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Risk of respiratory depression at use of nitrous oxide on individuals with cerebral palsy: a clinical trial

Risco de depressão respiratória no uso de óxido nitroso em indivíduos com paralisia cerebral: um ensaio clínico

Riesgo de depresión respiratoria por el uso de óxido nitroso en personas con parálisis cerebral: ensayo clínico

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Abstract
The dental care for individuals with cerebral palsy (CP) often result in the referral of patients for general anesthesia. Conscious sedation with nitrous oxide (N2O) could be an alternative resource, from a behavioral and physiological point of view, and could favor dental care in an outpatient setting. This study aimed to evaluate the influence of conscious sedation with N2O on respiratory rate (RR) and oxygen saturation (SpO2) in the dental treatment of individuals with CP. Seventy-seven patients with CP, over 3 years old, regardless of gender and ethnicity, were evaluated with the measurement of N2O titration, RR and SpO2 in four moments: initial, 5 minutes after sedation, 10 minutes after anesthesia and 5 minutes after removal of the N2O. Student's t test and ANOVA F were used, with a significance level of 5%. The variation in N2O titration did not generate significant variation in RR ($p = 0.122$). There was a significant difference in SpO2 between T1 and other times. It can be said that conscious sedation is not influenced by N2O titration, does not cause respiratory depression or any clinically significant change in SpO2, confirming the safety of use in an outpatient setting.
Keywords: Cerebral palsy; Dental care; Conscious sedation; Nitrous oxide.

Resumo
O atendimento odontológico a indivíduos com paralisia cerebral (PC) frequentemente resulta no encaminhamento de pacientes para anestesia geral. A sedação consciente com óxido nitroso (N2O) pode ser um recurso alternativo, do ponto de vista comportamental e fisiológico, e pode favorecer o atendimento odontológico ambulatorial. Este estudo teve como objetivo avaliar a influência da sedação consciente com N2O na frequência respiratória (FR) e saturação de oxigênio (SpO2) durante tratamento odontológico de indivíduos com PC. Setenta e sete pacientes com PC, maiores de

3 anos, independente de sexo e etnia, foram avaliados com a medida da titulação de N2O, FR e SpO2 em quatro momentos: inicial, 5 minutos após a sedação, 10 minutos após a anestesia e 5 minutos após a remoção do N2O. Foram utilizados o teste t de Student e ANOVA F, com nível de significância de 5%. A variação na titulação do N2O não gerou variação significativa na FR (p = 0,122). Houve diferença significativa na SpO2 entre T1 e outros momentos. Pode-se dizer que a sedação consciente não é influenciada pela titulação do N2O, não causa depressão respiratória ou qualquer alteração clinicamente significativa na SpO2, confirmando a segurança do uso em ambiente ambulatorial.
Palavras-chave: Paralisia cerebral; Assistência odontológica; Sedação consciente; Óxido nitroso.

Resumen
El cuidado dental para personas con parálisis cerebral (PC) a menudo resulta en la derivación de pacientes para anestesia general. La sedación consciente con óxido nitroso (N2O) puede ser un recurso alternativo, desde el punto de vista conductual y fisiológico, y puede favorecer la atención odontológica ambulatoria. Este estudio tuvo como objetivo evaluar la influencia de la sedación consciente con N2O sobre la frecuencia respiratoria (RR) y la saturación de oxígeno (SpO2) durante el tratamiento dental de personas con PC. Se evaluaron 77 pacientes con PC, mayores de 3 años, independientemente del sexo y la etnia, midiendo la titulación de N2O, RR y SpO2 en cuatro momentos: línea de base, 5 minutos después de la sedación, 10 minutos después de la anestesia y 5 minutos después de la eliminación del N2O. Se utilizó la prueba t de Student y ANOVA F, con un nivel de significancia del 5%. La variación en la titulación de N2O no generó una variación significativa en el RR (p = 0,122). Hubo una diferencia significativa en la SpO2 entre T1 y otros tiempos. Se puede decir que la sedación consciente no se ve influenciada por la titulación de N2O, no causa depresión respiratoria ni ningún cambio clínicamente significativo en la SpO2, lo que confirma la seguridad de su uso en un entorno ambulatorio.
Palabras clave: Parálisis cerebral; Cuidado dental; Sedación consciente; Óxido nitroso.

