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Oral Sedation in Dentistry: Evaluation of Professional Practice of Oral Hydroxyzine in the University Hospital of Rennes, France.

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ABSTRACT

Purpose:

Management of a child's anxiety early in their treatment is essential in dentistry. Sedative medications are used to overcome increased anxiety from previous appointments and to promote the cooperation of children during treatment. Hydroxyzine is currently prescribed to young patients as part of the first level of conscious sedation. The main objective was to evaluate the professional practice of oral hydroxyzine, when prescribed for children presenting anxiety during dental treatment procedure performed by students and senior practitioners.

Methods:

A retrospective study of dental records and questionnaires was conducted at the Dental Care Centre of the University Hospital of Rennes, France. Parameters related to the prescription of hydroxyzine in children were evaluated as potential predictors of the dental session success, with adjustments on potential confounders.

Results:

The therapeutic outcome was very encouraging with 78.3% of success during dental sessions under sedation with oral hydroxyzine. Anxiety levels before the dental procedure and the medication compliance of the child were the main predictors of success. On the other hand, lower age (< 6 years-old) and longer treatments (such as pulpotomy) worsened the outcome.

Conclusions:

Careful analysis of the literature and results of this work showed the safety of hydroxyzine within the maximum dose authorized without adverse effects, compared to other molecules described and commonly used in dentistry. No adverse effects during dental procedure were noted. This allows for minimal sedation with efficiency for the great majority of pediatric treatment. This solution should be the first step in sedation to help practicing clinicians.

Keywords: Conscious sedation; Premedication; Treatment protocols; Hydroxyzine; Child behavior; Dental anxiety.

INTRODUCTION

Dental treatment creates stress and anxiety and the relationship of trust between the patient and the practitioner is essential. This clinical reality is heightened when it comes to treating a child. The prevalence of anxious children ranges from 9% to 29% and decreasing with age, according to the literature (for review: Klingberg and Broberg 2007, Cianetti et al. 2017). Spotting and tracking anxiety, fear and stress are daily concerns for dentists. In pediatric dentistry, the management of anxiety is essential before treatment. The practitioner has different tools to limit and contain this stress, including positive communication, hypnosis, conscious parenteral and/or inhalation or orally administered sedation and finally general anesthesia.

Among the conscious medications, midazolam is a recommended drug which have proven its effectiveness despite associated adverse effects, according to a literature review based on the Cochrane meta-analysis (Ashley et al. 2018). As an alternative, hydroxyzine can be used in pediatric dentistry. Only one study using hydroxyzine as monotherapy has been reported in the literature reaching 100% of success at a dosage of 3 mg.Kg⁻¹ (Torres-Pérez et al. 2007). However, this protocol was not recommended by the authors as the behavior of the child was considered unreliable. Due to the large dosage and the small number of participants ($n = 18$) this effectiveness of hydroxyzine was not conclusive.

Oral hydroxyzine is usually prescribed to young patients as part of conscious sedation in the University Hospital. The main objective of this study was to evaluate the professional practice of oral hydroxyzine, for children presenting anxiety, during dental treatment procedure performed by students alongside senior practitioners (professors).

MATERIALS AND METHODS

This work is an observational case series study that describes the use of oral hydroxyzine as a sedation protocol in children, prior to a single session of dental treatment. The method used was a retrospective survey of patients' dental records and questionnaires.

Patients were followed by students and senior dentists in the University Hospital. All selected patients were consecutive children and adolescents in need of oral conscious sedation without complementary O₂/N₂O, with ASA PS < 2 (The American Society of Anesthesiologists Physical Status). They had no disability or contraindication to oral hydroxyzine.

In accordance with the care protocol in the University Hospital, during their first consultation, the medical history was explored, the clinical and radiological examinations were carried out, and a motivation for oral hygiene was performed. No treatment was given during this initial contact, but the dental equipment and chair were shown, allowing the operator to assess the overall attitude of the child based on his/her compliance. The child's understanding and the objective modified Venham's Clinical Anxiety Rating Scale (VCARS) were reported (Venham et al. 1980). If a VCARS ≥ 3 was reached during the first consultation, the patient was given a prescription for hydroxyzine (1 to 2 mg.kg⁻¹, accordingly to the recommendations for use of oral hydroxyzine), to be orally taken and administered by the parents 90 minutes before the next appointment. The dental treatment was then performed during a second visit.

