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Crossover Studies of Pediatric Dental Sedation are Inappropriate

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Crossover studies continue to be published in spite of warnings about their inherent risks in relation to behavioral outcomes. This study took the opportunity of access to secondary data analysis in order to demonstrate the impact of a crossover design on the outcomes of randomized clinical trials aimed at the behavior of children during dental treatment. We evaluated the effect of the sequence of sedative administration, the sedative and the participant's age on the behavior of children undergoing two sequential dental visits. Eighteen uncooperative healthy young children were equally randomly assigned to: (G1) 1.0 mg/kg oral midazolam (first session) and oral placebo (second session); (G2) oral placebo (first) and 1.0 mg/kg oral midazolam (second). One trained observer assessed children's behavior. Data were analyzed by three-way mixed ANOVA. Both midazolam [mean(SD); 71.7%(16.5)] and placebo [48.6%(33.1)] produced more struggling behavior when they were administered in the first session compared to the second one (p=0.001). For the placebo, children aged 2–3 years exhibited more struggling behavior [G1 54.9%(36.2); G2 80.5%(8.3)] than those aged 4–5 years (p=0.04). Also, the reduction of percentage of struggling behavior was higher in G1 for older children (76.2%) and in G2 for younger children (32.9%). There were significant interactions between drug and sequence of administration, and between drug and age. The results of our study confirm the conventional wisdom that crossover study design is inappropriate to evaluate children's behavior/anxiety related-dental treatment under sedation and the results of crossover studies of dental sedation should be treated with extreme caution.

Key Words: dental anxiety, dental care for children, moderate sedation, midazolam, behavior control, randomized clinical trial.

Introduction

Children's behavior may change over sequential dental visits (1). When a child is minimally or moderately sedated for dental treatment, the effect of one visit over another is obscure. An observational study with preschoolers reported that consecutive sedations in 7- to 10-day intervals worsened the child's cooperation during treatment (2). Although sedated children may show more controllable behavior compared to placebo (3), it is known that sedation can fail in guiding children's behavior in some cases (4). On the other side, drugs such as midazolam promote anterograde amnesia, a desirable sedative effect when dealing with pediatric patients (5).

The Cochrane Handbook's warns about the risk of performing crossover studies with interventions that may have lasting effect in subsequent trial periods (6). However, crossover clinical trials in pediatric dental anesthesia and sedation continue to be published (7,8). In a systematic review on pediatric dental sedation, 45 randomized controlled trials (RCT) were excluded from the analysis because they had a crossover design (9). In fact, it is assumed that the level of anxiety/behavior in the first session influences the anxiety/behavior in the second session (9), but that has not been proven in the pediatric dental sedation context.

To the best of our knowledge, only one crossover trial on pediatric dental sedation investigated the influence of the sequence of sedation appointments on children's overall behavior; accordingly, there was no carryover effect as assessed by generalized estimating equation (GEE) logistic regression (10). They compared three sedative regimens: oral meperidine, submucosal meperidine and oral midazolam in healthy preschoolers undergoing pulp therapy; thus, they did not have a control group and did not analyze the interaction between the drug and respective sequence of administration (10).

Therefore, it is important to elucidate whether crossover designs using amnestic drugs, compared to placebo, can impact the trial outcome with regard to sedation success or failure. This study investigated the effect of the allocation sequence of the drug (oral midazolam versus placebo), in addition to the drug itself and the child's age, on the behavior of uncooperative preschool children undergoing two sequential dental visits.

Material and Methods

Ethical Approval and Participants

This is a secondary analysis of data obtained in a randomized crossover triple-blind trial concerning dental sedation in preschool children who were referred to the

dental sedation center of the Federal University of Goias (NESO, 'Núcleo de Estudos em Sedação Odontológica'). This study was approved by the Research Ethics Board of the Federal University of Goias, Brazil (protocol #307/2011) and registered in the Clinical Trials database (NCT01795222). The main findings of this study have already been published (11).

A total of 31 children with a definitely negative or negative behavior (12) in a previous dental appointment were recruited from April 2012 to December 2012. Inclusion criteria were: healthy children aged 2–5 years; physical status I or II according to the American Society of Anesthesiologists (ASA); and requirement of at least two teeth restorations. Exclusion criteria were previous dental appointment under sedation; and use of systemic corticosteroids during the last month (13). Once the patients were identified as eligible, their parents received detailed written and verbal information about the study from a researcher. They were then invited to participate in this study and signed a consent form.

Sample size was estimated on the basis of the analyses required for the primary study (11). On the basis of these data, 14 children would be necessary to detect a difference between the two groups (81%) of this crossover study.