1. Introduction

Cerebral palsy (CP) is a disabling condition that has a well-recognized pattern of neurological development, which manifest at the beginning of brain development and persist throughout the individual’s life (Wimalasundera & Stevenson, 2016). It is the most common cause of physical disability in childhood (Mandaleson et al., 2015).

The problems of individuals with CP in dental care include diminished intraoral self-cleaning function due to the presence of abnormal involuntary movements of the facial, masticatory and lingual muscles, the presence of oral pathological reflexes and lack of understanding and cooperation with oral hygiene due to cognitive impairment (Akhter et al., 2017). In some cases, compromised function of the upper limbs can hinder the brushing movement, facilitating the accumulation of dental biofilm, which favors a higher prevalence of oral disease and the need for differentiated dental care (Ahmad et al., 2020; Cardona-Soria et al., 2020; Sedky, 2018). These factors often result in the referral of patients for general anesthesia during dental treatment, together with other individual medical complications (Ashley, Chaudhary & Lourenço-Matharu, 2018).

The difficulty of dentists and dental surgeons in providing care for patients with CP is that they often require additional resources, such as mechanical or chemical restraint, given the inefficiency of non-pharmacological methods. In patients who show severe problems with cooperation and handling, chemical restraint by sedation and general anesthesia should be considered as possibilities, in order to facilitate performing the dental treatment required (Cantador-Hornero et al., 2019). Currently, the inclusion of CP patients in the sphere of dental care is a reality that requires the development and adaptation of technologies that facilitate the same (Sacoor, 2017). Conscious sedation with nitrous oxide (N2O) could be an alternative resource for such patients, from a behavioral and physiological point of view, and could favor dental care in an outpatient setting (Ashley, Chaudhary & Lourenço-Matharu, 2018, Galeotti et al., 2016).

The effect of general anesthesia increases the risk of both intraoperative and postoperative death in CP patients submitted to repeated surgical procedures (Shaikh & Hegade, 2017). Thus, the use of an inhaled analgesia technique, nitrous oxide and oxygen, is the most suitable for routine treatment of adult and pediatric dental patients. It is safe, effective, with no undesirable side effects or significant morbidity, and does not cause addiction (Li et al., 2019; Prud'homme et al., 2019). In addition, it presents analgesic, sedative and slightly pronounced amnesic properties, a discreet hypnotic effect and minimal immobilizing property. These properties have been verified in several randomized, double-blind studies with a placebo group

(Bonafé-Monzó, Rojo-Moreno & Catalá-Pizarro, 2015). Given the pharmacokinetics and pharmacodynamics presented by nitrous oxide, this sedation technique is the most indicated for controlling everyday fear and anxiety. It is also well tolerated by the body, showing no important side effects and no strong contraindications (Bonafé-Monzó, Rojo-Moreno & Catalá-Pizarro, 2015; Prud'homme et al., 2019).

The titration property of a drug allows the dental surgeon to control its effects in a quick and practical manner, without having to estimate the exact dose for each patient (Li et al., 2019). This characteristic is one of the main reasons why the nitrous oxide and oxygen (N2O/O2) mixture is considered by most authors as the ideal technique for routine use in dental offices and outpatient services. If the patient inadvertently receives an excess of the drug, the effect can be rapidly attenuated by reducing the concentration administered (Bonafé-Monzó, Rojo-Moreno & Catalá-Pizarro, 2015; Li et al., 2019). Nitrous oxide acts on the central nervous system, and numerous authors cite its action on glutamate receptors (Dai et al., 2019).

Given the lack number of studies in the literature on the use N2O sedation in the dental care of individuals with CP, the purpose of this study was to evaluate the influence of conscious sedation with nitrous oxide on respiratory rate (RR) and oxygen saturation (SpO2) in individuals with CP.

