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Use of Glass Ionomer Cement Containing Antibiotics to Seal off Infected Dentin: a Randomized Clinical Trial

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Dental materials with antibacterial properties can prevent the harmful effects caused by oral cariogenic bacteria. This double-blind controlled clinical trial evaluated the performance of a glass ionomer cement (GIC) added with antibiotics for sealing infected dentin in atraumatic restorations of primary molars. The study enrolled 45 children (45 teeth) between 5 and 8 years of age, of both genders, divided into two groups: GC (n=22), where cavities were lined with a conventional GIC (Vidrion F) and GA (n=23), with cavities lined with Vidrion F added with 1% each of metronidazole, ciprofloxacin and cefaclor antibiotic. Both groups were restored with Ketac Molar Easymix. Molars with carious lesions on the inner half of dentin without clinical or radiographic pulp damage were selected. Patients were evaluated clinically (pain, fistulas or mobility) and radiographically (area of caries, periapical region and furcation) after 1, 3, 6 and 12 months. For statistical analysis, chi-squared or Fisher's exact tests were used with a 5% significance level. GA (82.6-95.7%) had better results than GC (12.5-36.4%) in all evaluations ($p<0.05$) and the difference in the success rate was 46.2-72.5% higher for GA. The use of the antibiotic-containing GIC liner on infected dentin proved satisfactory when applied in deciduous teeth.

Key Words: antibacterial agents, primary teeth, clinical trial.

Introduction

Currently, minimally invasive treatment of carious lesions has been emphasized in the literature (1). In this context, the ideal limit for removal of carious tissue has been questioned, including the need of total removal of infected and softened dentin to control the progression of dental caries (2-4). Additionally, the use of dental materials with antimicrobial properties that can induce the recovery of the remaining carious tooth has been discussed. Such products would decrease surviving microorganisms and, consequently, bacterial growth and pulp injury (3,5-9).

As an option to dental materials with antimicrobial properties, conventional glass ionomer cement (GIC) liner was mixed with 1% each of metronidazole, ciprofloxacin and cefaclor to produce an antibacterial GIC. In a laboratory evaluation of infected dentin sealed with this product, there was a 98.6% decrease in microorganisms, bacterial aggregates, and intertubular dentin with exposed collagen fibers and dentinal tubules (3). When conventional GIC was added with 1.5, 3.0 and 4.5% of ciprofloxacin, metronidazole and minocycline it was effective for inhibiting *S. mutans* and *L casei,* and the addition of a 1.5% antibiotic mixture was optimal to provide appropriate physical and bonding properties (7).

Following the principle of minimally invasive dentistry, atraumatic restorative treatment (ART) involves the simplified removal of carious tissue using hand instruments only and restoration with GIC, with satisfactory clinical and laboratory results (10-12), but there are no short-term randomized clinical trials testing the use of antibiotics combined with GIC for such purpose.

Since ART is a strategy for promoting oral health, it is important to evaluate dental materials that might reduce the number of viable bacteria in carious dentin, which would confer greater applicability of that strategy because it could also be used in deep cavities.

This study evaluated the clinical and radiographic effects of an antibacterial GIC as liner material in atraumatic restorations of primary molars without removing infected dentin.

Material and Methods

This study was conducted ethically according to the Helsinki Declaration and was approved by the Ethics Committee of the Center for Health Sciences of Federal University of Paraíba, João Pessoa, PB, Brazil (Process #1535/07) and the clinicaltrials.gov identifier was NCT01449136.

This was a randomized, double-blinded clinical trial. The products were similar in form, color, weight and packaging, except for the label with the code "A" and "B". Neither the professional nor the patients were aware of the content in the packages. The products were tested alternately according to the type of dental cavity to be restored (single or multiple surfaces) to obtain stratified

randomization (p>0.05) taking into consideration the shape of the cavity in each group to avoid bias. Hence, if product A was used in a cavity, the next similar cavity would receive product B. The first product to be used was selected from a list of even and odd numbers equivalent to product A and B, respectively. This information was disclosed by the druggist only at the moment of statistical analysis. Product A was GIC without antibiotics and product B was GIC with antibiotics.

Regarding the eligibility criteria, patients were enrolled if they had carious lesions on the inner half of dentin and it was estimated as reaching half the distance between the dentinoenamel junction and the pulp chamber or the pulp horn (2) with access to dentin spoons of a primary molar. An informed consent for was signed by parents or guardians. Exclusion criteria included children presenting primary molars with damaged pulp diagnosed clinically (pain, fistulas, tooth mobility) or radiographically (bone or dental pathology), taking antibiotics, and those who refused the treatment or had any systemic disease. Participants were evaluated for exclusion criteria in Brazilian public schools. Inclusion criteria were verified in a private dental office.

