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Efficacy of the non-instrumentation endodontic treatment with CTZ paste in primary molars: Protocol of a multicenter randomized clinical trial with two years of follow-up

Eficácia do tratamento endodôntico não-instrumental com pasta CTZ em molares decíduos: Protocolo de um ensaio clínico randomizado multicêntrico com dois anos de acompanhamento

Eficacia del tratamiento endodóntico no instrumentado con pasta CTZ en molares primarios: Protocolo de un ensayo clínico aleatorizado multicéntrico con dos años de seguimiento

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Abstract
Objective: There is a lack of high-quality evidence on the efficacy of the non-instrumentation endodontic treatment (NIET) in primary molars, compared to the conventional endodontic treatment technique. This protocol describes a multicenter randomized clinical trial that aims to evaluate the efficacy of a NIET technique for primary molars using a paste containing antibiotics (chloramphenicol and tetracycline – CTZ group) compared to a control group of conventional technique and root filling with zinc oxide eugenol (ZOE). *Methodology*: Children aged 3 to 9 years (N=218) will be randomly allocated to one of the groups: CTZ or ZOE. In CTZ, after the location of root canals entrance, irrigation will be performed using 1% sodium hypochlorite and CTZ paste will be placed over the root canal entrances, with no instrumentation of the root canals. In ZOE group, manual instrumentation of root canals with endodontic K-files will be performed, and then, the root canals will be filled with ZOE paste. At the same appointment, teeth will be restored with a double-seal of glass ionomer and a bulk fill resin composite. Children will be followed-up for 6, 12, 18 and 24 months. The primary endpoint will be the success of endodontic treatments evaluated by clinical and radiographic criteria after 24 months. *Conclusions*: NIET with CTZ paste could be an option to manage primary teeth, once the technique could have non-inferior efficacy to the conventional technique that involves root canal instrumentation. The approach could have good acceptance from children and parents considering the reduced clinical time.
Keywords: Endodontic treatment; Primary teeth; Non-instrumentation technique; CTZ paste; Pulpectomy.

Resumo
Objetivo: Faltam evidências de alta qualidade sobre a eficácia do tratamento endodôntico não-instrumental (NIET) em molares decíduos, em comparação com o tratamento endodôntico convencional. Este protocolo descreve um ensaio clínico randomizado multicêntrico que visa avaliar a eficácia de uma técnica NIET em molares decíduos utilizando a pasta CTZ (cloranfenicol e tetraciclina e óxido de zinco) em comparação com um grupo controle de técnica convencional com obturação dos canais radiculares com óxido de zinco e eugenol (OZE). *Metodologia*: Crianças de 3 a 9 anos (N=218) serão alocadas aleatoriamente em um dos grupos: CTZ ou OZE. No grupo CTZ, após a localização da entrada dos canais radiculares, será realizada irrigação com hipoclorito de sódio 1% e a pasta CTZ será inserida sobre as entradas dos canais radiculares, sem instrumentação prévia. No grupo OZE, será realizada a instrumentação manual dos canais radiculares com limas endodônticas tipo K e os canais radiculares serão preenchidos com pasta OZE. Na mesma consulta, os dentes serão restaurados com uma camada de ionômero de vidro, seguida de resina composta bulk fill. As crianças serão acompanhadas por 6, 12, 18 e 24 meses. O desfecho primário será o sucesso dos tratamentos endodônticos avaliado por critérios clínicos e radiográficos após 24 meses. *Conclusões*: A técnica não-instrumental com pasta CTZ pode ser uma opção para o manejo de dentes decíduos, uma vez que pode ter eficácia não inferior à técnica convencional. A abordagem poderia ter boa aceitação das crianças e pais considerando o tempo clínico reduzido.
Palavras-chave: Tratamento endodôntico; Dentes decíduos; Técnica não-instrumental; Pasta CTZ; Pulpectomia.