2. Methodology

Prior to initiating data collection, this study was submitted for approval by the Research Ethics Committee of Cruzeiro do Sul University (Unicsul) and was approved under protocol no. CE/UCS–044/2010. This report consists in the compilation of unprecedented complementary data related to the risk of respiratory depression covered by the clinical trial registered at the ClinicalTrials.gov of U.S National Library of Medicine under clinical trial number NCT02322983 (Baeder et al., 2017).

A term of free, informed consent was signed by the parents or guardians of participating patients, in accordance with the norms of Resolution 466/2012 of the Brazilian National Health Council of the Ministry of Health, published in Diário Oficial da União (similar to US Federal Register) no. 301, on June 13th, 2013.

In this study, 77 patients with CP who attended the outpatient clinic of the Lar Escola São Francisco at the time of data collection were invited to participate. All the patients agreed to participate in the study and no sample loss occurred. The inclusion criteria were: a diagnosis of CP; patient of either sex age over 3 years old; patient with any of the clinical forms of CP; patients with carious lesions in at least two upper molars, deciduous or permanent, with indication for the use of anesthetic during the restorative procedure. The exclusion criteria were: patients with chronic respiratory problems, such as chronic bronchitis, chronic obstructive pulmonary disease and/or acute respiratory problems, such as flu with nasal congestion and active pneumonia; CP patients with associated genetic syndromes; patients whose parents or guardians refused to sign the terms of free, informed consent and consent to administer conscious sedation.

The physiological recordings of RR and SpO2 were measured by a digital sensor using an Ianum multi-parameter 8.4" TFT-LCD monitor (ANVISA, nº 900507301215) manufactured in the USA for adult, pediatric and neonatal use. A Matrx MDM Flowmeter (ANVISA nº 900507301215) was used for analgesia.

This study was a non-randomized experimental clinical trial, conducted in the outpatient dental clinic of the Lar Escola São Francisco, São Paulo - SP, Brazil. Dental care routines were established in order to standardize the procedure and ensure the reproducibility of the sedation method.

The initial consultation included the participant's full medical history, the collection of sociodemographic data and a dental examination. Data on the clinical form of CP were collected from patient medical records, and transcribed to the evaluation sheet especially developed for this research. At this time, the parents/guardians were provided with all necessary clarifications regarding the sedation technique and type of dental procedure that would be performed. The criteria for caries diagnosis during the examination followed those proposed in Oral Health Surveys: Basic Methods, fourth edition, published by

World Health Organization (WHO, 1997).

In the second consultation, the patient was positioned in the dental chair using mechanical restraint for stabilization. A suitable nasal mask was chosen and adapted to the patient. Next, the monitoring equipment were positioned and the behavioral and physiological recordings were initiated and noted on the evaluation sheet. The dentist operated the equipment to determine the right proportion of the gases N2O/O2, in order to achieve optimal sedation, in accordance with the criteria established in previous study (Drosner, 2013). In this study, adequate sedation of the CP patient was achieved when they showed a certain degree of relaxation that made them more cooperative with the treatment.

Evaluation of physiological parameters of respiratory rate (RR) and oxygen saturation (SpO2) were conducted at four times: T1 (pre-sedation), with the patient sitting in the chair, basal physiological parameters were measured; T2 (optimal titration), 5 min after placing the mask on the patient, having established the optimal titration for sedation; T3 (sedated patient); measured 10 min after the onset of the procedure (first molar restoration, permanent or deciduous) – all patients were treated under local anesthesia (weight-based dosage of mepivacaine:epinephrine at 1:100,000) (Guimarães et al., 2017); and T4 (oxygenation), 5 min after the removal of nitrous oxide, while maintaining oxygenation.

Comparisons between means of continuous variables between the two groups were performed using the Student t and ANOVA F tests. For the evaluation of variables (RR and SpO2) over time, Brunner's model for adjusted nonparametric repeated measures was used. All calculations were performed using the statistical software R 3.0.2 (R Core Team, 2014). The tests considered a 5% level of significance. Graphs were produced using the ggplot2 package.

3. Results

The results for the categorical variables are presented in tables of absolute and relative frequencies, while continuous variables are presented as position statistics (mean, minimum, maximum) and scale (standard deviation).

