Subcutaneous Midazolam with and without Ketamine for Sedation In Children Undergoing Dental Treatment: A Pilot Study

Flores-Castillo D* / Martínez-Rider R** / Ruiz-Rodríguez S*** / Garrocho-Rangel A**** / Lara-Guevara J***** / Pozos-Guillén A******

Aim: *The objective of this study was to evaluate the efficacy of subcutaneous (SC) sedation using midazolam with and without ketamine in non-cooperative pediatric patients undergoing dental treatment.* ***Study Design:*** *A prospective, randomized, controlled, double-blind, crossover pilot clinical trial was carried out in 13 children, aged between 17-46 months, ASA l, Frankl 1. Two sedation schemes were administered SC: Midazolam alone (M), and a combination of Midazolam-Ketamine (MK). Both regimens were administered to the same patient in two consecutive treatment sessions, in accordance with a random assignment. Overall behavior, movement, and crying were assessed according to the modified Houpt scale. Heart rate, blood pressure, blood oxygen saturation, and possible side effects were also monitored.* ***Results***: *The percentage of non-crying children was always higher in the treatment with MK compared with the treatment with M, but without a significant statistical difference. Regarding variable body movement, the percentage of children without movement was higher in the MK group, although only up to minute 10; no significant differences were found at 20, 30, and 40 minutes, and from minute 40, body movement was lower in the M group.* ***Conclusions***: *Midazolam alone and the midazolam-ketamine combination administered subcutaneously resulted in a safe and efficient pharmacological method for providing moderate sedation to non-cooperative pediatric patients undergoing dental treatment.*

Key words: *subcutaneous; sedation; midazolam; ketamine; dental.*

INTRODUCTION

Although the majority of children accept dental treatment willingly without complaint, the youngest children exhibit fearful, non-cooperative, or negative behavior due to their immature cognitive skills and require behavior modification measures in order to receive safe and high-quality dental procedures.[1] Despite conventional behavior modifications (tell-show-do, positive reinforcement, voice control, distraction, etc.) and because physical restraint without sedation might be regarded as psychologically and ethically unacceptable, many children require the use of pharmacological approaches, such as moderate or deep sedation, and even general anesthesia.[1-5]

The ideal sedative agent must consistently and predictably reduce patient anxiety and improve the child's behavior in order to facilitate the accomplishment of dental treatment, delivering a more positive experience to the child.[6] Diverse drugs, alone or in combination, have been studied for moderate sedation in children, mainly narcotics, antihistamines, hypnotics, and benzodiazepines, employing different administration routes.[2,6]

Midazolam and ketamine, administered individually or combined, have extensively proven to be safe and efficient for the management of non-cooperative patients, under appropriate dosages regimens. The safety of any sedative for premedication must be the primary concern of practitioners who treat young patients.[4,7,8]

From the Facultad de Estomatología, Universidad Autónoma de San Luis Potosí, Mexico

*Dulce Flores-Castillo, DDS, Resident, Pediatric Dentistry Postgraduate Program.

**Ricardo Martínez-Rider, DDS, Associate Professor, Oral and Maxillofacial Surgery Department.

***Socorro Ruiz-Rodríguez, DDS, MS, Associate Professor, Pediatric Dentistry Postgraduated Program.

****Arturo Garrocho-Rangel, DDS, PhD, Associate Professor, Pediatric Dentistry Postgraduated Program.

*****Javier Lara-Guevara, MD, Associate Professor, Oral and Maxillofacial Surgery Department.

******Amaury Pozos-Guillén, DDS, PhD, Associate Professor, Basic Sciences Laboratory.

Send all correspondence to:

Amaury de Jesús Pozos Guillén, Facultad de Estomatología, Universidad Autónoma de San Luis Potosí, Av. Dr. Manuel Nava #2, Zona Universitaria, C.P.78290; San Luis Potosí, SLP. México.
Phone: 52 (444) 8262357 X 114.
E-mail: apozos@uaslp.mx.

Midazolam is a short-acting benzodiazepine indicated for premedication, sedation, induction, and maintenance of anesthesia. It has been regularly and successfully utilized by anesthesiologists as premedication for general anesthesia in pediatrics.[6,9] It is a derivate of the imidazo-benzodiazepines with high affinity for the benzodiazepine receptor. It is characterized by rapid onset (10–20 min) and recovery and short-length action, due to its fast biotransformation. This sedation agent possess intense anxiolytic, anterograde, amnesic, and sleep-inducer effects, but no analgesic action; when used alone, however, midazolam is limited to short-duration dental procedures (20–90 min) with good or excellent results in 60–80% of cases.[9,10]