Dental treatments included restorations of permanent or deciduous teeth, endodontic treatment of deciduous teeth (mainly pulpotomy), and extraction of permanent or deciduous teeth. Local anesthesia was administered using the electronically assisted injection systems SleeperOne 5™ or QuickSleeper 5™ devices (Dental Hi Tec™). The dental procedures were conducted by multiple operators, including students about to graduate (5th and 6th grade) and seniors.

From September 2019 to February 2020, a questionnaire was completed at the end of the second visit by the operators, which collated the following data:

- characteristics of the patient: age, gender, weight;

- oral hydroxyzine prescription and compliance: dose, medication intake time, compliance to medication (did the child take all of his medication?), first exposure to oral hydroxyzine or not;
- patient's behavior: VCARS before, during and after the dental procedure;
- dental treatment: injection technique (infiltration or intra-osseous) and its completion, type of treatment planned for the visit (restorative, endodontic or extraction) and its achievement.

The main evaluation criteria and outcomes were the VCARS score during the dental procedure and the complete achievement of the treatment (therapeutic success). In the statistical analyses, factors considered as potential predictors were the pharmacological parameters: oral hydroxyzine dosage ($\text{mg}\cdot\text{kg}^{-1}$), the interval between drug intake and the dental treatment (min) and the compliance to medication. The factors considered as potential confounders were "age" and "gender" of the patient, "first exposure to oral hydroxyzine", "type of treatment planned", "injection technique used", "VCARS score before the dental procedure", "appointment time slot" and "highest grade operator that intervened during the procedure".

In some cases, the treatment was changed into atraumatic restorative treatment or in sealants. To avoid bias in the therapeutic success rate, they were classified as a therapeutic failure, since these treatments were alternative solutions when facing a non-cooperative patient.

The number of patients who received oral hydroxyzine prescription during the study period determined the sample size. During the study period, 2 757 children were admitted in the University hospital, including 2 280 (82.2%) for treatment. Of these, 210 (9.2%) benefited from conscious hydroxyzine sedation prescription. For the statistical analysis 184 questionnaires were selected; the remaining 26 were excluded due to completion errors (Figure 1).

The statistical analysis was carried out with the R kernel (v 3.5.0) in the RStudio environment (v 1.2.5033) (R Core Team 2018). Tables were generated with the 'qwraps2' and 'stargazer' packages, the figures with 'ggplot2' (DeWitt 2019; Marek 2018; Wickham 2016). Data are presented as percentages for qualitative variables, and as mean \pm standard deviation for quantitative variables. The results of the statistical tests were considered significant at $p < 0.05$. The distribution of continuous

variables was evaluated with the Shapiro-Wilk test which rejected the hypothesis of a normal distribution. The analysis of continuous variables was therefore carried out with the Mann-Whitney test. The analysis of the qualitative variables was carried out with the χ^2 test, or with the Fisher test when the conditions for the validity of χ^2 were not met. Odds-ratio (OR) are presented with 95% confidence intervals (95% CI). The association between the success of the dental procedure and the characteristics related to the prescription and intake of oral hydroxyzine was evaluated using a multiple linear regression model (with the VCARS score during procedure as the dependent variable), and a logistic regression model (with the therapeutic success as the dependent variable). The explanatory variables were the factors considered as potential predictors or confounders previously described. Forty-eight patients had missing data (type of treatment planned and/or injection technique), and were not included in the regression models. The results presented indicate the coefficients (standard error) for each explanatory variable.

RESULTS

The overall characteristics of the patient and pharmacological parameters for the second visit with treatment are presented in Table 1. Patients were mainly in early childhood (6.8 ± 2.2 years), with a male/female ratio of 56.5%. The average hydroxyzine dosage was 1.63 ± 0.39 mg.kg⁻¹. According to the self-reported medication intake time, hydroxyzine was orally administered 90 ± 26 min before dental procedure, which corresponded well to the prescription. The compliance to medication reached 85.9% (158/184).

In most cases, the dental procedure was successful at 78.3% (144/184 of therapeutic success) and no adverse effect during the procedure was observed. No significant difference was found in the characteristics of the patient according to the therapeutic outcome. Among the pharmacological parameters, the compliance to the medication was significantly associated with a therapeutic success ($p = 0.01$); logistic regression gave an OR = 3.26, 95% CI 1.36 - 7.83 ($p = 0.008$).

The data related to the second consultation are presented in Table 2. In general, we observed low VCARS scores in the population studied, with similar values before and after the procedure, and a peak during the procedure. Treatments were mainly restorative (54.5%), on an anaesthetized tooth (73.9%), and performed by 5th grade students (67.9%).