Forty-five children (45 primary molars) from 5 to 8 years of age were randomly divided into two groups: group GC (n=22) was lined with conventional GIC (Vidrion F; SS White, Rio de Janeiro, RJ, Brazil) and group GA (n=23) was lined with Vidrion F mixed with 1% each of metronidazole, ciprofloxacin and cefaclor antibiotics (Formula & Ação, São Paulo, SP, Brazil). The dentin conditioner was 11.5% polyacrylic acid (Vidrion Condicionador de Dentina; SS White) and the restorative material for both groups was Ketac Molar Easymix (3M ESPE, São Paulo, SP, Brazil). The sample was calculated considering a maximum acceptable error of 5%, power of 70%, equal to 1.0 ratio between the two products, expected difference of 5 between groups, which resulted in at least 21 cases for each group, using the Epi Info (version 6.0) software.

Each tooth was isolated from contact with saliva using cotton rolls. Only enamel caries were removed with dentin spoons (3). With this procedure, a modification of the atraumatic restorative treatment was performed. Matrix and a wedge were placed as needed. The site was conditioned with polyacrylic acid for 30 s, washed (15 s) and dried (5 s). The GIC liner and the GIC restorer were handled

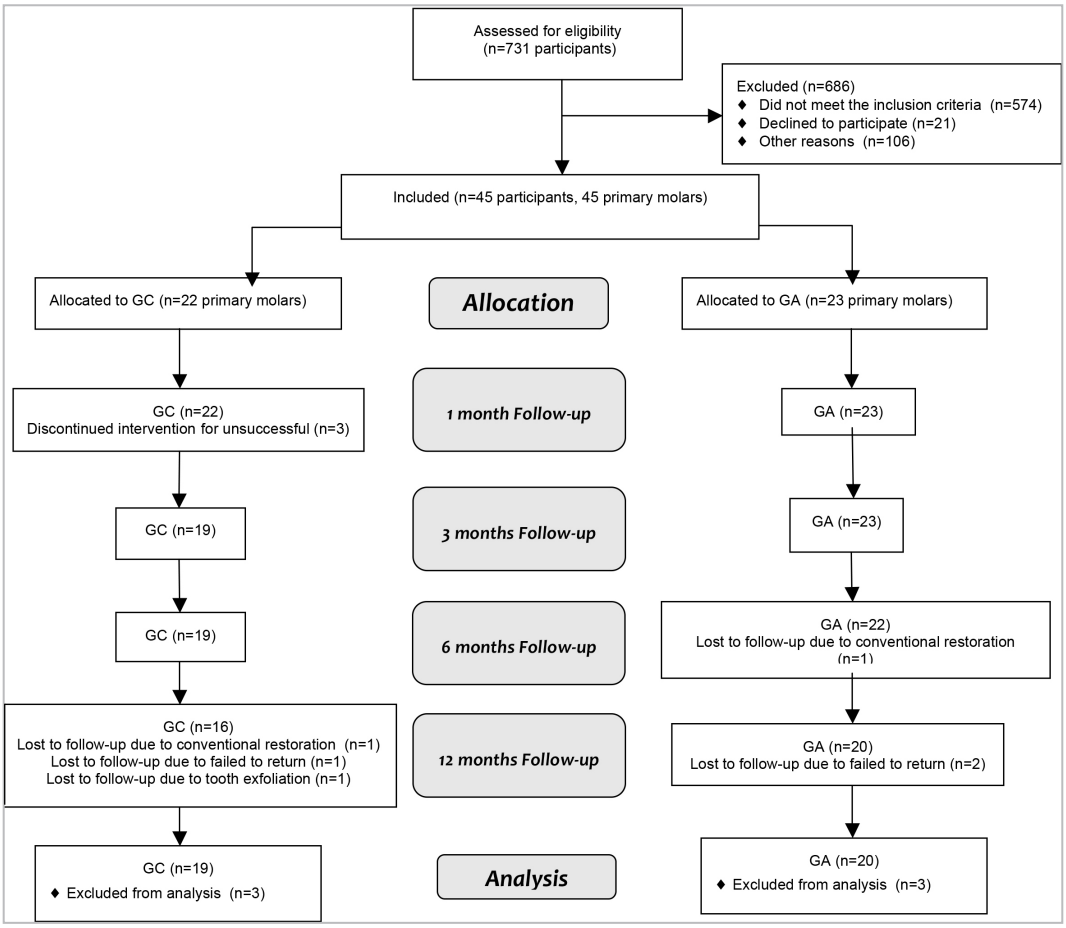

Figure 1. Diagram showing the flow of participants at each stage of the randomized trial. CONSORT (Consolidated Standards of Reporting Trials), 2010.

and inserted according to the manufacturer's instructions. Finger pressure was applied, the restoration was protected with petroleum jelly and after occlusal adjustment, the final restoration was protected again with petroleum jelly.