Mean patient age was 11.8 years old with a standard deviation (SD) of 6.4 years. The patients required 10 to 60% N2O for sedation, with a mean of 35.6% (SD±10.4).

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Table 1. Descriptive variables of patient age, respiratory rate, sedation time, oxygen saturation, nitrous oxide and oxygen concentrations.

Variable	N	Minimum	Maximum	Mean	SD	Median
Age (years)	77	3	32	11.8	6.4	10
RR (T1)	77	14	18	16.2	1.2	16
RR (T2)	77	14	18	16.1	1.0	16
RR (T3)	77	14	18	16.0	1.0	16
RR (T4)	77	14	18	16.0	1.0	16
Time in min	77	10	90	34.4	14.9	30
SpO_2 (T1)	77	89	99	96.0	1.5	96
SpO_2 (T2)	77	90	100	97.7	1.3	98
SpO_2 (T3)	77	90	100	97.6	1.3	98
SpO_2 (T4)	77	90	99	97.7	1.3	98
% N_2O	77	10	60	35.6	10.4	40
% O_2	77	40	95	64.6	10.8	60

RR, respiratory rate; SpO_2, oxygen saturation; %N_2O, nitrous oxide percentage; %O_2, oxygen percentage; SD, standard deviation. For continuous variables: T1, presedation; T2, optimal titration; T3, patient under sedation during procedure; T4, oxygenation, after removal of N_2O. Source: Own authorship.

Individuals with different clinical forms of CP participated in the study: diparesis (31.2%), hemiparesis (36.3%), quadriparesis (27.3%) and choreoathetoid CP (5.2%).

During and after the procedure, inhalation sedation was effective, no change in RR was observed and SpO2 remained within expected physiological norms. No significant differences were verified for RR, SpO2 and patient age, and RR and SpO2 showed no significant standard deviations, indicating the stability of these values.

Table 2. Mean, standard deviation and p values for patient age, respiratory rate, oxygen saturation and nitrous oxide and oxygen percentages at the time the patient was fully sedated (T3).

Variable	Mean	SD	p value*
Age (years)	11.82	6.43	0.393
RR (T3)	16.04	1.01	0.855
SpO_2 (T3)	97.6	1.32	0.105
% N_2O	35.65	10.37	0.397
% O_2	64.61	10.81	0.305

RR, respiratory rate; SpO_2, oxygen saturation; %N_2O, nitrous oxide percentage; %O_2, oxygen percentage; SD, standard deviation. *Student t test. Source: Own authorship.

Figures 1 and 2 and Table 3 show the time course of the variables measured, assessing RR and SpO2 at T1, T2, T3, and T4. For each variable, the mean and 95% confidence intervals are shown.

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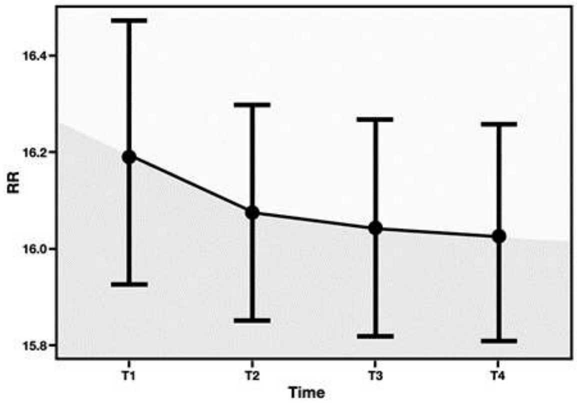
Figure 1. Profile of the mean respiratory rate (RR) over time.