In case of therapeutic failure, patients were significantly more anxious, with VCARS scores almost three times higher than patients with successful treatment ($p < 0.001$). The type of treatment planned and the success of anesthesia differed according to the therapeutic outcome, with an increased proportion of endodontic treatment and failed anesthesia in the therapeutic failure group ($p = 0.028$ and $p < 0.001$, respectively).

Linear and logistic regression models were computed to assess the pharmacological parameters of oral hydroxyzine intake as predictors for the patient's anxiety and therapeutic success (Table 3).

In the multiple linear regression, the VCARS score during procedure was reduced by an average of 0.86 when the patient was compliant to medication ($p < 0.05$). One level of VCARS score before procedure increased on average by 0.66 the VCARS score during procedure ($p < 0.0001$). Patients requiring supplementary intervention

by senior dentists presented a higher VCARS score, when compared to patients treated by 5th grade students (+1.40, $p < 0.01$) or by 6th grade students (+1.19, $p < 0.05$).

In the logistic regression, the association between the compliance to medication and a successful treatment was confirmed with the calculation of an adjusted OR = 6.28, 95% CI 1.39 - 28.41 ($p < 0.05$). The successful achievement in endodontic treatment was lower than restorative procedures (OR = 0.07, 95% CI 0.01 - 0.40, $p < 0.01$) or extraction (OR = 0.17, 95% CI 0.03 - 0.98, $p < 0.05$). The VCARS score before the procedure was associated with the therapeutic outcome (OR = 0.48, 95% CI 0.29 - 0.79, $p < 0.01$).

Finally, an analysis by age group was carried out to compare 3-5 to 6+ years-old children. A successful treatment was more frequently found in the oldest (81% of treatment achieved versus 65%, $p = 0.04$) with lower VCARS score during dental procedure ($p = 0.02$) (Supplementary Table 1).

DISCUSSION

Sedation protocols and adverse effects in the literature.

Different protocols such as monotherapy or combination of drugs are used in dentistry to prevent anxiety. A summary of these protocols with doses, success and adverse effect is available in Table 4. In our study, the dental treatment was successful in 78.3% of the dental sessions with the use of hydroxyzine as monotherapy.

The literature about midazolam used as monotherapy is heterogenous, in terms of therapeutic success (44–100%), number of participants (12–57), and dosage form (enteral: 0.2–1 mg.kg⁻¹, intranasal: 0.2–0.5 mg.kg⁻¹, intramuscular: 0.2 mg.kg⁻¹). Adverse effects such as nausea, vomiting and oxygen desaturation were reported and the higher the dosage increased the more frequent they were noticed (Day et al. 2006; al-Rakaf et al. 2001; Sado-Filho et al. 2019; Somri et al. 2012). Studies reporting N₂O as monotherapy revealed that dental treatment was completed in 52% of cases at a concentration of 40% (Lahoud and Averley 2002) and up to 85% with an equimolar mixture (Nelson et al. 2017) with no adverse effect reported. In two studies reporting the use of hydroxyzine in combination with midazolam, 69% and 100% of dental treatments completed were found with a greater success with the highest dosage but the number of participants were low ($n = 10$ and 18 respectively) (Ghajari et al. 2016; Torres-Pérez et al. 2007). When combined with an opioid (Meperidine), success increased up to 95% but adverse effects such as nausea, vomiting and severe desaturation (90%) were described (Lenahan et al. 2015). Hydroxyzine combined with N₂O allowed the treatment in 66% of cases ($n = 15$) according to Baygin (Baygin et al. 2010). This study also showed the same success rate with a combination of ketamine / midazolam / N₂O or N₂O used alone but with adverse effects such as enuresis, bronchospasm, hypersalivation, hallucination, epistaxis and earache. Finally, other associations with or without the integration of hydroxyzine in the protocol showed success rates ranging from 66 to 100% with midazolam and ketamine (Baygin et al. 2010; Sado-Filho et al. 2019), 87% with midazolam / hydroxyzine / meperidine / N₂O (Lane et al. 2015), 91 to 100% with midazolam / N₂O (Lam et al. 2005).