Resumen
Objetivo: Hay una falta de evidencia de alta calidad sobre la efectividad del tratamiento endodóntico no instrumentado (NIET) en molares primarios en comparación con el tratamiento de endodoncia convencional. Este protocolo describe

un ensayo clínico aleatorizado multicéntrico que tiene como objetivo evaluar la efectividad de una técnica NIET para molares primarios utilizando pasta CTZ (cloranfenicol y tetraciclina y óxido de zinc) en comparación con un grupo control de técnica convencional y obturación de conductos con óxido de zinc y eugenol (OZE). *Metodología*: Los niños de 3 a 9 años (N=218) serán asignados aleatoriamente a uno de los grupos: CTZ u OZE. En el grupo CTZ, luego de ubicar la entrada del conducto radicular, se realizará irrigación con hipoclorito de sodio 1% y se colocará la pasta CTZ sobre las entradas del conducto radicular, sin instrumentación previa. En el grupo OZE, los conductos radiculares se instrumentarán con limas de endodoncia tipo K y se rellenarán los conductos radiculares con pasta OZE. Los dientes se restaurarán con una capa de ionómero de vidrio, seguido de una resina compuesta bulk fill. Los niños serán seguidos durante 6, 12, 18 y 24 meses. El resultado primario será el éxito de los tratamientos evaluado por criterios clínicos y radiográficos después de 24 meses. *Conclusiones*: La técnica no instrumental puede ser una opción para el manejo de los dientes temporales, ya que puede no tener una eficacia inferior a la técnica convencional. El enfoque podría ser bien aceptado por los niños y los padres considerando el tiempo clínico reducido.
Palabras clave: Tratamiento endodóntico; Dientes primarios; Técnica de no instrumentación; Pasta CTZ; Pulpectomía.

1. Introduction

Endodontic treatment with conventional chemo-mechanical preparation of root canals has been advocated to treat primary teeth with irreversible inflamed or necrotic pulp (Coll, Vargas, *et al*., 2020; Duarte *et al*., 2020). However, there is no consensus on whether there is a superior technique protocol or filling material to be used in endodontic treatment of primary teeth (Coll, Vargas, *et al*., 2020; Smaïl-Faugeron *et al*., 2018). Methodological heterogeneity between studies, including design, treatment protocol, and reported outcomes difficult the comparison among studies. Moreover, most clinical trials on this issue have presented low- to moderate- certainty of evidence (Coll, Vargas, *et al*., 2020). In addition, several factors may influence the conventional endodontic treatment success, such as the complex root morphology of the primary teeth, age and cooperation of the patient, medical history, and the presence of pathologic or physiologic root resorption (Coll, Vargas, *et al*., 2020; Duarte *et al*., 2020).

As an alternative biologic approach to the conventional endodontic treatment for non-vital primary teeth, the concepts of Lesion Sterilization Tissue Repair (LSTR) and Non-instrumentation Endodontic Treatment (NIET) have been introduced (Hoshino *et al*., 1996; I. Sato, et al., 1996; T. Sato, et al., 1993). The NIET technique advocates the use of an antibiotic mixture placed in the pulp chamber, with no instrumentation of the root canals (Takushige, et al., 2004). The 3Mix mixture (minocycline, metronidazole, and ciprofloxacin) blended in propylene glycol or polyethylene glycol (macrogol) is the most commonly used in NIET; however, alternative mixtures have been proposed (Chouchene, et al., 2021).

A mixed antibiotic paste composed of chloramphenicol, tetracycline, zinc oxide, and eugenol as the vehicle, the CTZ paste, was first described by Cappiello in 1964 (Cappiello, 1964). The use of the CTZ paste complies with the precepts of NIET, once it is placed only in the entrance of root canals, with no previous instrumentation (Cappiello, 1964; De Deus Moura *et al*., 2016). Currently, the CTZ paste seems to be used mainly by underdeveloped or developing countries such as Latin countries (De Deus Moura *et al*., 2016; Luengo-Fereira *et al*. 2019; Sousa *et al*., 2020) and India (Lokade, et al., 2019). Despite being biocompatible (Lima *et al*., 2015), there are few long-term reports on its clinical efficacy (Lokade *et al*., 2019; Luengo-Fereira *et al*., 2019). In addition, the few clinical trials (Lokade *et al*., 2019; Luengo-Fereira *et al*., 2019) evaluating the CTZ paste success recruited underpowered samples and used different control groups, making it difficult to compare and extrapolate the results. Thus, it is claimed that the clinical indication for the use of CTZ paste in primary teeth is still conditioned to the best evidence provided by well-designed randomized clinical trials, with larger sample sizes and longer follow-ups.

