Clinical and Radiographic Evaluation of Formocresol and Chloramphenicol, Tetracycline and Zinc Oxide-Eugenol Antibiotic Paste in Primary Teeth Pulpotomies: 24 month follow up

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***Objective**: The purpose of the present study was to evaluate clinically and radiographically the effectiveness of formocresol and the antibiotic paste CTZ (chloramphenicol, tetracycline and zinc oxide-eugenol) in primary teeth pulpotomies, during a 6, 12 and 24 month period. **Study design:** A total of 80 pulpotomies were performed in 58 patients between three and six years of age. The patients were selected and assigned to two groups: Group I Formocresol (FC, n=40), Group II chloramphenicol-tetracycline-zinc oxide eugenol (CTZ, n=40). The teeth were restored with glass ionomer and pre-formed stainless steel crowns. The treated teeth were evaluated clinically and radiographically at 6, 12 and 24 months. **Results**: After 24 months of follow up a 100% and 94.3% clinical success was obtained, in the CTZ and formocresol groups respectively (x^2= 0.450, p>0.05). The radiographic success was of 97.4% and 94.3% respectively (x^2= 0.920, p>0.05). **Conclusion**: The performance of the antibiotic paste CTZ was superior to formocresol. No statistically significant differences were observed between the treatment groups either clinically or radiographically. More randomized clinical trials should be performed before it can be indicated safely.*

***Keywords**: Primary molars, pulpotomy, formocresol, antibiotic paste.*

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INTRODUCTION

One of the main goals of pediatric dentistry is to maintain adequate anatomical and functional conditions of the primary dentition until its physiologic exfoliation. This is fundamental to avoid changes in mastication, speech and phonetics, as well as to maintain the length of the dental arch, esthetics and prevention of oral habits. For this reason, all available resources must be used to avoid premature loss. [1,2]

The prevalence of dental caries in the primary dentition is still high in the pediatric population, even though efforts and advances in the promotion of oral health have been made.[3] This situation increases the possibility of pulpal affectation, exposing the tissue to oral microbiota, taking the pulp to an irreversible state, and the necessity to perform a pulpal treatment.[4,5] Currently, different techniques and protocols for pulp treatment of primary teeth, depending on the extension of the damage and pathological involvement of the pulp are available.[1,6] The pulpotomy is the main therapeutic alternative indicated for the treatment of primary teeth with vital, reversible coronal pulpal inflammation, when there is no evidence of radicular signs or symptoms of pulp degeneration.[7] This procedure is founded in the fact that after surgical amputation of the infected coronal pulp, the radicular pulp tissue stays in a healthy state, favoring the existence of a natural environment for the normal development of the succedaneous tooth.[8,9]

The ideal material for pulp capping must have good physical and biological properties, such as sealing of the pulp remnants, non-resorbable, be biocompatible and present antibacterial activity. Considering these elements is important because of the necessity to avoid errors in the endodontic treatment and diffusion of inflammatory processes throughout the root canal.[10]

Formocresol is a potent germicide used to fix viable issues. It was first used by Sweet in 1930 as a technique of multiple sessions in the pulpotomy treatment of primary teeth. The objective of this technique was mummify the tissue completely. It has been indicated that the complete fixation of the tissues theoretically devitalizes and sterilizes the radicular pulp, avoiding infection and internal resorption. Nevertheless, because of the difficulties in cooperation and for financial reasons, the time and number of sessions has been reduced.[11,12] This compound has been considered as the gold standard for the treatment of vital pulpotomies in temporary dentition for a long time. Although it has had years of successful use, concern has been raised about its potential for toxicity,[13,14] allergenicity, mutagenicity, carcinogenicity, teratogenic effects in animals,[15] chromosomal damage to dental pulp cells in tissue culture,[16] Chromosomal breaks and aberrations in peripheral lymphocytes[15] and stem cell mutagenesis.[17,18] In the presence of formaldehyde, an increased risk of myeloid leukaemia has been found.[19] In June 2011, the United States Department of Health and Human Health Services issued a report[20] that classified formaldehyde as a carcinogen for humans. The dental profession has therefore looked for alternative pulpotomy medicaments that are both clinically and biologically more acceptable.[21]

The complex anatomy of primary teeth,[22] the wide range of materials and medicaments that currently exist and the difficulty of a correct case diagnosis,[7] has favored the use of antibiotic pastes as an alternative in the endodontic therapy, mainly for is antimicrobial capacity, low cost, quick application which requires low operating time; it can also be indicated in non-cooperative patients,[23] independently from the pulpal diagnosis.[24]