These comparisons highlight greater success in treatments compared with our sedation protocol, but they are associated with multiple adverse effects. Nausea,

vomiting, drowsiness and oxygen desaturation are also reported in studies that have the pharmacological objective of looking for adverse effects (Huang and Tanbonliong 2015; Ritwik et al. 2013). An American case report analysis looking at severe neurological damage and death showed that combinations of more than 3 drugs, overdose, and lack of training are the causes of these accidents. In addition, dentists are the most represented practitioners because they have been known to use combinations of 3 or more drugs (Coté et al. 2000). For example, Shapira *et al.* used sedation combining 3.7 mg.Kg⁻¹ of hydroxyzine, 0.6mg.Kg⁻¹ of midazolam and N₂O (Shapira et al. 2004). To secure sedation, in 2006, the AAP (American Academy of Pediatrics) and the AAPD (American Academy of Pediatric Dentistry) published guidelines that define 3 levels: minimal, moderate or deep. They also underline the training required and the necessary equipment (Pediatrics et al. 2006). Then, in 2016, the ADA (American Dental Association) published a similar procedure for performing sedation or general anesthesia by dentists (Clough et al. 2016). Finally, Clough *et al.* showed that dentists do not use the ASA PS score enough for sedation.

Safety of hydroxyzine

During this practice evaluation, no adverse effects were reported by the children undergoing treatment, parents or practitioners during the dental procedure. Hydroxyzine prescriptions comply with the maximum dosage indicated in the monograph (Prescribers' digital reference 2020). There was no overdose or inappropriate use of this medication. The use of an antihistamine in a pediatric dentistry is justified by its pharmacological safety profile (Motola et al. 2017). However, a 1994 study showed that second generation antihistamines, and to a lesser extent hydroxyzine, which is first generation, could induce QT interval prolongation (Smith 1994). In 2014, a study showed that this lengthening is mainly the consequence of action on the cardiac potassium channels without implicating hydroxyzine (Olasińska-Wiśniewska et al. 2014). In 2017, a pharmacovigilance review on hydroxyzine gave an account of 59 cases of long QT between 1955 and 2016 and demonstrated that it only appeared if there was a pre-existing heart disorder, an overdose or a genetic anomaly of the modulation of the cardiac ion channels (Schlit et al. 2017). Finally, a case report described the appearance of ventricular tachycardia in a 9-year-old girl following anti-pruritus treatment without a blood test link being able to confirm it (Wong and Rasool 2004).

Compliance of the patient

The pre-operative behavior of the child is decisive because the compliance to medication (hydroxyzine fully taken) indicates a drop in the VCARS score during the treatment and is correlated with the success of the treatment (OR = 3.26 and adjusted OR = 6.28). A similar result was found by Lenahan *et al.* with 85% success when drugs were taken on a voluntary basis. However, this result dropped to 59% when taken involuntarily (Lenahan *et al.* 2015), as in our study which stands at 57%. The lower the VCARS score before the treatment, the easier the treatment to be performed. Therefore, the evaluation of the child's behavior during the first consultation is essential because the practitioner can detect an impulsive character which is predictive of difficult treatment (Lane *et al.* 2015) or the child's ability to control himself (Nelson *et al.* 2017). The use of *tell play do* during this consultation reduces anxiety and therefore the child's VCARS score (Vishwakarma *et al.* 2017), and this technique is used within the University hospital. The use of this behavioral approach by students during the first consultation may be worth evaluating in order to optimize stress management in young patients.

Age of patients and operators

This study showed that younger children are more difficult to treat, with a higher VCARS score and a less successful treatment as described by Lenahan *et al.* (sedation efficiency score of 73% for 3-4 year olds and 92% for 7 year olds and over (Lenahan *et al.* 2015)). In a contradictory study, Day *et al.* showed a reverse success rate, with 91% among the youngest compared with 65% of the oldest. This latter result is probably linked to a doubling of the dosage between the two groups (Day *et al.* 2006).

The increasing VCARS score according to the operator's experience can be easily explained by the learning context of a University Hospital. The senior practitioners (professors) become involved during the treatment when the VCARS score of the child dramatically increases.

Alternative or complementary solutions

To improve and optimize the treatment of our young patients, it is necessary to consider a complementary, non-pharmacological approach before the use of another drug, nitrous oxide or even general anesthesia. Indeed, a comparison between the use of hypnosis and midazolam in children undergoing outpatient surgery under

general anesthesia showed a lower level of anxiety, better acceptance of the inhalation induction, fewer post-operative behavior disorders and a better experience in the hypnosis group (Calipel et al. 2005). The *tell show do* is already implemented during the first consultation, but there are other lines of thought to promote a soothing and reassuring atmosphere. It is also possible to act as soon as the child arrives because the waiting room environment decreases pre-operative anxiety (Fux-Noy et al. 2019). The presence of parents also reduces anxiety for the first visit, although in some cases they may be a source of stress (McNeil et al. 2019). Two literature reviews concluded that distraction techniques are effective with a low level of evidence (Goettems et al. 2017; Robertson et al. 2019). Listening to music during treatment had contradictory results in reducing anxiety and pain (Gupta et al. 2017; Navit et al. 2015; Singh et al. 2014). The use of a virtual reality headset that inhibits anxiety-provoking visual stimuli in the dental office also showed its effectiveness (Koticha et al. 2019).