Ketamine is an intravenous or intramuscular general anesthetic, indicated in surgical or diagnostic procedures when muscular relaxation is required. It also provides a dissociative sedation state together with a powerful analgesic effect, and high overall success rates have been reported without significant side effects. Despite ketamine's reported psychotomimetic properties (such as hallucinations) in many patients when administered intravenous (IV) or intramuscular (IM), its association with benzodiazepines may attenuate these side effects.[11-13]

The subcutaneous (SC.) route represents a non-invasive alternative for the administration of drugs, especially hypnotic and non-volatile hydro- or liposoluble narcotic agents. The drug absorption rate varies depending on the tissue's blood supply. The SC route is indicated in circumstances in which the patient cannot take the drug orally or when the symptoms are not sufficiently controlled when this route is used. This administration route offers advantages such as being safe, unaggressive, and more comfortable for patients, does not require hospitalization, permits great patient autonomy, is easy to use, and has a less reported incidence of side effects.[14]

The objective of the current study was to evaluate the efficacy of sedation through the SC route using midazolam with and without ketamine in dental procedures under local anesthesia and protective stabilization in non-cooperative pediatric patients.

MATERIALS AND METHOD

A prospective randomized, double-blind, crossover, clinical pilot trial was conducted according to the ethical guidelines established by the Helsinki Declaration and approved by the Institutional Research Ethics Committee. The parents of patients included in this study signed a written informed consent, which specified the objectives and benefits of the study, the procedures planned, as well as possible risks and secondary effects of the sedative medications employed. This study was carried out according to American Academy of Pediatric Dentistry (AAPD) guidelines for safe pharmacological sedation in children.[3] Patients of both genders, aged between 15 and 48 months, American Society of Anesthesiologists (ASA) 1, Frankl behavioral rating scale class 1, with or without previous dental experiences, requiring two sedation sessions for dental procedures under local anesthesia, were candidates for inclusion in the study, excluding patients eligible for general anesthesia because of the procedure extension, with mental or physical deficiencies such as overweight or known hypersensitivity to benzodiazepines or ketamine. Once included, the patients were randomly assigned by a computer-generated random number sequence into one of two study groups in a crossover manner as follows: Group A: Midazolam (M) (RELACUM®, PISA Laboratories), 0.4 mg/kg 15 min before the procedure, and Group B: M (0.4 mg/kg) plus Ketamine (0.1 mg/kg) (MK) (RELACUM® PISA/ANESKET® PISA) 15 min prior to the procedure. Both dosage schemes were administered SC, employing the traditional syringe and needle.

During the first dental visit, the patient was thoroughly evaluated and it was determined whether the patient was eligible for sedation. The second appointment began with rubber cup and pumice prophylaxis, under extensive verbal communication and behavior modification techniques and, simultaneously, assessment of the patient's anxiety and behavior using the Frankl scale. The sedation procedure was explained in detail to the parents or legal guardians, along with instructions for hygiene and dental plaque control. A written ASA general health assessment by the Department of Pediatrics was requested for each child. Once patient eligibility was confirmed and parental written consent was received, the first treatment session was scheduled.

At that appointment, patients were received in a quiet operating room. After confirming the child's health condition at the time, a blinded experienced anesthesiologist, administered SC in the deltoid muscle region, each sedation regimen according to the randomization sequence, 15 min before the patient's sitting in the dental chair. The patient remained with the parent, while a nurse placed a pulse oxymeter and a baumanometer for monitoring and recording blood oxygen saturation, blood pressure, and heart rate every 10 min. A "papoose" board was adjusted for wrapping the patient, and a nasal oxygen cannula was carefully set in place.

Dental procedures were performed by the same operator, using lidocaine 2% with epinephrine as local anesthetic (4 mg/kg), with rubber dam isolation when necessary. Throughout the entire session, the child was carefully monitored (every 10 min), while assessing of sedation quality and patient behavior, always under continuous verbal communication. Once the procedure was finished, isolation, monitoring, and restriction devices were removed, and the parent or guardian was asked to come into the operating room. Then, parent and patient remained in the recovery room for one hour, under observation of levels of consciousness, ventilation, and body movement, or any complication. When all of the hospital discharge criteria were met, post-operative indications were prescribed in written form and the second sedation session was scheduled.

Dental treatment sessions were video-taped. Overall patient behavior, body movement, and crying were assessed according to the modified Houpt sedation rating scale[15] by

an independent observer who was blinded to the treatment assigned and who was considered an expert in the interpretation of this scale. The time elapsed between administration of the medication and the moment at which the patient sat in the dental chair and the time length for completing each treatment session were also recorded.

Initially, a descriptive analysis of patient sample characteristics was performed. Then, for quantitative variables such as latency period and operative time lengths (in minutes), the comparative non-parametric Wilcoxon rank sum test was applied, while for qualitative data (crying, body movement, and general behavior), the Fisher exact test was utilized. A significance level of 0.05 was selected.