Study Design

The anatomy of this crossover trial for comparison of midazolam and placebo comprises two periods that each child has to complete in the course of the study, allowing 7 days for the washout phase (Fig. 1). In this case, each patient serves as his or her own control and the comparison of both treatments should be done considering groups, as follows: G1 and G2.

Children randomized to Group 1 (G1) received moderate sedation with oral midazolam (Dormire® 2 mg/mL, Cristalia, São Paulo, Brazil; 1.0 mg/kg, maximum 20 mg) in the first session and oral placebo in the second session. Participants randomised to Group 2 (G2) received oral placebo in the first session and crossover to oral midazolam in the second session (Fig. 1).

Randomization and Blinding

One researcher carried out a permuted-block randomization through the website www.stattools.net/index.php. Only the pediatrician and anesthesiologist were unblinded in case of any possible sedation emergency. The rest of the research team, including parents and children, were masked, and the oral placebo was a magistral solution with the same characteristics as the active drug solution. Further details of this trial were in the primary analysis study (11).

Dental Treatment

Firstly, the pediatrician confirmed the child's overall health and the proper fasting status. Next, the child took the medication (oral midazolam or placebo) according to the group allocation. The child's dental treatment commenced 20 min after medication administration and was performed by the same pediatric dentist in both sessions. The child was accompanied by one of the parents during the dental sedation treatment.

The procedure consisted of one tooth restoration at each appointment using rubber dam isolation and local anesthesia (2% lidocaine with epinephrine 1:100,000, Nova DFL, Rio de Janeiro, Brazil). Passive protective stabilization was also used in both sessions for all children. Dental treatment with protective stabilization and no sedative (placebo) is considered ethical in Brazil due to unavailability of settings to provide pharmacological behavioral guidance (14). Additional details on the dental sedation procedures can be assessed in the primary analysis study (11).

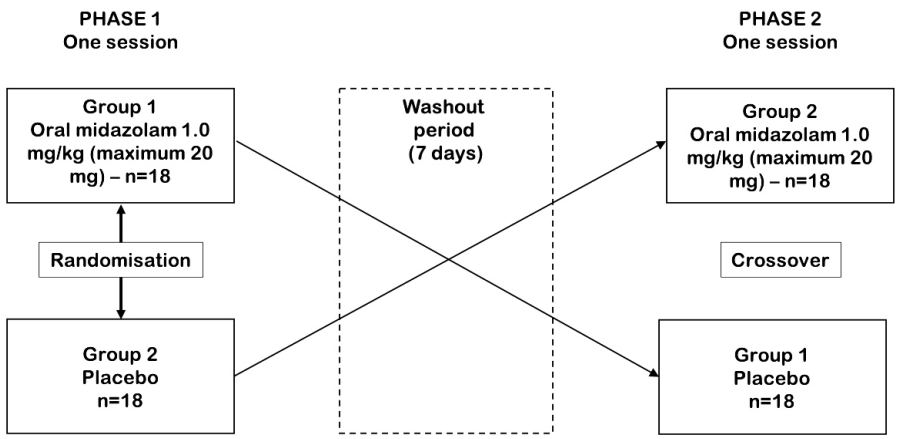

Figure 1. Crossover study design.

Measures

All dental procedures were recorded with a digital camera for posterior analysis of children's behavior as primary outcome measures. One trained and calibrated observer (intra-examiner kappa 0.9; 7-day interval assessment of children's behavior during dental

treatment not included in this sample) assessed children's behavior using the OSUBRS scale (15), minute by minute.

Four aspects are assessed in the OSUBRS scale, involving head and limb movements, crying, and physical resistance, and classified as follows: 1) no crying and no movement (quiet), 2) crying and no movement, 3) movement without crying and 4) crying and movement (struggling) (15).

Data Analysis

Data were entered and analyzed using the IBM SPSS 23.0 (IBM Corporation, New York, NY, USA) and Prism software (GraphPad Prism 6; GraphPad Software, San Diego, CA, USA). The Shapiro-Wilk test confirmed the normality of data for midazolam (p=0.29) and placebo (p=0.14). The percentage of OSUBRS 4 score (considering the pursuit outcome variable – struggling behavior) was normally distributed, and there were no outliers in the data, as assessed by inspection of a boxplot, so descriptive data are presented as means and standard deviation (SD).