Finally, Mejàre *et al.* encourages the conduct of primary clinical studies in order to obtain new recommendations and the generation of high quality evidence, as it has been done for the role of fluoride in the prevention of carious disease (Mejàre et al. 2015).

This professional practice evaluation has several biases in its performance. First, the hospital selection of patients is often referred by private practitioners for reasons of excessive stress, traumatic experience or failure to treatment. In addition, there is an inter-operator bias due to the multiplication of participants (5th or 6th grade students and senior) with different levels of expertise and experience. Indeed, verbal, non-verbal and body communications are not calibrated, and these would be avenues to consider in future evaluations. Finally, the adverse effects were only reported during the dental procedure and thus, future studies should include a follow up through the next 24 hours.

CONCLUSIONS

- Conscious sedation with hydroxyzine following the maximum dosage recommendation for monotherapy is a good alternative for anxiety management during dental treatment.
- Almost 8 out of 10 paediatric patients at the Dental Care Centre of the University Hospital in Rennes benefited from a successful planned treatment.
- The results based on 184 paediatric patients were comparable to those found in the literature but without any noticeable adverse effects during the sessions. Extractions and restorative treatments in the oldest children (6 years and over) were also easier to perform.
- Behavior was predictive of the therapeutic outcome, since compliance to the prescription and low VCARS score before the procedure advance the treatment success.

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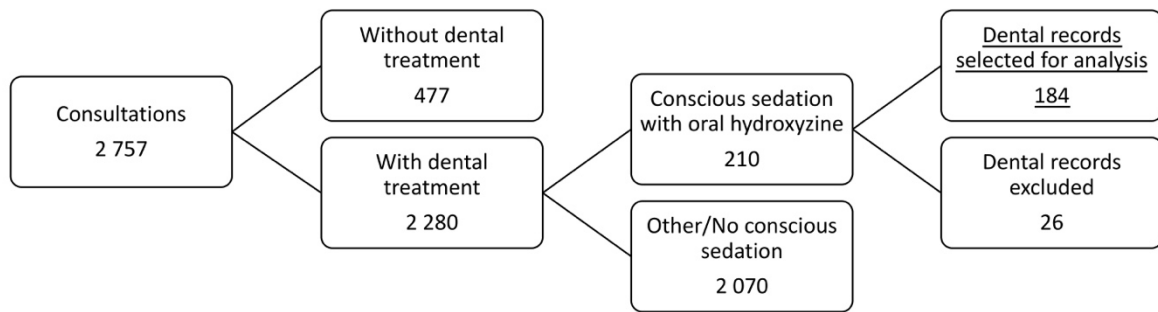


Figure 1: Flow chart for the selection of dental records analysed in the study.

Table 1: Characteristics of patients, oral hydroxyzine prescription and compliance in the general population and according to the therapeutic outcome during the second visit with treatment.

	(n = 184)	Success (n = 144)	Failure (n = 40)	p- value
Age (years)	6.80 ± 2.23	6.94 ± 2.33	6.32 ± 1.76	0.118 ^a
Gender				
Male	104 (56.5%)	82 (56.9%)	22 (55.0%)	0.826 ^b
Female	80 (43.5%)	62 (43.1%)	18 (45.0%)	
Weight (kg)	22.92 ± 7.64	23.24 ± 8.03	21.75 ± 5.94	0.395 ^a
Prescription (mg hydroxyzine/kg)	1.63 ± 0.39	1.61 ± 0.39	1.67 ± 0.38	0.302 ^a
Compliance to medication				
Yes	158 (85.9%)	129 (89.6%)	29 (72.5%)	0.010^c
No	26 (14.1%)	15 (10.4%)	11 (27.5%)	
Interval between drug intake and dental treatment (min)	89.96 ± 26.01	90.29 ± 27.23	88.75 ± 21.27	0.966 ^a
First use of hydroxyzine				
Yes	86 (46.7%)	67 (46.5%)	19 (47.5%)	0.913 ^b
No	98 (53.3%)	77 (53.5%)	21 (52.5%)	

Bold *p*-values are statistically significant at: *p*<0.05.

^aMann-Whitney, ^bχ², ^cFisher tests; statistically significant at: *p* < 0.05.

Table 2: Description of patient's behavior and dental treatment parameters, in the general population and according to the therapeutic outcome during the second visit with treatment.