Therefore, the present multicenter randomized clinical trial aims to evaluate the efficacy of a NIET technique, using the CTZ paste, compared with a conventional technique with root canal instrumentation and filling using zinc oxide and eugenol (ZOE) paste. The working hypothesis is that the success rate of the NIET is non-inferior to the success obtained with

conventional endodontic treatment involving manual instrumentation of root canals filled with ZOE paste, considering a pre-specified non-inferiority margin after 24 months of follow-up.

2. Methodology

2.1 Ethical considerations

The present study protocol was reported according to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Chan *et al*., 2013) and the Reporting of Noninferiority and Equivalence Randomized Trials: Extension of the CONSORT Statement (Piaggio, et al., 2012).

This protocol was approved by the local ethical committees from the four enrolled centers: the School of Dentistry of the University of São Paulo (USP), Federal University of Santa Catarina (UFSC), Rio de Janeiro State University (UERJ), and Iguaçu University (UNIG), under the number CAAE: 42602820.0.1001.0121. In addition, the protocol was registered in the Clinical Trials database (Identifier: NCT04942158). Participants will only be included after the children assent to the study and their legal guardians have signed an informed consent form.

2.2 Study Design

This investigation is a multicenter, randomized, non-inferiority, open-label, parallel two-arms clinical trial, with a 1:1 allocation ratio and two years of follow-up. The differences between the two techniques do not allow to blind the operator, the participant, and the evaluator. Recruitment will be taking place from October 2021 to September 2022. After recruitment, patients will be followed-up for two years.

2.3 Sample size

The sample size calculation was performed on the Sealed Envolope® website (https://www.sealedenvelope.com/power/binary-noninferior/). A success rate of 92% (Coll, Vargas, *et al*., 2020) of primary teeth submitted to conventional endodontic treatment was considered. Considering a non-inferiority margin of 15%, a significance level of 5% and a power of 90%, a sample size of 114 participants was achieved. Adding 20% to this value due to possible losses and 60% due to the multicenter design (20% to each additional center), a minimum required sample size of 218 participants was obtained (109 per group).

The non-inferiority margin was the value corresponding to approximately 50% of the difference (27%) found between the LSTR and conventional endodontic treatment success rates in a previous systematic review (Coll, Vargas, *et al*., 2020).

2.4 Eligibility criteria

Children aged 3 to 9 years with a primary molar with clinical and/or radiographic signs of irreversible inflamed pulp or non-vital pulp will be selected. Children with special needs, immunocompromised patients, with a reported allergy to the medications used in the study, and those with negative behavior in the initial clinical examination will be excluded.

Concerning the teeth, the occurrence or history of spontaneous pain, fistula, abscess, and swelling will be assessed clinically. Radiographically, primary molars with inter or periradicular radiolucency not involving the follicle of the permanent successor tooth, with at least two-thirds of root length, with no signs of internal or external pathologic root resorption, and no signs of perforation of the pulp chamber floor will be considered for inclusion.

Teeth with (1) non-restorable crowns, (2) continuous bleeding after removal of the coronary pulp, (3) pulp canal obliteration, and (4) serious reduction in bone support or extreme tooth mobility will be excluded.

2.5 Sequence generation and allocation concealment

Children will be randomly assigned into the groups considering the strata of each research center (USP, UFSC, UERJ, and UNIG), in permuted blocks of 2, 4, and 8. The sequence allocation will be generated by an external assistant on the website Sealed Envelope (https://www.sealedenvelope.com/) and the generated sequence will be closed in opaque sealed envelopes numbered by the external assistant.

2.6 Operators' training

Before patient recruitment, the four operators (one from each center) will be trained to perform both techniques (NIET and conventional endodontic technique). The training will be conducted initially with theoretical classes. In addition, the methodology will be tested clinically in children that will not be included in the study.