As suggested for crossover trials (16), the patients were randomly assigned to receive midazolam and placebo as follows: In the midazolam/placebo group (G1), the children received midazolam at the first and placebo at the second session, and in the placebo/midazolam group (G2), the children had placebo in the first session and midazolam in the second one. This was because children in the experimental group may show systematic differences in outcome due to time effects (17). Therefore, in crossover trials, paired sample analyses are not advisable and can lead to flawed evidence (17).

A three-way mixed ANOVA was conducted to include three independent variables (drug, sequence of drug administration and child's age), which were mixed between group and repeated-measures variables (18). The main effect was the mean (SD) of the percentage of the struggling behavior (OSUBRS score 4), the outcome variable. According to the rationale proposed by Wellek and Blettner (2012), the within-subjects factor adopted was drug (oral midazolam and oral placebo) and the between-subjects were sequence of drug administration (G1 and G2) and children's age group (2–3 years and 4–5 years) (17). As the variable 'drug' has only two levels, the condition of sphericity is met (18). The significance level for statistical tests was set at 5%.

Results

Eighteen healthy children (11 girls and 7 boys) with an average age of 46.8 months (SD 13.9), more than half of whom (n=10) were under 4 years old met the inclusion criteria and participated in the study. No children dropped out throughout the study; thus, a total of 36 sessions were performed. Half of the participants received oral midazolam and the other half received oral placebo at the first dental visit, and they were crossed over at the second appointment. The flow diagram was reported in the primary analysis study (11).

Descriptive Data for Children's Struggling Behavior

Table 1 depicts the children's struggling behavior in both groups (G1 and G2) divided in two age groups (younger children, 2–3 years old; older children, 4–5 years old). The overall mean score 4 occurrence for midazolam was 52.7% (SD 29.8) and for placebo, 47.6% (SD 33.3). Accordingly, children in G1 and G2 had a reduction in the percentage of scores 4 from the first to the second session. However, the percent reduction was higher in G1 for older children (76.2%) and in G2 for younger children (32.9%).

In G1, children received midazolam at the first and placebo at the second session. For them, the percentage receiving a score of 4 was higher when they received oral midazolam compared to oral placebo, regardless of age (Table 1). In G2, children had placebo in the first session, and midazolam in the second one. The percentage of children receiving scores of 4 in both age groups was higher when they received oral placebo compared to oral midazolam (Table 1).

Multivariate Analysis

A mixed ANOVA was carried out to better understand the effects of drug, sequence of administration and age group on the percentage of children exhibiting struggling behavior. There was homogeneity of variances for the percentage receiving an OSUBRS score of 4 for both drugs: midazolam (p=0.22) and placebo (p=0.10) as assessed by Levene's test for equality of variances.

There was no significant main effect for 'drug', indicating that the frequencies of OSUBRS score 4 for midazolam and placebo groups were in general the same, F (1,14) =2.198, p=0.16, power 0.28, as well as for

Table 1. Descriptive data for percentages of OSUBRS score 4 (struggling behavior) according to sequence and age groups

Age groups (years old)	Percentage of the OSUBRS score 4 mean (SD)			
	G1 (midazolam/placebo)		G2 (placebo/midazolam)	
	Midazolam (First session)	Placebo (Second session)	Placebo (First session)	Midazolam (Second session)
2 - 3	71.3 (11.2)	54.9 (36.2)	80.5 (8.3)	54.1 (9.9)
4 – 5	73.3 (37.8)	17.5 (5.1)	32.7 (28.5)	23.4 (29.3)
Total	71.7 (16.5)	46.6 (35.5)	48.6 (33.1)	33.6 (28.2)

'sequence' of drug administration, F (1,14) =0.282, p=0.60, power 0.08. There was a significant main effect for the age category of children, F (1,14) =5.274, p=0.04, power 0.57, which indicates that children aged 4 and 5 years showed OSUBRS scores of 4 less frequently.

There was an interaction effect between the type of drug and the sequence of administration, F (1,14) =19.362, p=0.001, power 0.98. It indicates that the frequency of observation of OSUBRS score 4 with midazolam and placebo differed according to the sequence in which the drug was administered. When midazolam was given in the first session, an OSUBRS score of 4 was observed more often than when it was given in the second session. Also, when the placebo was administered in the first session, there was a greater frequency of OSUBRS score 4 than when the placebo was administered in the second session (Fig. 2).

There was an interaction effect between the type of drug and the age category of the child, F (1,14)=5.339, p=0.04, power 0.58. This reveals that the frequency of OSUBRS score 4 observed with midazolam and placebo differed according to the child's age. For the placebo but not for midazolam, an OSUBRS score of 4 was more frequently observed in children aged 2–3 years (Fig. 3).

