperidine	15 (50)	15 (50)	30 (100)
Midazolam	8 (26.7)	22 (73.3)	30 (100)
Oral meperidine	14 (46.7)	16 (53.3)	30 (100)

Cochran test. *P*=0.037

treatment, also vomiting occurred in two cases of oral meperidine (one during treatment and the other at the recovery time). No other adverse effects were observed such as apnea or desaturation.

DISCUSSION

There is a growing need for the use of sedative drugs in controlling highly uncooperative pediatric dental patients, which could rise cooperation and ease dental procedures. According to the results of this study, the rate of successful sedation prior to dental treatment with either routes of meperidine administration was three times more than midazolam. Midazolam is widely known as an effective sedative agent for many medical and dental procedures.[1-10] However, midazolam with the recommended dose of 0.5 to 0.75 mg/kg has little to no effect in children younger than 3-4 years.[14,21] Kain (2007) reported that the plasma levels of midazolam and its metabolite 1-hydroxy midazolam; were equivocal in both responders and nonresponders, with responses being quite different in children younger than 4 years of age. Hence this finding should be attributed to pharmacodynamic rather than pharmacokinetic variables. In other words, midazolam is absorbed, distributed and metabolized in a similar manner in both responders and nonresponders, but the interaction between midazolam and the type A GABA receptors, responsible for antianxiety effects, is essentially different in different ages. The ontogeny of these receptors including their expression, distribution and coupling with midazolam is an issue, which is still under investigation in children of various age groups.[8] Similar results were obtained in this investigation. It was also noted that older children (4-6 years of age) show six times more success for overall behavior than younger ones (2-3 years of age). An overall success rate of 54% has been reported recently by Baygin (2010) with a dose of 0.75 mg/kg midazolam too.[22]

Despite all expectations, meperidine was not found to be fully beneficial in the current study. Since half of the cases were under the age of 3 years, it seems that minimal sedation even with a drug like meperidine, will not improve child's behavior profoundly in such a young age. From a pharmacological point of view, opioids such as meperidine are subject to extensive first-pass metabolism (a large proportion is broken down in the liver). So if they are administered orally, only 40-50% of the dose reaches the central nervous system.[23,24] Hamunen, *et al*. reported that meperidine

pharmacokinetic parameters were found to be similar to those of adults, with an average half-life of 3.0 hours.[25] Obviously what a clinician should primarily achieve is to facilitate the communication and potentiate the effects of behavioral modification expected from the drug's effect, which needs further proof in uncooperative age groups. In cases where no positive drug effect is achieved for sedating children, general anesthesia is offered as an alternative to complete the treatment process.

Based on the results of the current investigation, both oral and submucosal meperidines were in a similar range of safety and behavioral modification. However, it seems that oral administration is preferred by patients based on its higher acceptance.

On the other hand it has been found that child temperament is an important issue in responsiveness to midazolam. More emotional and more anxious children[14] may not well cope with treatment by midazolam as well as those with psychosomatic behavior problems and inflexible temperament,[23] or impulsivity.[24] These variables could be the reasons for low compliance observed in this study, as half of the subjects were younger than age 3, with almost all showing extremely uncooperative behavior (rated as Frankl 1).

An overall decrease in dental fear following the three sedation appointments were observed with only three individuals indicating some degrees of fear remaining afterwards. Isik (2010) has reported significantly better outcomes associated with midazolam sedation in children with temperament characteristics such as inflexibility and psychosomatic symptoms. It is well evident that a successful sedation is not necessarily guaranteed after oral midazolam premedication.[23] Rodrigues (2003) reported that the use of midazolam-hydroxyzine combination lead to a poorer result comparing to midazolam alone, since hydroxyzine did not potentiate the effect of midazolam in spite of previous expectations[12] as seen by the current results. Injective form of midazolam was used through oral route as a part in combination with aqueous solution of sucrose in this investigation. Since midazolam has a pka of 6.15 (a pH that the ionized and non-ionized forms of drug are in balance), a major part of the medicine is ionized in the presence of gastric fluids; the bioavailability is therefore 15 to 27%.[25] Levine (1993) suggests midazolam may augment transmucosal absorption in viscous syrup,

bypassing the portal metabolism and increasing the absorption rate of the drug.[11]

The rate of acceptable behavior with meperidine was about 46.7% and 50% for oral and submucosal administration, respectively. Higher success rates are reported by Cathers (2005) and Song (2003). It should be noted that the mean age of patients is an important variable in the success rate of sedation as higher values in the aforementioned studies (50, 51 months) compare to 41 months in the present study. In addition, Cathers (2005) believed that the sequence of meperidine administration clearly affects the results, as patients who received oral meperidine in the first session were twice likely to have a more successful sedation compared to those who received the submucosal type first.[5] Such a correlation was not found in this study.

Beside the efficacy, safety of the drugs used is an important issue specially for treating children in the dental office. No episodes of desaturation (saturation below 90%) with either of the drug regimens were observed during this study. In the case of transient hypoxemia, oxyhemoglobin level did not come any lower than 93% and was relieved primarily by changing the head position and jaw trust maneuver, although an oxygen source and nose mask was available. Stability of the other physiological parameters was also observed, except the heart rate in the midazolam group, which showed alterations from baseline measurements. This finding is in consistence with Chawdhry (2005)[26] and Golpayegani, *et al.* (2012).[27] However, these changes were remained in the range of upper natural limits adjustable to behavioral patterns such as crying during midazolam sedation or as natural outcome of sleep.

Other adverse reactions include mild or moderate inflammatory response and mucosal edema at the injection site of meperidine, in a few cases. Mucosal reaction has been mainly reported in adults due to a larger volume of the medicine.[6] Two cases of nausea and vomiting were also reported following the use of oral meperidine and after the completion of treatment. This phenomenon is a common outcome in outpatient dental care and attributes to stimulation of medullary chemoreceptor with movement.[28]

It is believed that in addition to the dental fear, other aspects of child's personality and temperament should be evaluated before judging the medicine's effectiveness, two important factors which could have a direct impact on these studies.

CONCLUSIONS

1. Under the condition of this study, submucosal and oral forms of meperidine were equally effective and significantly more than midazolam in providing sedation for children ($P = 0.009$).
2. No significant relationship was found between overall behavior and sequence of sedation regimens using GEE test ($P = 0.28$).
3. No adverse effect was observed from the use of these drugs, with only midazolam increasing the heart rate, though within the normal physiological range.

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