RESULTS

A total of 13 children were enrolled in this pilot study. They were ages 17–46 months, with a mean weight of 12.80 ± 3.73 kg, with Frankl 1 anxiety and/or cooperation levels, indicating subsequent management under pharmacologic sedation. Both sedative drug schemes were administered to the same patient according to a random assignment in two consecutive treatment sessions. Along these two sessions, monitored physiological parameters remained satisfactorily stable in both study groups.

No statistically significant differences were found between the groups when comparing the time elapsed since administration of the medication until the moment that the patient was seated in the dental chair, or the latency period ($P = 0.5023$). However, during the second stage (dental procedure length), we obtained a value of $P = 0.0422$, this lasting significantly longer in the M group (Table 1). On the other hand, no statistically significant differences were found when comparing heart rate values between the two drug regimens at different times; likewise, when crying was evaluated, the percentage of crying children was less in the MK group in comparison with the M treatment group, although without statistically significant differences in the different evaluation times as follows: min 10, $P = 0.2487$; min 20; $P = 0.4331$; min 30, $P = 0.4472$, and min 40, $P = 0.6733$ (Table 2).

When comparing body movement between the groups (Table 3), there was a statistically significant difference only in minute-10 measurement ($P = 0.0271$), and for the remainder of the time points, no significant differences were found as follows: min 20, $P = 0.1093$; min 30, $P = 0.3485$, and min 40, $P = 0.5372$. In general, the percentage of children with no body movements was considered clinically higher during the first 30 min in the MK group.

Finally, and in accordance with the general behavior scale, when all of the variables were taken together in both sedative regimens, this yielded the result that 53.85% of children with score 4 (no crying or body movement) belonged to the MK group, and 69.23% with score 3 (some crying and/or body movement without interrupting treatment) belonged to the M group, but no significant difference was displayed ($P = 0.2275$) (Table 4).

TABLE 1. Comparison of elapsed time lengths between drug administration and the moment when the patient was seated on the dental chair (T1) and along dental procedures (T2) in each study group.

Treatment session time length*	Mean ± SD	Median (Range)
(M) T1	11.38 ± 2.84	10 (7–15)
(M) T2	30.92 ± 10.46	32 (15–47)
(MK) T1	10.46 ± 1.80	10 (8–15)
(MK) T2	39.00 ± 8.55	42 (21–48)

*Expressed in minutes. SD = Standard deviation.

TABLE 2. Comparison of crying.

Time (minutes)	Treatment	4*	3*	2*	1*
10	M	5 (38.46%)	6 (46.15%)	2 (15.38%)	0
	KM	8 (61.53%)	5 (38.46%)	0	0
20	M	6 (50.00%)	5 (41.67%)	1 (8.33%)	0
	KM	9 (69.23%)	4 (30.77%)	0	0
30	M	5 (62.23%)	2 (25.00%)	1 (12.50 %)	0
	KM	7 (63.64%)	4 (36.36%)	0	0
40	M	1 (50.00%)	1 (50.00%)	0	0
	KM	4 (66.67%)	2 (33.33%)	0	0

*Houpt scale: 4- No crying, 3- Intermittent crying, 2- Continuous crying, 1- Uncontrollable crying.

TABLE 3. Comparison of body movement evaluation.

Time (minutes)	Treatment	4*	3*	2*	1*
10	M	7 (53.85%)	6 (46.15%)	0	0
	KM	12 (92.31%)	1 (7.69%)	0	0
20	M	8 (66.67)	4 (33.33%)	0	0
	KM	12 (92.31%)	1 (7.67%)	0	0
30	M	7 (87.50%)	1 (12.50%)	0	0
	KM	10 (90.91%)	0	1 (9.09%)	0
40	M	2 (100.00%)	0	0	0
	KM	5 (83.33%)	1 (16.67%)	0	0

*4- No movement, 3- Movement that does not interfere with treatment, 2- Movement that makes treatment difficult, 1- Movement that interrupts treatment. M = Midazolam; K = Ketamine; KM = combination of Midazolam and Ketamine.

TABLE 4. General behavior scale

Treatment	4*	3*	2*	1*
M	30.77%	69.23%	0	0
KM	53.85%	38.46%	7.69%	0

*4-No crying or movement; 3-Some crying and/or movement without interrupting the treatment; 2-Difficulty in performing the treatment; 1-Non-stop crying and movement, treatment is extremely difficult. M = Midazolam; KM = Combination of Midazolam and Ketamine.