This evidence has allowed, since several years in Latin America, the use of a paste based on antibiotics that contains a mixture of chloramphenicol, tetracycline and zinc oxide-eugenol called CTZ,[25] which was first described in 1959 by Spoiler and Cappiello, for the treatment of temporary molars with pulpal involvement.[2,26,27] In its composition it contains chloramphenicol 500mg, tetracycline 500mg, zinc oxide 1000mg and eugenol (1 drop),[27] of which the last two are added during the operatory act.[2]

There are studies that indicate that the effectiveness of CTZ antibiotic paste (chloramphenicol, tetracycline and zinc oxide-eugenol), is due to its antimicrobial action, mainly due to the presence in its composition of two broad spectrum antibiotics: tetracycline and chloramphenicol.[27,28,29] The first drug is an antimicrobial that acts against a large number of aerobic bacteria, facultative anaerobes and spirochetes, as well as Gram(+) and Gram(-) microorganisms. Is contraindicated in young children and pregnant women.[30] Amongst the adverse side effects, allergic and autoimmune drug reactions have been reported, however allergic reactions are considered less frequent compared to other drugs.[31] The second drug is a broad-spectrum antibiotic, which can be bactericidal at high concentrations, offers excellent effectiveness against Gram(-) bacteria and against all anaerobes; due to its great solubility allow a wide distribution by the tissues and body fluids, increasing its power of action. Its prolonged use and in very high doses can lead to adverse effects at the hematological level. According to Sanchez *et al*,[31] allergic reactions to this drug are very rare. The Zinc oxide-eugenol, provides analgesic properties and a potent antibacterial action against Staphylococcus, Micrococci, Bacillus and Enterobacteria for more than 30 days.[29]

The CTZ paste (Chloramphenicol, Tetracycline, Zinc Oxide Eugenol) application technique is easy, simple, can be performed in one session, has antibacterial power, promotes stabilization of bone resorption and does not cause tissue sensitivity.[2,28] Additionally, it does not require root canal instrumentation, regardless of pulpal diagnosis,[24] this offers a great advantage in the treatment of non-cooperative patients, facilitating the management of pediatric patient behavior,[23] reducing operative time.[2,28] However, at the moment of being employed, the pigmentation of the crown of the treated tooth must be taken into account (as a possible disadvantage).[32]

Although the clinical success is known for the conventional endodontic treatment with formocresol and the use of other materials, evidence about the use of antibiotic pastes in the pulpotomy treatment of primary molars with vital pulps is limited. The purpose of the present study was to evaluate clinically and radiographically the effectiveness of the use of antibiotic paste CTZ (chloramphenicol, tetracycline and zinc oxide-eugenol) in the pulpotomy treatment of primary molars in a 6, 12 and 24 month period.

MATERIALS AND METHOD

The study counted with the approval of the Health Sciences Area Bioethics Committee of the Zacatecas Autonomous University (File 10/014). 80 first and second temporary molars in 58 children of both sexes were selected, ages from three to six years of age, all preschoolers from the Calera de Victor Rosales municipality, in Zacatecas, Mexico. The legal representative received detailed information and signed an informed consent form as authorization for the participation in this study, and in compliance with the principles of the Helsinki Declaration.[33]

Patient selection criteria:[9,28] Cooperative patients without history of systemic disease; absence of any type of medical treatment or continuous use of any medication; absence of drug allergies, anesthetics and environmental allergies; patient and parent compliance with the treatment.

Teeth selection criterion:[9] teeth without clinical or radiographic pulpar degeneration.

Clinical selection criteria:[9,28] teeth with deep decay lesions and no symptoms; without prior treatment; with pulp vitality exposed by decay; no spontaneous pain, absence of edema, pain, fistula, pathological mobility; teeth with manageable pulpar hemorrhage.

Radiographic selection criteria:[9,28] teeth without pathological root resorption; with no periradicular or furcal radiolucency; with healthy periodontal space; Teeth with less than 1/3 physiological root resorption.

Exclusion Criteria:[28] Patients with clinical and radiographic signs and symptoms of radicular pulp degeneration, history of spontaneous pain, edema, reddening, heat, localized abscess, fetid smell from the pulp chamber and or purulent exudate, pathologic movement, evidence of cellulitis, dark and thick bleeding. Radiographically: radiolucent image in the periapical and/or interradicular region, signs of pathologic internal or external root resorption, radiolucency in root furcation.