Periapical radiographs were obtained using the parallelism technique with film-holders and a 0.5 s fixed exposure time. They were manually processed in a portable darkroom: 90 s for developing, washed for 15 s, fixed for 10 min, washed in tap water and were allowed to dry.

Clinical and radiographic evaluations were performed initially, and after 1, 3, 6 and 12 months. Figure 1 shows the flow of the participants through each stage of the randomized trial, according to CONSORT (Consolidated Standards of Reporting Trials) (13). All procedures and clinical and radiographic examinations were performed by a single, previously trained and calibrated researcher.

Intra-examiner differences in the clinical (retention of the restoration) and radiographic (qualitative and quantitative) criteria were evaluated using Kappa statistics. Ten percent of the sample was reexamined and the results were interpreted using a scale (14).

Absence of pain, fistula and tooth mobility throughout the study was considered as clinical success. The radiographic examination was quantitative and qualitative. All the radiographs were compared with the initial radiographs. The quantitative analysis evaluated the changes in the radiographic imaging of the carious lesions (increased, decreased, unchanged) (15). The radiographs were digitized and sent to a software company (Radiomemory; Radiocef Studio2, Belo Horizonte, MG, Brazil) to accurately measure distances between anatomical points selected by the operator. The greatest mesiodistal (horizontal) and inciso-gingival (vertical) diameters of the carious lesions (radiolucent zone beneath the restoration) were measured and converted into areas. The quantitative analysis was considered satisfactory when the area of caries decreased or remained unchanged when compared to baseline.

The qualitative analysis examined radiographic changes in the periapical region and furcation of teeth. Changes were considered satisfactory when no bone or dental disorder was detected and unsatisfactory when inter-radicular or periapical radiolucencies, or external or internal resorption was detected (16). Radiographic success was defined as a decrease or no change in the area of caries together with absence of bone or dental disorders.

Overall success was defined as clinical and radiographic success achieved simultaneously. During the study, conventionally restored or exfoliated teeth and patient non-attendance were considered as lost cases.

Data were analyzed using descriptive (absolute and percentage) and inferential (Fisher's exact and chi-square tests) statistics with significance level at 5%. The SPSS (version 13.0; SPSS Inc., Chicago, IL, USA) was employed for the analyses.

Results

The sample consisted of 45 children: 29 (64.4%) girls and 16 (35.6%) boys. The most prevalent age was 6 years (n=16, 35.6%), followed by 7 years (n=15, 33.3%), 5 years (n=10, 22.2%), and 8 years (n=4, 8.9%). The family income of the majority (73.3%) was up to the national minimum wage (US$ 255.00). Most parents (84.4%) had over 5 years of schooling.

The intra-examiner agreement was k=0.87 for the marginal integrity of the restoration, k=0.91 for the quantitative radiographic examination and k=0.86 for the qualitative radiographic examination. All of these are considered good reliability coefficients (14).

As regards the evaluation of clinical success at different follow-up times, it was observed that GA (100.0%) had better results than GC (86.4%) in 1-month follow-up with no significant difference between the products (p=0.109, Fisher's exact test). In the other follow-up periods, GC and GA obtained 100% of clinical success and the statistical performance could not be determined due to the lack of clinical categories about failure of both groups. There were three cases of clinical failure in GA.

Table 1 presents the differences in caries area between baseline and the evaluations performed at 1, 3, 6 and 12 months according to the group (radiographic quantitative analysis). The success rate (decreased + unchanged) observed in auxiliary calculations was higher in GA (95.6-82.6%) than in GC (12.5-45.5%) and the differences were significant at all time points ($p<0.05$).

About the qualitative radiographic analysis at different follow-up times, it was observed that GA (100.0%) had better results than GC (86.4%) at 1-month follow-up, with no significant difference between the products (p=0.109, Fisher's Exact test). In the other follow-up periods, GC and GA obtained 100% of satisfactory qualitative radiographic analysis and the statistical performance could not be determined due to the lack of unsatisfactory qualitative radiographic analysis of both groups. During the study, there were three unsatisfactory qualitative radiographic analyses for GA.