2.7 Clinical examination

An initial clinical exam will be performed in a dental office by the operators using light, a dental mirror and a dental probe, after prophylaxis to identify eligible participants. Teeth with clinical indication of pulp involvement will be radiographed to verify the radiographic eligibility criteria. To standardize the radiographic take, a parallelism x-ray positioner (RINN XCP® Film Holding System, Dentsply Maillefer, Ballaigues, Switzerland) will be used, with an F-speed dental x-ray film (Carestream, New York, United States of America).

2.8 Interventions

In both groups, topical anesthesia with 20% benzocaine gel (Benzotop, Nova DFL, Rio de Janeiro, Brazil) will be performed by applying the gel on dried mucosa for two minutes. After appropriate local anesthesia with lidocaine 2% with epinephrine 1:100 000 (Alphacaine, Nova DFL, Rio de Janeiro, Brazil) and rubber dam isolation, the pulp chamber will be accessed with a properly sized round diamond bur (KG Sorensen, São Paulo, Brazil) at high speed under water-cooling. The access cavity will be refined with a noncutting tip Endo-Z bur (Dentsply Maillefer, Ballaigues, Switzerland). After the location of root canals entrances, the sealed envelope will be opened to randomize the group.

In CTZ group (experimental group), the procedure will continue with the irrigation of the pulp chamber using 1% sodium hypochlorite (NaOCl). After drying the pulp chamber with sterile cotton rolls, the CTZ paste will be placed into the root canal entrances using a dental probe explorer, and pressure will be applied with sterile cotton balls. Then, a layer of glass ionomer cement (Encapsulated Riva Self Cure, SDI Ltd., Victoria, Australia) will be placed, to prevent contact of the restorative material with the paste. The teeth will be restored with a bulk fill resin composite (Filtek Bulk Fill Posterior Restorative, shade A1; 3M ESPE, Minnesota, United States of America), using a three-step etch-and-rinse adhesive (Adper Scotchbond Multipurpose, 3M ESPE, Minnesota, United States of America), according to the manufacturer recommendations.

In the teeth allocated to the ZOE group (control group), the working length (WL) will be determined by subtracting 1mm from the preoperative radiographic measurements performed in each root. The root canal instrumentation will be performed with 21mm stainless steel endodontic hand K-files, with International Organization for Standardization (ISO) tip ranging from #10 to #40. Irrigation will be performed using 1% NaOCl. After the last file, final irrigation will be conducted with ethylenediaminetetraacetic acid and tergentol (EDTA-T) 17% and 0.9% sodium chloride solution, and the root canals will be dried with paper points. Then, the root canals will be filled with a ZOE paste (Biodinâmica, Rio de Janeiro, Brazil) inserted into the root canals with a Lentulo spiral (WL – 2mm). The same restorative protocol will be performed, similar to the CTZ group.

2.9 Primary outcome

The primary outcome of the present study is the success of the endodontic treatment. This is a dichotomous variable that will be defined through clinical and radiographic evaluation after 24 months. Clinical criteria for determining success will be the absence of pain, fistula, edema, and pathological mobility, presence of periodontal health, or physiological exfoliation. Radiographic signs of success will be: (1) reduction or non-evolution of the previous endodontic radiolucency, (2) root resorption compatible with the eruptive phase, (3) absence of pathological root resorption, and (4) restorative material isolating the filling paste from the oral cavity. In the occurrence of any signs of failure, the treatment will be considered unsuccessful. The main comparisons between the groups will be done considering the frequency rate of success treatment 24 months after the treatment when the absence of failure was detected in all follow-ups (6, 12, 18, and 24 months).

2.10 Secondary outcomes

A secondary outcome considered in our study is the clinical operating time. This time will be recorded starting from the topical anesthesia until the removal of the rubber dam isolation using a digital chronometer by a dental assistant. The mean time (quantitative variable) will be compared between the groups.

Another secondary outcome is the children's behavior during the treatment, which will be assessed by an external researcher using the Frankl scale (Frankl, 1962). The ordinal scale classifies the behavior during the treatment according to four categories, varying from definitely negative behavior (score 1) to definitely positive behavior (score 4). The assessor will classify the children's behavior in the period after the local anesthesia until the removal of rubber dam isolation. This outcome will be analyzed as a qualitative ordinal variable.