	(n = 184)	Success (n = 144)	Failure (n = 40)	p-value
VCARS score before procedure	0.85 ± 1.14	0.67 ± 0.94	1.52 ± 1.50	< 0.001^a
VCARS score during procedure	1.88 ± 1.75	1.36 ± 1.42	3.75 ± 1.51	< 0.001^a
VCARS score after procedure	0.89 ± 1.24	0.63 ± 0.95	1.82 ± 1.65	< 0.001^a
Dental treatment				
Restorative	96 (54.5%)	80 (55.6%)	16 (40.0%)	0.028^c
Endodontic	16 (9.1%)	9 (6.2%)	7 (17.5%)	
Extraction	64 (36.4%)	55 (38.2%)	9 (22.5%)	
Successful anesthesia				
Yes	136 (73.9%)	116 (80.6%)	20 (50.0%)	< 0.001^b
No	48 (26.1%)	28 (19.4%)	20 (50.0%)	
Injection technique				
Infiltration	60 (44.1%)	55 (47.4%)	5 (12.5%)	0.062 ^b
Intraosseous	76 (55.9%)	61 (52.6%)	15 (37.5%)	
Operator				
5th grade student	125 (67.9%)	100 (69.4%)	25 (62.5%)	0.654 ^b
6th grade student	30 (16.3%)	23 (16.0%)	7 (17.5%)	
Senior	29 (15.8%)	21 (14.6%)	8 (20.0%)	
Time slot				
Early morning	43 (23.4%)	33 (22.9%)	10 (25.0%)	0.895 ^b
Late morning	47 (25.5%)	38 (26.4%)	9 (22.5%)	
Early afternoon	53 (28.8%)	40 (27.8%)	13 (32.5%)	
Late afternoon	41 (22.3%)	33 (22.9%)	8 (20.0%)	

Bold p-values are statistically significant at: $p < 0.05$.

^aMann-Whitney, ^bX², ^cFisher tests.

VCARS: Vehnam's Clinical Anxiety Rating Scale.

Table 3: Regression models with parameters related to patient, oral hydroxyzine prescription and dental treatment as explanatory variables for the patient's anxiety during the dental procedure, and for the therapeutic success.

	<i>Dependent variables:</i>	
	VCARS score during procedure	Therapeutic success
	<i>Multiple linear regression</i>	<i>Logistic regression</i>
Prescription of hydroxyzine	-0.033 (0.355)	-1.175 (0.938)
Interval between drug intake and dental treatment	0.003 (0.005)	0.013 (0.017)
Compliance to medication: No	0.858* (0.389)	-1.837* (0.770)
Gender: Female	-0.012 (0.260)	-0.224 (0.633)
Age	-0.075 (0.060)	0.078 (0.184)
First use of hydroxyzine: No	-0.063 (0.265)	-0.691 (0.687)
Dental treatment: Endodontic	0.429 (0.443)	-2.638** (0.874)
Dental treatment: Extraction	0.217 (0.296)	-0.841 (0.761)
VCARS score before procedure	0.664**** (0.131)	-0.735** (0.255)
Time slot: late morning	0.347 (0.388)	-1.519 (0.963)
Time slot: early afternoon	0.620 (0.374)	-0.642 (0.905)
Time slot: late afternoon	0.163 (0.409)	-0.282 (0.995)
Injection technique: Intraosseous	0.153 (0.287)	-1.375 (0.709)
Operator: 6 th grade student	0.206 (0.355)	-0.194 (0.850)
Operator: Senior	1.395** (0.423)	1.585 (0.998)
Observations	136	136
R2	0.387	
Adjusted R2	0.310	
Log Likelihood		-40.891
Akaike Inf. Crit.		113.782
Residual Std. Error	1.450 (df = 120)	
F Statistic	5.048**** (df = 15; 120)	

Bold values indicate statistically significant results at: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

VCARS: Vehnam's Clinical Anxiety Rating Scale.

Table 4: Summary of the previously published sedation protocols used in pediatric dentistry.