Experimental Design: A Randomized Controlled Clinical Trial and parallel groups, through a non-probabilistic sampling by convenience was performed. The selected participants were randomly assigned to two treatment groups of 40 molars each, Group I: formocresol (n=40); Group II: CTZ antibiotic paste (chloramphenicol, tetracycline and zinc oxide-eugenol; n=40).

A trained dentist performed all pulpotomies, in one session, under absolute isolation, with local anesthesia [Scandonest® 3% (mepivacaine hydrochloride 3%), Novocol, Inc., Ontario, Canada]. Material manipulation was performed by another trained dentist. For both groups, carious tissue was removed with sterile dentin excavators #17 and #18 Hu-Friedy® and access to the pulp chamber was achieved. Afterwards, the roof of the pulp chamber was removed with sterile round carbide bur #5 at high speed. Pulp was amputated at the root canal orifice level with sterile dentin excavators and compensatory opening with sterile Endo-Z® bur DENTSPLY USA. Any remaining coronal pulp tissue was completely removed with a sharp excavator, The bleeding caused during the operatory act was controlled with physiologic serum irrigation, using disposable 10 ml syringe and dried with sterile cotton pellets, pressing for 3 to 5 minutes. After the hemorrhage ceased, one of the materials, formocresol or CTZ (chloramphenicol, tetracycline and zinc oxide-eugenol) antibiotic paste, was randomly selected and applied.

Group I–Formocresol technique (FC)

Once bleeding was controlled, a sterile cotton pellet was impregnated with formocresol solution (Viarden®) and placed in the pulp chamber for 3 minutes, after which the cotton pellet was removed from the cavity and it was confirmed that the bleeding had stopped and the pulp tissue had turned brown. Once the pulp tissue was fixed, IRM® (Dentsply-USA) cement was placed and packed to the bottom of the pulp chamber. The cavity was filled with glass ionomer cement (Ketac Molar® 3M ESPE AG, Germany).

Group II–Antibiotic paste technique (CTZ-Chloramphenicol, Tetracycline and Zinc Oxide-Eugenol): Once the cameral pulp was totally removed and bleeding was controlled, the antibiotic paste CTZ (powder formula with 500 mg Tetracycline, 500 mg chloramphenicol and ZOE, mixed with eugenol in a 1:1:2 proportion)[27] was packed to the bottom of the pulp chamber (approximate thickness 2mm), afterwards IRM® (Dentsply-USA) cement was placed and he cavity filled with glass ionomer cement (Ketac Molar® 3M ESPE AG, Germany).

Evaluation of pulpotomy treatment: Periapical radiographs were obtained immediately after the pulpotomy treatment. Fifteen days after treatment was performed, the patients were observed to corroborate absence of pathologic clinical and radiographic signs and symptoms. Afterwards stainless steel crowns (3M Dental Products® USA) were placed and cemented with glass ionomer cement (Ketac Cem®, 3M ESPE AG, Germany). Occlusion was checked and adjusted.[28] The clinical and radiographic evaluations were performed at 6, 12 and 24 months, by an operator that did not intervene in the execution of the procedures and without knowing the type of treatment performed in each one of the molars. To evaluate the success of the treatment the following criteria was considered:

Clinical evaluation: spontaneous pain; sensibility to percussion or palpation; presence of fistula, scar of fistula, change of color; purulent exudate, cellulitis, pathological mobility, lymphadenopathy of the related region.

Radiographic evaluation: presence of a radiolucency of the periapical or furcation, pathological internal or external root resorption, widening of the periodontal space, calcification of the pulp canal.

Restoration evaluation: Damage to the margins of the crown, deformities of the crown and changes in occlusion.

The presence of any of these elements previously described was considered as treatment failure.

Statistical analysis

The statistic processing of the information was performed with SPSS-Windows V17.0 (SPSS, INC, Chicago IL). For the comparison analysis, Pearson´s Chi square Test was used at a 5% significance level.

RESULTS

After 24 months of evaluation, the totality of the patients finished the study, of which 27 (46.6%) were female and 31 (53.4%) were male.

At 6 months, 92.5% success was observed in Group I (FC), while 97.5% success in Group II (CTZ- Chloramphenicol, Tetracycline and Zinc Oxide-Eugenol). In the FC group, 3 failures were observed (reddening and swelling of the gingiva). In the CTZ group, one failure was registered (scar of fistula) (x^2=0.610, p>0.05). For the 12 month evaluation, 94.6% of success in the FC group was presented, meanwhile 94.9% in the CTZ group. Among the failures, two cases of fistula scarring and mobility in the FC group, while two cases of gingival reddening and swelling in the CTZ group were observed. (x^2=0.648, p>0.05). At the end of 24 month, the clinical success rates for FC and CTZ were 94.3% and 100% respectively; only two failures were observed in the FC group showed sinus tract (x^2=0.450, p>0.05) Table 1.