Children's self-reported discomfort after the intervention will be evaluated using the Facial Image Scale (Buchanan & Niven, 2002), immediately at end of the intervention. This is an ordinal scale with five representative faces ranging from a very sad and crying face (score 5) to a very happy and smiley face (score 1). An external assessor will show the scale for the children and will ask: "Which of these faces reflects how you feel after treating your tooth?". This outcome will be summarized and compared as a qualitative ordinal variable.

The occurrence of postoperative pain, edema, and fistula will be evaluated 48 hours following the intervention. The operator will make a phone call to the children's parents. These outcomes will be evaluated through 3 questions that will be done by the assessor: Has your kid reported pain in the treated teeth (yes or no)? Have you noticed some edema (swelling) or fistula with pus (yes or no)? and Did your kid need analgesic medication intake (yes or no)? These variables will be compared separately between the groups as dichotomous variables.

The short- and long-term impact of the treatments on Oral Health-Related Quality of Life (OHRQoL) reported by the children will be evaluated by considering the scores obtained through a questionnaire answered by children. The Child Perceptions Questionnaire (Barbosa, et al., 2011) for children from 8 to 10 years old (CPQ8-10) will be applied at the baseline, after the inclusion of the children (before the disclosure of the allocated group). The instrument has 25 questions, and five answer options for each question. A score ranging from 0 to 4 is given for each question, and the final score is obtained by the sum of all items. The higher the score obtained, the worse the OHRQoL. After 1 week of the treatment, the questionnaire will be re-applied to evaluate the short-term effect of the treatment on the OHRQoL. Likewise, after 24 months, the children will respond the CPQ8-10 to evaluate the long-term effect of the treatment. For both short- and long-term effect, we will calculate and compare the mean of change scores and the effect sizes between the groups.

Another secondary outcome will be the short- and long-term impact of the treatment on OHRQoL reported by the parents. For this, we will use the Early Childhood Oral Health Impact Scale (ECOHIS) (Martins-Júnior, et al., 2012). The instrument has 13 questions and six answer options for each question. A score ranging from 0 to 5 is given and the final score

is obtained by the sum of all items. The higher the score obtained, the worse the OHRQoL. The questionnaire will be applied before the treatment and one week after to assess the short-term impact and after 24 months to evaluate the long-term impact of the treatment on the OHRQiL reported by the parents. Likewise, change scores and the effect sizes will be compared between the groups.

The costs of each procedure, not considering the follow-up evaluations or failures, will be calculated per each patient treated. Then, the cost-efficacy will be assessed. The costs of each treatment will be added to the cost of the failures and will be adjusted by the efficacy obtained with each treatment. The direct costs of the procedures performed in each group will be measured and evaluated, as well as the cost of labor of professionals involved in clinical care (direct costs). The costs of all materials used will be calculated using the average market value at different dental supply stores. Labor costs will be measured by the time required to carry out the treatment. The patient's transportation costs and the costs of the caregivers' absence from the workplace (indirect costs) will also be assessed.

2.11 Data analysis

All analyses will be conducted in the intention-to-treat (ITT) population. The clinical and radiographic success of the interventions (primary outcome) will be dichotomized as success and failure. The main analysis will be done by comparing the frequency of treatment success in each group after 24 months considering the non-inferiority limit of 15% and using the Miettinen-Nurminen's method. Sensitivity analysis will be conducted considering when the failure occurred (survival analysis) using non-inferiority Cox regression.

All secondary outcomes will be also compared using the ITT approach but considering two-tailed hypotheses. The clinical operating time will be summarized as means and standard deviation or medians and interquartile range, considering the data distribution assessed by the Shapiro-Wilk test (normal or non-normal). The groups will then be compared with Student's t-test or Mann-Whitney test, according to data distribution.

The children's behavior during the treatment (secondary outcome) will be presented in frequencies. The behavior will be compared between the groups with the Mann-Whitney test.

The immediate discomfort reported by the patients (secondary outcome) will be summarized as means and standard deviation or medians and the interquartile range, according to data distribution. Likewise, the groups will be compared with the Mann-Whitney test.