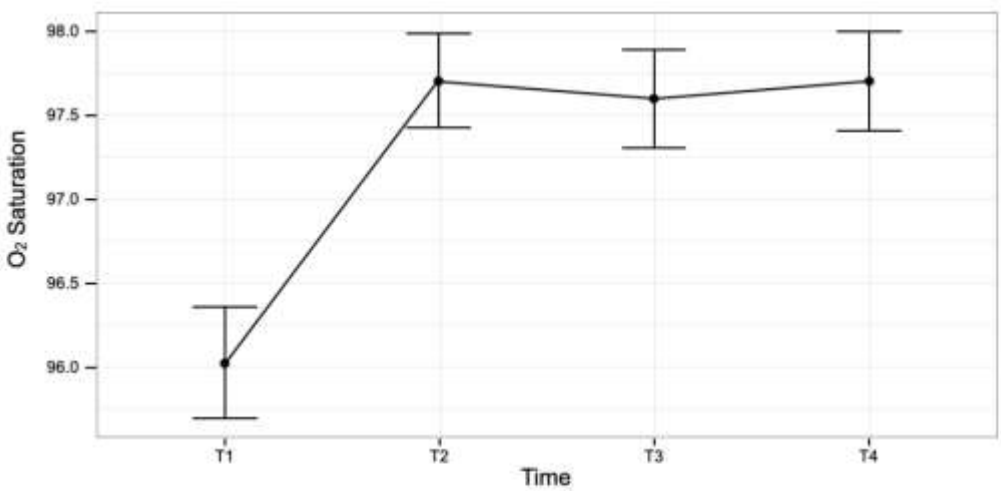


Source: Own authorship.

Using Brunner's model, the overall p value for RR repeated measures over time was 0.122, indicating that no significant variation in RR occurred over time.

Figure 2 shows the mean values for SpO2 at T1, T2, T3 and T4.

Figure 2. Profile of the mean oxygen saturation (SpO2) over time.



Source: Own authorship.

For SpO2, the p value was less than 0.001, therefore multiple comparisons were performed using Wald's model for nonparametric repeated measures, compared in pairs at different times.

Table 3. Multiple comparisons of mean oxygen saturation (SpO2) between all four times.

Times	Statistics	Degrees of freedom	p value
1-2	144.839	1	**<0.001**
1-3	104.537	1	**<0.001**
1-4	140.626	1	**<0.001**
2-3	2.241	1	0.1344
2-4	0.069	1	0.793
3-4	1.507	1	0.2196

Source: Own authorship.

There was a notable increase in mean SpO2 from T1 to T2 that was then sustained until the end of the procedure. Table 1 shows that the mean initial SpO2 of 96.0% (T1) increased to 97.7% (T2), and remained at that level until the final measurement (97.7%, T3; 97.8%, T4).

The percentage of nitrous oxide used in this study was not influenced by the different variables and times studied.

4. Discussion

To our knowledge, this is the first study to demonstrate the effects of nitrous oxide through the evaluation of physiological parameters during dental care on children with CP. Analysis of the results could suggest that sedation with nitrous oxide is a simple, safe and effective process when used as an auxiliary resource in the dental care of individuals with CP. The main parameters for its indication and use are the focus of this discussion.

Cerebral palsy is an umbrella term that defines a group of individuals with heterogeneous clinical manifestations of different types of movement disorders (spasticity, dyskinesia (athetosis/dystonia) and ataxia), with different clinical forms (quadriparesis, hemiparesis and diparesis). These individuals present high levels of caries experience and periodontal disease (Jan & Jan, 2016; Wimalasundera & Stevenson, 2016). The sample of patients studied here presented the characteristics described above and included individuals with diparesis (31.2%), hemiparesis (36.3%), quadriparesis (27.3%) and choreoathetoid CP (5.2%).

The profile of the population studied shows that individuals were aged between 3 and 32 years old, and were fairly evenly distributed between the clinical forms of diparesis, hemiparesis and quadriparesis. Dyskinetic patients (choreoathetoid) represented only 5% of the sample, agrees with several studies by other authors, who observed a lower incidence of choreoathetoid CP in their samples (Sedky, 2018).

Nitrous oxide has low anesthetic potency. Under normal conditions of temperature and pressure, it requires a minimum alveolar concentration of 104% for the anesthetic effect to become apparent. Given this pharmacodynamic characteristic, nitrous oxide is generally used in combination with inhalation or intravenous anesthetics in general anesthesia (Stevens et al., 1975). Thus, under the conditions used in this study, it only induced sedation without the risk of promoting general anesthesia in the patients. Despite the criticism and warnings expressed in the literature concerning the safety of the clinical use of nitrous oxide during anesthesia, continuous use is fairly rare worldwide (Bonafé-Monzó, Rojo-Moreno & Catalá-Pizarro, 2015). The absence of clinical complications in this experimental clinical study reinforces the indication of nitrous oxide as an auxiliary resource in dental care.