Finally, there was no significant interaction between the sequence of drug administration and the age category, F(1,14) =0.757, p=0.40, power 0.13, or among drug, sequence of administration and age, F(1,14) =0.829, p=0.38, power 0.14.

Discussion

To our knowledge, this is the first study to bring forward evidence favouring the existence of carryover effects of drug experiments in crossover trials regarding pediatric dental sedation. The main outcome, i.e., children's behavior during sedation comparing midazolam versus placebo, depended on the sequence of midazolam administration. In turn, the drug itself had no effect on children's behavior, because both oral midazolam and oral placebo resulted in similar high frequencies of struggling behavior in children.

Our results regarding the effect of the interaction between the drug and the sequence of administration add to another investigation that showed no impact of the sedation sequence of three sedative regimes as analyzed by GEE (10). Likewise, we did not find a main effect for 'sequence' of administration, that is, when this variable was analyzed separately from the drug. However, when we employed the interaction 'drug' and 'sequence', which they did not do (10), a carryover effect was demonstrated and highlighted that the midazolam-related OSUBRS score 4 was significantly more frequent when midazolam was administered in the first compared to the second session. Even though the dental team is tailored to welcome as well as to offer comfort with or without sedation to all patients, the first contact could generate anxiety and it would be reflected in bad behavior (19).

Based on this, we hypothesize that the child who received placebo in the first session, associated with non-pharmacological behavior-guiding techniques, would begin a rapport with the dental team that would favor the learning of cooperation with dental treatment in the second session when midazolam was given. Moreover, even though the aforementioned study (10) had many similarities with the present investigation (e.g. children's age, standardized dental procedures in the repeated sessions), they observed children's behavior according to an overall score, whilst we employed a continuous variable (percentage of OSUBRS

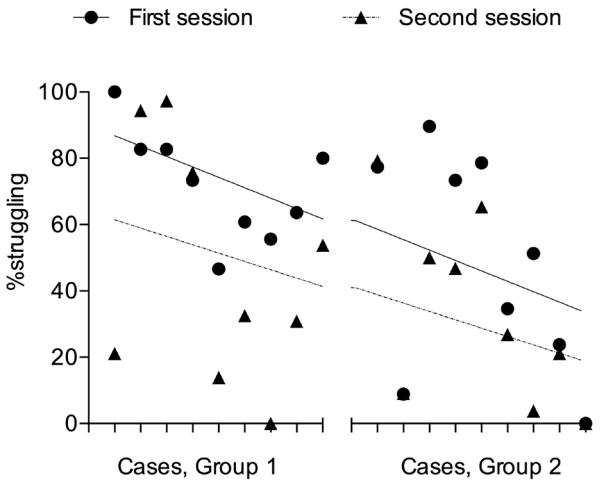

Figure 2. Percentage of struggling behavior in Groups 1 (first session = midazolam) and 2 (first session = placebo).

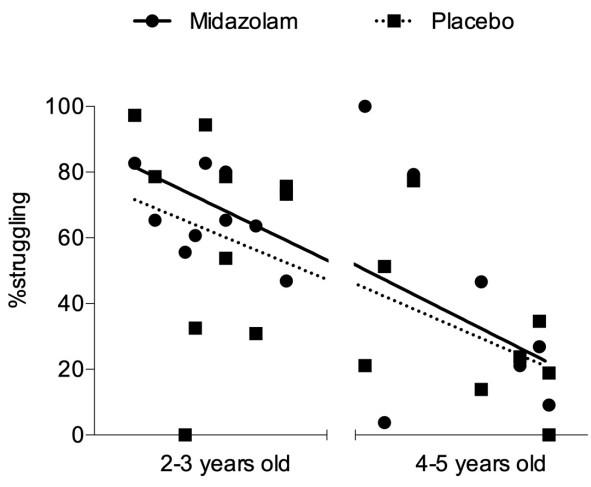

Figure 3. Percentage of struggling behavior in the two age ranges (2-3 and 4-5 years old).

score 4) that could better represent the child's behavioral nuances during dental sedation.

In this way, in agreement with the published systematic review (9), it is really not advisable to have crossover designs in pediatric dental sedation trials, even considering the periods of drug elimination between sessions. In our case, we used oral midazolam, the pharmacokinetics of which is approximately 20–90 min of action and a half-life of 3 h (20). Therefore, it was planned a 1-week interval between the two dental sessions. However, this was not enough to eliminate the carryover effect of the children's emotional responses to dental treatment.