Journal	Years	n	Age (year)	Evaluation	Methods and sedation type	Success rate ^a	Side effects	Reference
Hydroxyzine as monotherapy								
Journal of pediatric dentistry	2007	18	1 - 10	- Ohio state behavior rating scale - Heart rate - O ₂ saturation	Hydroxyzine 2 mg.Kg ⁻¹ 2h before + 1 mg.Kg ⁻¹ 20min before	100%	- ^b	(Torres-Pérez et al. 2007)
Midazolam as monotherapy								
International journal of pediatric dentistry	2012	90	3 - 10	- Wisconsin sedation scale - Houpt behavior score - Parent satisfaction - Success of dental treatment	O ₂ 2 L.min ⁻¹ Possible manual restraining used 3 groups with Midazolam		O ₂ saturation < 94%	Nausea Drowsiness (Somri et al. 2012)
		- 30			- 0.5 mg.Kg ⁻¹	80%	- ^b	10%
		- 30			- 0.75 mg.Kg ⁻¹	93%	13%	23%
		- 30			- 1 mg.Kg ⁻¹	100%	33%	43%
Journal of pediatric dentistry	2013	28	2.5 - 7	- Ohio state behavior rating scale -success treatment = 60% time quiet	Midazolam 0.5 mg.Kg ⁻¹	85.7%	Vomit Prolonged recovery 24 hours later : Nausea/vomiting, irritability, agitation, drowsiness, hallucination	(Sado-Filho et al. 2019)
International journal of pediatric dentistry	2001	38	2 - 5	- Houpt Behavior Rating Scale	Possible Papoose board 3 groups with Midazolam intra-nasal			(al-Rakaf et al. 2001)
		- 12			0.3 mg.Kg ⁻¹	79%	- ^b	
		- 13			0.4 mg.Kg ⁻¹	96%	- ^b	

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			- 13		0.5 mg.Kg ⁻¹	100%	Diplopia	
European Archives of Paediatric Dentistry	2006	101	1 - 11	- Success of dental treatment	Two dental clinics Midazolam			(Day et al. 2006)
		- 44	2.9 ±1.6		0.5-0.7 mg.Kg ⁻¹	91%	NC	
		- 57	5.0 ±1.9		0.2-0.3 mg.Kg ⁻¹	65%	NC	
N₂O as monotherapy								
Anesthesia progress	2017	48	3 - 8	- Behavior score - Frankl score	Internet streaming video N ₂ O 50%	85%	NC	(Nelson et al. 2017)
Anaesthesia	2002	170	3 - 10	- VCARS - Level of consciousness	N ₂ O 40%	52%	- ^b	(Lahoud and Averley 2002)
European journal of anaesthesiology	2010	15	5 - 8	- Ramsay Sedation Score - Bis - Frankl behavior rating score	N ₂ O 40%	66%	Hiccough, nausea, otalgia, epistaxis	(Baygin et al. 2010)
Association of medications								
The journal of pediatric dentistry	2007	36	1 to10	- Ohio state behavior rating scale - Cardiac Frequency - O ₂ saturation				(Torres-Pérez et al. 2007)
		- 18			Midazolam 0.5 mg.Kg ⁻¹ + Hydroxyzine 1.5 mg.Kg ⁻¹	100%	- ^b	
		- 18			Chloral 50 mg.Kg ⁻¹ + Hydroxyzine 1.5mg.Kg	100%	1 child with saturation <90%	

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Journal of pediatric dentistry	2013	56	2.5 - 7	- Behavior score					(Sado-Filho et al. 2019)
		- 28			Midazolam 0.5 mg.Kg ⁻¹ intra nasal + Kétamine 3 mg.Kg ⁻¹	92.9%		Nausea/vomiting, irritability, agitation, hallucination	
		- 28			Midazolam 0.5 mg.Kg ⁻¹ per os + Kétamine 3 mg.Kg ⁻¹	89.3%		Nausea/vomiting, irritability, drowsiness, agitation, hallucination	
Anaesthesia	2002	241	3 - 10	- VCARS - Level of consciousness	N ₂ O 40% + Sevoflurane 0.1 to 0.3%	89%	- ^b		(Lahoud and Averley 2002)
Journal of Dentistry of Tehran	2015	20	3 - 6	Houpt Behavior Rating Scale					(Ghajari et al. 2016)
		- 10			Midazolam 0.3 mg.Kg ⁻¹ + Hydroxyzine 1 mg.Kg ⁻¹	56%	NC		
		- 10			Midazolam 0.5 mg.Kg ⁻¹ + Hydroxyzine 1mg.Kg ⁻¹	69%	NC		
Pediatric dentistry	2015	61	3 - 8	- temperament scale - Houpt Behavior Rating Scale - Success of dental treatment	Midazolam 0.3 mg.Kg ⁻¹ + Hydroxyzine 1 mg.Kg ⁻¹ + Mépéridine 1.5 mg.Kg ⁻¹ + N ₂ O 50% + Internet streaming video	87%	NC		(Lane et al. 2015)
The Journal of Clinical Pediatric Dentistry	2015	248	3 - 7	- Behavior during the dental treatment - Frankl score - Sedation score	Mépéridine 2.2 mg.Kg ⁻¹ + Hydroxyzine 1 to 2 mg.Kg ⁻¹	81.5%		Nausea/vomiting O ₂ saturation <90%	(Lenahan et al. 2015)