Radiographic evaluation

At 6 months, two of the treated molars with FC presented irregular widening of the periodontal ligament space, while one molar of the CTZ group maintained a radiolucent image at the furcation level (x^2=1, p>0.05). At the 12 month evaluation, the radiographic failures observed in the CTZ group (1 irregular widening of the periodontal ligament space) were less (5%) than in the FC group (7.9%); 2 radiolucent images in apical and at furcation level, and 1 irregular widening of the periodontal ligament space (x^2=0.590, p>0.05). By the end of 24 months follow-up, the overall failure radiographically was three, two in FC group (radiolucent images in apical and at furcation level) and one in CTZ group (irregular widening of the periodontal ligament space), which was statistically not significant (x^2=0.920, p>0.05) Table 1.

Clinical/radiographic evaluation

In **Table 2**, a relation of the clinical and radiographic findings for both groups at 6 months is presented, in the FC group 92.5% (37) clinical success was observed, however, clinical and clinical/radiographic failures were found 7.5% (3), and 5% (2) respectively; for the CTZ group clinical success of 97.5% (39), with only one clinical/radiographic failure was found (x^2=0.643, p>0.05). At 12 months, the clinical/radiographic failures for the FC group was 5.4%, meanwhile in the CTZ group was 2.6% (x^2=0.710, p>0.05). After 24 months of follow-up, only the FC group presented two (5.7%) clinical/radiographic failures (x^2=0.207, p>0.05) Table 2.

Table 1. Clinical and Radiographic Success-failure of materials at 6th, 12th and 24th months (FC: Formocresol, CTZ: Chloramphenicol-tetracycline-Zinc Oxide and Eugenol)

	Clinical Follow-up						Radiographic Follow-up					
	6th months		12th months		24th months		6th months		12th months		24th months	
Groups	Success	Failure	Success	Failure	Success	Failure	Success	Failure	Success	Failure	Success	Failure
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
FC (n=40)	37 (92.5)	3 (7.5)	35 (94.6)	2 (5.4)	33 (94.3)	2 (5.7)	38 (95)	2 (5)	35 (92.1)	3 (7.9)	33 (94.3)	2 (5.7)
CTZ (n=40)	39 (97.5)	1 (2.5)	37 (94.9)	2 (5.1)	37 (100)	0 (0.0)	39 (97.5)	1 (2.5)	38 (97.4)	1 (2.6)	37 (97.4)	1 (2.6)
Total (n=80)	76 (95)	4 (5)	72 (94.7)	4 (5.3)	70 (97.2)	2 (2.8)	77 (96.2)	3 (3.8)	73 (94.8)	4 (5.2)	70 (95.9)	3 (4.1)
	*p = 0.610		*p = 0.648		*p = 0.450		*p = 1		*p = 0.590		*p = 0.920	

* Chi square test

Table 2. Comparison of Clinical and Radiographic Behavior at 6th, 12th and 24th months (FC: Formocresol, CTZ: Chloramphenicol-tetracycline-Zinc Oxide and Eugenol)

Groups	6th months				12th months				24th months			
	CS	CF	RF	CR	CS	CF	RF	CR	CS	CF	RF	CR
	n	n	n	n	n	n	n	n	n	n	n	n
FC	37	3	2	2	35	2	3	2	33	2	2	2
CTZ	39	1	1	1	37	2	1	1	37	0	1	0
Total	76	4	3	3	72	4	4	3	70	2	3	2
	*p = 0.643				*p = 0.710				*p = 0.207			

CS: Clinical Success; CF: Clinical Failure; RF: Radiographic Failure; CR: Clinical and radiographic failure; +Sum of failures; *Chi square test.