When comparing microsomal enzymes used in the metabolism of prescription drugs continuously prescribed and administered to patients with CP and local anesthetics, Baeder, Figueirêdo and Dos Santos (2015) reported that the biotransformations mediated by the hepatic cytochromes P450, when using the same microsomal enzyme, can directly interfere in the pharmacological effect, promoting the formation of potentially toxic metabolites. Since nitrous oxide is inorganic and does not undergo hepatic metabolism, it is a safe sedation option that avoids liver problems, particularly in patients who are administered medications continually.

The association between nitrous oxide and psychoactive drugs usually promotes the potentiation of the sedative effects (Done et al., 2016; Cantador-Hornero et al., 2019). According to the results obtained in this study, no potentiation of sedative effects occurred due to concomitant use of psychoactive drugs and nitrous oxide. The physiological parameters, RR and SpO2, showed no unexpected or abnormal changes during the procedure (Table 1). Brondani's data on the association between nitrous oxide and psychoactive drugs indicated no change in RR and SpO2 (Brondani et al., 2003), corroborating our observations regarding the clinical safety of the concomitant use of nitrous oxide and psychoactive drugs in patients with CP.

Analysis of the results for RR when using nitrous oxide showed no statistically significant changes. As described in the literature, the safe use of nitrous oxide is due to its selective action on the cerebral cortex, which does not include depressing the respiratory centers located in the brain stem (Prud'homme et al., 2019).

Regarding oxygen saturation, desaturation has mainly been reported when involving chemical sedation by benzodiazepines. According to Jay et al. (2017), the main side effect of benzodiazepines is respiratory depression, so recording oxygen saturation is essential for monitoring respiratory and cardiovascular function. Patients submitted to sedation should always show oxygen saturation above 90%. In this study, oxygen saturation remained stable, with a mean value above 97% throughout the procedure. Multiple time comparisons for oxygen saturation (SpO2) showed significant differences over time in patient oxygenation ($p<0.001$) that resulted in improved oxygen saturation, though these changes are not clinically relevant.

One of the most difficult aspects of dental treatment for individuals with CP concerns their neurological motor disorders. The extent of these disorders often requires the professional to use stabilization measures and restrain the patient in order to ensure safe dental treatment (Sacoor, 2017).

Our findings show that individuals with severe locomotion impairment corresponded to 32.3% of the sample, such that physical restraint was necessary to achieve adequate patient stabilization. Sedation techniques that promote general muscle relaxation are essential for performing dental procedures. Thus, although there is no direct correlation between severe movement impairment and nitrous oxide titration, it is still recommended to facilitate the cooperation of the patient during the dental procedure.

The methodology of the present study was carefully developed to minimize bias and to ensure an adequate internal validity, leading to the applicability and generalizability of the results. To report limitations related to the study design, it can be emphasized that the use of saliva to determine plasma levels of hormones has been increasing considerably, and constitutes a non-invasive and painless method, easy to collect, which has demonstrated its applicability and sensitivity in several studies. Dental treatment is often associated with anxiety and stress, producing a significant increase in the levels of these steroid hormones compared to subjects who would not be treated. Thus, evaluating cortisol levels during the procedure steps could offer more data to assess possible changes related to stress during treatment with nitrous oxide.

5. Conclusion

Our analysis of conscious sedation using nitrous oxide during dental care in individuals with CP suggests that sedation with nitrous oxide is indicated in patients with CP. Respiratory depression was not observed when using conscious sedation during dental care, and the supply of oxygen in the mixture of gases increased oxygen saturation (SpO2).

Therefore, this research proposes the safety of using conscious sedation with nitrous oxide in the dental treatment of individuals with cerebral palsy. Also provides relevant information for dental surgeons about the use of sedation techniques that promote general muscle relaxation, essential for performing dental procedures in patients with movement disorders.

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