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European journal of anaesthesiology	2010	45	5 - 8	- Ramsay Sedation Score - Bis - Frankl behavior rating score				(Baygin et al. 2010)
		- 15			Hydroxyzine 1 mg.Kg ⁻¹ + N ₂ O 40%	66%	Nausea, cough	
		- 15			Midazolam 0.7 mg.Kg ⁻¹ + N ₂ O 40%	74%	Nausea, cough, hiccough, enuresia, bronchospasm	
		- 15			Kétamine 3 mg.Kg ⁻¹ + midazolam 0.25 mg.Kg ⁻¹ + N ₂ O 40%	66%	Nausea, hypersalivation, hallucination	
Anesthesia progress	2005	23	2 - 9	- Houpt Behavior Rating Scale				(Lam et al. 2005)
		- 12			Midazolam 0.2 mg.Kg ⁻¹ intramuscular + N ₂ O 50%	100%	NC	
		- 11			Midazolam 0.2 mg.Kg ⁻¹ intranasal +N ₂ O 50%	91%	Drowsiness	
Midazolam versus hypnosis								
Pediatric anesthesia	2005	50	2 - 11	- MYPAS - PHBQ	Before full anesthesia, comparison of 2 groups :			
					- Hypnosis - Midazolam 0.2 mg.Kg ⁻¹	100%	When hypnosis is used - less Anxiety during induction - less behavior trouble 48h post-operative	(Calipel et al. 2005)

NC: non communicated; ^a: sedation or therapeutic success rate, as reported by the authors; ^b: no adverse effects reported. VCARS: Venham's clinical anxiety rating scale; Bis: bispectral index score; MYPAS: Modified Yale Preoperative Anxiety Scale; PHBQ: Post-hospitalization Behavioral Questionnaire

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Supplementary Table 1: Description of patient's characteristics, compliance and behavior, oral hydroxyzine prescription, and dental treatment according to the age.

	Age: 3 to 5 (<i>n</i> = 43)	Age: 6 and older (<i>n</i> = 105)	<i>p</i> -value
Gender			
Male	23 (53.5%)	67 (63.8%)	0.243 ^b
Female	20 (46.5%)	38 (36.2%)	
Dosage (mg hydroxyzine/kg)	1.67 ± 0.39	1.59 ± 0.40	0.081 ^a
Compliance to medication			
Yes	35 (81.4%)	92 (87.6%)	0.325 ^b
No	8 (18.6%)	13 (12.4%)	
Delay drug intake – dental treatment (min)	88.14 ± 23.12	92.02 ± 28.45	0.997 ^a
First use of hydroxyzine			
Yes	24 (55.8%)	50 (47.6%)	0.365 ^b
No	19 (44.2%)	55 (52.4%)	
VCARS score before procedure	1.14 ± 1.49	0.74 ± 0.91	0.282 ^a
VCARS score during procedure	2.51 ± 1.98	1.68 ± 1.60	0.020^a
VCARS score after procedure	1.14 ± 1.49	0.77 ± 1.04	0.256 ^a
Dental treatment			
Restorative	24 (55.8%)	52 (49.5%)	0.236 ^b
Endodontic	5 (11.6%)	6 (5.7%)	
Extraction	12 (27.9%)	42 (40.0%)	
Successful anaesthesia			
Yes	30 (69.8%)	79 (75.2%)	0.493 ^b
No	13 (30.2%)	26 (24.8%)	
Injection technique			
Infiltration	11 (25.6%)	39 (37.1%)	0.235 ^b
Intra-osseous	19 (44.2%)	40 (38.1%)	
Operator			
5 th grade student	22 (51.2%)	81 (77.1%)	0.007^b
6 th grade student	11 (25.6%)	11 (10.5%)	
Senior	10 (23.3%)	13 (12.4%)	
Time slot			
Early morning	15 (34.9%)	20 (19%)	0.020^b
Late morning	13 (30.2%)	22 (21.0%)	
Early afternoon	11 (25.6%)	32 (30.5%)	
Late afternoon	4 (9.3%)	31 (29.5%)	
Therapeutic success			
Yes	28 (65.1%)	85 (81.0%)	0.040^b
No	15 (34.9%)	20 (19.0%)	

^aMann-Whitney, ^bX² tests; statistically significant at: *p* < 0.05.