DISCUSSION

Pulp therapy in primary teeth occasionally results difficult to perform; difficulty in behavior management of the infant patient, the morphologic differences of primary teeth, the complexity of the root canals, low certainty in the root resorption process, and the difficulty for the placement of the material inside the root canals are common causes.[34]

Treatment alternatives proposed for this therapy are pulpotomy and pulpectomy. Pulpotomy is a common treatment procedure for cariously exposed pulps in primary teeth. This procedure helps to maintain the integrity of primary teeth that have inflammation limited to the coronal pulp. The main goals for this technique are to preserve the radicular pulp, maintain vitality and ultimately to retain the tooth.[35] On the other hand, pulpectomy is a radical treatment used when the pulp is in an irreversible pathologic state, where all the pulp tissue is removed, both coronal and radicular, eliminating all bacteria present.[28]

The use of antibacterial drugs topically and systemically, has been practiced in medicine and dentistry for years, mainly to treat infectious processes associated to teeth with pulpal affection. It has been reported that administrating an antibiotic systemically, only a small part of the concentration of the drug reaches the root canal, which has little benefit; for this reason, the application of local antibiotics allows to administer higher concentrations and avoid complications.[36]

This evidence has permitted the installment of non-instrumented endodontic treatment for several years in the Pediatric Dentistry Postgraduate Program Clinic of the Zacatecas Autonomous University, through the use of an antibiotic paste which contains a mixture of antibacterial drugs for the treatment of teeth with pulp affection and doubtful prognosis. This biologic approach is considered innovative, because no mechanical instrumentation is required, which avoids the widening of the root canals, unnecessary irritation of the periapical tissues, reduction of operatory time (being done in one visit) and being able to be applied in a satisfactory way in small children during early childhood.[28,34]

One of the main difficulties found was the scarce literature conclusive about the subject, especially when it comes to vital pulpotomies, reason for which in vitro, in vivo, and necrotic pulp research was used, where its effectiveness and biocompatibility was demonstrated, which are considered main reference parameters for the study of biological properties, especially for materials that are in the mouth for a prolonged time.

During the evaluations, our results did not show statistically significant differences in the success and failure rates between the groups. However, a clinical efficacy of 94.6% (12 months) and 94.3% (24 months) in the FC group was found, similar to studies of 12 and 24 months of follow-up reported by Yildirim *et al* [9] 96.9%, Ruby *et al* [37] 100%, Aminabadi *et al*[38] 90% and Sunitha *et al* [39] 94%. In respect of the radiographic success of FC, it was 92.1%

(12 months) and 94.3% (24 months), this differs from previous studies of Alolofi *et al* [35] 73.3%, Juneja *et al* [40] 73.2%, Ansari *et al* [41] 67.7%, and Havale *et al* [15] 56.7%. It has been indicated that formocresol is able to fix superior parts of the radicular pulp tissue rather than stimulate healing. The apical part of the pulp showed characteristics of inflammation, which in turn increases the probability of periapical changes.[35]

The group of molars that received the application of CTZ paste (Chloramphenicol, Tetracycline and Zinc Oxide-Eugenol) obtained high success rates of clinical and radiographic efficiency of 94.9% and 100% at 12th and 24th months of evaluation, respectively. These results concur with previous studies by Takushige *et al* [42,43], who observed good clinical evolution in 95% of molars treated with non-instrumented-antibiotic paste technique. It also concurs with Nakornchai *et al* [44] who reported 100% clinical success and 76% radiographic success, and with Luengo *et al*[28] who found 80% clinical and radiographic success. On the other hand, they slightly differ, from the clinical view, from the values reported by Trairatvorakul[45] who shows 75% of clinical success and low radiographic success of 36.7%. Mariz *et al* [2] reported a 60.6% of clinical success and 54.5% radiographic, while Daher *et al* [36] indicated low clinical and radiographic success 27.8%, widely differing from our findings.

A previous study suggests that the clinical success of CTZ paste can be attributed to the fact that in primary teeth, the presence of accessory conducts, porosity and permeability in the pulp chamber floor indicate a probable connection between the pulp tissue and the periodontal tissues. The combination of antibacterial drugs can dissipate easily through these regions and induce a sterile zone. Another important factor is the antisepsis performed in the zone and the placement of the paste that with its bacteriostatic action reduces the bacterial load, since its placement, the existing microbiota is modified making the number of microorganisms decrease and modifying their pathogenicity.[28]

Finally, the pulpotomy with CTZ is a minimally invasive technique and does not require filing or widening of the root canals, permitting the culmination of the treatment procedure in one visit, facilitating a better behavior management of the pediatric patient, and therefore reducing operatory times. Nonetheless, a higher amount of controlled clinical studies, where not only is the efficacy is evaluated, but it is compared with other medicaments in an effective way for the pulp treatment of temporary teeth is suggested and recommended.

CONCLUSION

The antibiotic paste CTZ (Chloramphenicol, Tetracycline and Zinc Oxide-Eugenol) does not demonstrate statistical superiority to formocresol, so its use for the treatment of pulpotomies of teeth with vital pulps is not fully justified and the possible risk of allergic reactions in patients must be considered. More randomized clinical trials should be performed before it can be indicated safely.

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