Moreover, in this study, another important variable that significantly impacted in the children's behavior was 'age', analyzed both as a main effect and an interaction with 'drug'. Older children (4–5 years old) showed less struggling behavior as a whole and when the placebo data were analyzed. Accordingly, another study showed that older children (4–6 years of age) showed six times more favourable behavior than younger children (2–3 years of age) during procedural sedation (10).

It is noteworthy that there was an improvement regarding the reduction in the percentage of struggling behavior from the first to the second visit, which was remarkable in older children at G1. This is probably due to the amnestic properties of the midazolam, which is able to produce loss of memory of procedures (5). In fact, a previous study demonstrated that 0.2 mg/kg of intranasal midazolam in combination with nitrous oxide produced more anterograde amnesic effects evaluated by a recall test for children 24–28 months old during dental treatment compared with 3.7 mg/kg of hydroxyzine (21). In addition, older children tend to be more cooperative because they are expected to be more understanding than younger children (22).

Our findings demonstrated no main effect of sedative by itself on child behavior, which was similar using oral midazolam or placebo. In a previous, primary analysis (paired Student's t-test) using data from this same trial (11), we also did not find any significant differences regarding midazolam and placebo. In another study with a parallel design, there was no difference between oral placebo and oral midazolam in children under 3 years; however, when oral midazolam was combined with oral ketamine, the behavior was improved (14). Both studies used the OSUBRS scale to evaluate children's behavior in a dental setting (11,14). The target population of our study was pediatric dental patients who were referred to receive dental treatment under sedation due to uncooperative behavior at a previous appointment. As such, children referred for use of advanced behavioral techniques use more behavioral strategies, such as crying, movement and verbal protest in a dental setting (23). Thus, our findings corroborate that study (23).

The main limitation of our study was the sample size, as the power of the majority of analyses varied from low to moderate. We cannot affirm, for example, that midazolam and placebo do not differ in controlling children's struggling behavior because the power for that analysis was approximately 30%. However, the sample size was more than enough to show the interaction effect of the drug administration sequence on children's behavior, considering that the power of the analysis for these specific variables was >90%.

Our results might be generalizable to trials investigating children's behavior related to pharmacological or non-pharmacological techniques in the dental setting, especially regarding the statistical analyses we used here. As others have cautioned, crossover designs are not regular studies aiming paired observations, but they require precautions regarding treatment and period effects (17). As far as we are concerned, no other crossover trial in pediatric dental sedation has used the recommended formal structure of two study periods (sessions) that we used here (17).

To conclude, it is fair to recognize the impact of the sequence of drug administration in two sequential visits, as well as the child's age, on struggling behavior in uncooperative preschool children undergoing pediatric dental sedation for restorative treatment. The results of this study confirm the unsuitability of crossover clinical trials to investigate the efficacy of sedation in pediatric dentistry.

Resumo

Pouco se sabe sobre o impacto de um delineamento cruzado nos desfechos de ensaios clínicos randomizados voltados ao comportamento de crianças durante tratamento odontológico. Este estudo objetivou avaliar o efeito da sequência de administração do sedativo, da droga em si e da idade dos participantes no comportamento de crianças que receberam duas consultas odontológicas consecutivas. Dezoito crianças saudáveis não colaboradoras, 2-5 anos de idade, foram randomizadas em dois grupos: G1 – 1,0 mg/kg midazolam oral (primeira sessão) e placebo oral (segunda sessão); G2 - placebo (primeira) e 1,0 mg/kg midazolam oral (segunda). Um observador treinado avaliou o comportamento infantil. Os dados foram analisados por ANOVA de três fatores (alfa=0,05). Midazolam [média(DP); 71,7%(16,5)] e placebo [48,6%(33,1)] resultaram em mais comportamento não cooperativo quando administrados na primeira sessão comparado com a segunda (p=0,001). Com o uso do placebo, crianças de 2-3 anos de idade exibiram mais comportamento não cooperativo [G1 54,9%(36,2); G2 80,5%(8,3)] que as de 4–5 anos de idade (p=0,04). Além disso, a porcentagem de redução do comportamento não cooperativo foi maior em crianças mais velhas em G1 (76,2%) e em crianças mais novas em G2 (32,9%). Considerando a avaliação do comportamento infantil sob sedação, a primeira sessão odontológica influenciou a segunda visita. Os resultados deste estudo confirmam a especulação de que o delineamento cruzado é inadequado para avaliar o comportamento odontológico relacionado à ansiedade/comportamento infantil; os resultados dos ensaios cruzados de sedação odontológica devem ser tratados com extrema cautela.

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