The occurrence of postoperative pain, edema, fistula, and analgesic intake will be presented in frequencies. The comparison between groups will be assessed with Pearson's chi-squared test.

To evaluate both short- and long-term impacts of the treatments on OHRQoL, the differences (baseline minus follow-up) in mean scores will be calculated. A positive number will indicate improved OHRQoL, a negative number will indicate a negative impact on OHRQoL, and zero indicates no change. Mean differences will be compared among groups with Student's t-test or Mann-Whitney test, according to data distribution.

The cost-efficacy (secondary outcome) will be calculated considering the ratio between the total cost of each technique and tooth survival after two years (incremental cost-efficacy ratio).

For all analyses, a significance level of 5% will be applied.

3. Discussion

Recently, the NIET technique was included as a treatment option in the updated guideline on the use of non-vital therapies in primary teeth of the American Academy of Pediatric Dentistry (Coll, Dhar, *et al*., 2020). However, its recommendation was limited to cases of primary teeth with root resorption or to retain teeth for up to 12 months that otherwise

would be extracted. These recommendations were based on a systematic review (Coll, Vargas, *et al.*, 2020) that reported that for teeth with no external and internal root resorption, the NIET success rate was 65% compared to 92% of conventional endodontic treatment success rate, after 12 months of follow-up. The choice of using ZOE as the control group in the present study was based on the same systematic review (Coll, Vargas, *et al*., 2020), once the authors reported that the success of pulpectomies performed with ZOE did not differ from that observed using Vitapex after 18 months of follow-up, and was superior to iodoform alone.

NIET has been proposed as a potential alternative to conventional endodontic treatment as it is a simpler and faster technique, which does not require root canal instrumentation and multiple sessions to be concluded, even in the presence of periapical lesions. Two systematic reviews presented very low to moderate evidence that the success rate of NIET, based on clinical and radiographic findings, is similar to conventional endodonic treatment (Agarwal, et al., 2019; Duarte *et al*., 2020).

It is evident, though, that the quality of evidence and strength of recommendation on the use of NIET are still conditioned to the execution of new well-conducted randomized trials, with larger sample sizes and longer follow-ups. Furthermore, the available evidence on the success of NIET is based on studies that used the traditional (minocycline, metronidazole, and ciprofloxacin) or modified 3Mix paste. Studies on the clinical and radiographic success of the CTZ paste are limited both on quantity and quality.

To the best of our knowledge, there is only one well-conducted randomized clinical trial comparing the NIET technique with CTZ paste and the conventional endodontic treatment with ZOE paste (Moura *et al*., 2021). The 12 months of follow-up results showed no significant difference in clinical or radiographic success rates between the two techniques. In addition, the mean clinical time spent on treatment in the CTZ group was twice as short compared to the ZOE group.

The reported reduced clinical time in the CTZ group reflects the simplification of the technique (Moura *et al*., 2021), a quicker and simpler procedure, which is an advantage considering the need for children's cooperation during the treatment. In addition, the CTZ paste promotes the reduction of pathogenic bacteria within the root canals, considering those accessory canals in inaccessible locations (Garrocho-Rangel, et al., 2021). Furthermore, it was previously reported (de Oliveira *et al*., 2021) that an endodontic treatment with the CTZ paste had a 58.33% lower execution cost than the conventional endodontic treatment using an iodoform paste (US$6.73 and US$16.15, respectively). This is an important aspect to be considered especially in the public health system.

In addition to the primary outcome, patient-centered secondary outcomes will also be assessed in the present study, once the patient's perceptions and opinions are fundamental for the decision-making process on evidence-based dentistry. If our non-inferiority hypothesis is confirmed, the indication of the NIET technique with CTZ paste would be supported. Moreover, we expect that the present study protocol encourages researchers to conduct new well-designed randomized clinical trials on the topic to enhance the quality of the evidence.

4. Conclusion

The present study will evaluate the efficacy of a NIET technique using a paste containing antibiotics (CTZ paste), compared to the conventional endodontic treatment technique, to verify whether the CTZ paste is a viable treatment option for non-vital primary molars.

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