DISCUSSION

Fear, uncertainty, or poor behavior management by the dentist can hinder adequate treatment of dental caries and its consequences, mainly in young children. Although behavior management techniques play an important role in the control of anxiety, some children continue to experience have difficulty tolerating dental treatment. Historically, these cases have been approached with the use of deep sedation or general anesthesia, and although a percentage of children will always require such procedures, these measures must be avoided whenever possible due to the uncommon associated risk of death; additionally, some deep sedative drugs can also act as general anesthetics and the difference in the required doses to take a sedated patient to an anesthetized patient can be very small, or patient response to them is variable. Thus, premedication with moderate sedation is currently considered an adequate option for these children.[2,4]

The pharmacological agents most frequently used in pediatric sedation include narcotics, antihistamines, hypnotics, benzodiazepines, and others. They are administered by diverse routes (oral, rectal, nasal, and parenteral) either alone or in a wide variety of combinations and in different dosage regimens.[14-16] After an exhaustive literature search, we consider that, to our knowledge, this clinical study is among the first to evaluate the sedative properties of the midazolam/ketamine drug combination subcutaneously administered to pediatric patients in a dental setting. Our findings suggest that the combination of midazolam and ketamine administered SC in young, non-cooperative, and anxious children renders good sedation with better patient behavior during dental treatment sessions than midazolam alone. Ketamine used in minimal amounts (<3 mg/kg) possesses analgesic, sedative, and amnesic properties, but at higher (anesthetic) doses may cause vascular effects.[17,18] Therefore, in this study we decided to employ a drug combination with a micro dose of 0.1 mg/kg administered SC. In the majority of sedation studies conducted with similar pediatric patients, ketamine was orally or intranasally administered at higher doses ranging from 3–6 mg/kg, but such regimens increase the risk of causing hallucinations.[4,10,11] For invasive procedures in pediatric patients with cancer, a dose of ketamine 1 mg/kg IV was used with a high overall success rate.[19] Thus, the dosage used in this study had a high safety margin. Likewise, midazolam has been employed as premedication for dental procedures in non-cooperative children, either orally, rectally, or intravenously, in doses ranging from 0.3–1.0 mg/kg, resulting in good sedation outcomes with no significant side effects.[4,10,13,20]

Previous studies have shown the pharmacological efficacy and safety of the midazolam/ketamine combination in sedative premedication procedures in pediatric dental patients, but employing administration routes other than subcutaneous.[21-24]

In a review of the literature on the efficacy of conscious sedation drugs and dosages for behavior control in pediatric dentistry, Laurenço-Matharu *et al* [25] included 61 controlled, randomized, parallel or cross-over group clinical trials comparing two or more drugs/techniques/placebo, with a total of 3,246 patients aged up to 16 years old (1966–2004). The review reported that blinding in some of these studies was complicated, mainly due to two reasons: first, evaluators and operators frequently work separately, and second, the physical characteristics of the equipment involved and the drugs employed; in our study, only the outcome evaluator was blinded. Furthermore, the study design chosen was predominantly cross-over, as ours. It is important to note the possibility that, in cross-over designs, the anxiety and behavior exhibited during the second treatment session is influenced by the experience of the child in the first sedation. This literature review reported that of 61 studies, 3 evaluated ketamine alone, 22, midazolam alone, and only 3 assessed the midazolam-ketamine combination. Finally, the authors concluded that they "were not able to reach any definitive conclusion on which was the most effective drug or method of sedation used for anxious children", and also that there is some weak evidence that midazolam administered orally is effective for children undergoing dental treatment.

Bahetwar *et al* [4] evaluated and compared the efficacy and safety of intranasal administration of midazolam (0.3 mg/kg), ketamine (6 mg/kg), and their combination (0.2 mg/kg and 4 mg/kg, respectively) for obtaining moderate sedation. Onset of action was significantly faster with ketamine ($p < 0.01$) regarding midazolam alone. Global success rates were significantly different: 89% for ketamine alone; 84% for the MK combination, and 69% for midazolam alone ($p = 0.01$). Vital signs remained within physiological limits and no adverse effects were reported. The findings of this study are, in general, consistent with those obtained from ours.

There are other examples of studies combining midazolam/ketamine.[26-28] These studies compared the efficacy of oral sedation with this combination and with midazolam alone in non-cooperative children. The findings of such studies, such as ours, confirm that the combination of midazolam and ketamine, employing different administration routes and dose regimens, is a safe and effective sedative alternative to suitably control children's behavior, with a lack of serious side effects, aside from being clinically superior to midazolam alone. Finally, we suggest performing additional clinical controlled trials that enroll a larger sample size of pediatric patients with similar inclusion characteristics to those of the present and other reports, in order to confirm the adequateness of the SC route for administering the midazolam/ketamine combination, in terms of therapeutic efficacy and safety during dental treatment.

CONCLUSIONS

Our findings support the evidence that midazolam alone, and especially midazolam/ketamine in combination, administered SC delivered equivalent safe and efficient moderate sedation sessions in anxious and non-cooperative pediatric dental patients. Both the drug combination and the SC route together represent a potential alternative for providing safe and good moderate sedation to non-cooperative children undergoing dental treatment.

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