Table 2 shows the overall success (clinical and radiographic) for each period, according to group. There were significant differences between groups ($p<0.05$) and GA outperformed GC. The difference in success rates between groups observed in auxiliary calculations was 46.2% (82.6% vs. 36.4%) at 1 month, 64.1% (95.7% vs. 31.6 %) at 3 months, 69.8% (90.9% vs. 21.1%) at 6 months and 72.5% (80.0% vs. 12.5%) at 12 months.

Figures 2 and 3 show the performance of antibacterial

GIC as liner material in the atraumatic restoration when no infected dentin was removed.

Discussion

The restorative material used in this study (Ketac Molar Easymix) was selected because of its reported satisfactory clinical performance in atraumatic restorations (17,18). Although the literature (18) indicates that the success of ART is lower for cavities with multiple surfaces, these were included in the study due to the difficulty in obtaining teeth that met the inclusion criteria. There was no significant difference between the allocation to GC and GA according to the number of surfaces.

It is worth mentioning that the marginal integrity of restorations could also influence the performance of the tested liner material because an adequate seal restricts the substrate in the microenvironment of the cavity, reducing the viability of microorganisms (19). Also, ART success is influenced by the operator's skills (11) and so a single researcher performed all atraumatic restorations in order to mitigate this bias.

Regarding the liner, a GIC with antibiotics (metronidazole, ciprofloxacin, cefaclor) was chosen because of good preliminary laboratory results and its possible use for the treatment of caries in primary teeth (3). The combination of metronidazole, ciprofloxacin and cefaclor with other dental materials has shown biocompatibility and an antibacterial effect in laboratory and clinical studies(3,20-22), suggesting satisfactory repair of the dentin-pulp complex.

When assessed alone in the clinical and qualitative radiographic examinations, the performance of GC was numerically lower than that of GA, but the groups did not differ significantly at the 1-month follow-up. On the other hand, the performance of GA was significantly superior to

Table 1. Quantitative radiographic analysis, according to group

Differences among caries areas	Vidrion F		Vidrion F + antibiotics		Total group		p values
	n	%	n	%	n	%	
Baseline - 1 month							
Decrease	4	18.2	17	73.9	21	46.7	$p^{(2)} = 0.001^*$
Unchanged	6	27.3	2	8.7	8	17.8	
Increase	12	54.5	4	17.4	16	35.6	
Total[1]	22	100.0	23	100.0	45	100.0	
Baseline - 3 months							
Decrease	4	21.1	21	91.3	25	59.5	$p^{(3)} < 0.001^*$
Unchanged	2	10.5	1	4.3	3	7.1	
Increase	13	68.4	1	4.3	14	33.3	
Total[1]	19	100.0	23	100.0	42	100.0	
Baseline - 6 months							
Decrease	3	15.8	19	86.4	22	53.7	$p^{(2)} < 0.001^*$
Unchanged	1	5.3	1	4.5	2	4.9	
Increase	15	78.9	2	9.1	17	41.5	
Total[1]	19	100.0	22	100.0	41	100.0	
Baseline - 12 months							
Decrease	2	12.5	16	80.0	18	50.0	$p^{(2)} < 0.001^*$
Unchanged	-	-	1	5.0	1	2.8	
Increase	14	87.5	3	15.0	17	47.2	
Total[1]	16	100.0	20	100.0	36	100.0	

(*) Significant difference at 5%. (1) The difference in the values of n was due to the fact that one tooth has not been assessed. (2) Using the Fisher's Exact test.

that of GC in the quantitative radiographic analysis (Table 1).

The high percentage of overall success of atraumatic restorations lined with the antibacterial GIC (Table 2) in this study suggests that the carious lesions stagnated or that dentin bridges were formed. These observations need further evaluation.

The conventional GIC reduced significantly the amount of microorganisms in carious dentin (16). It seems that the superior performance of the antibacterial GIC used in this study was due to the addition of the antibiotics. They may have increased the antimicrobial activity of the conventional GIC, resulting in a significant reduction or total inactivation of the microorganisms in dentin (3). Thus, using antibacterial GIC as a liner material preserves dental tissues and reduces the risk of pulp exposure and the need of repairing the remaining dentin, consistent with the precepts of minimally invasive dentistry (1).

Table 2. Evaluation of the overall success at different follow-up times, according to group

Overall success	Vidrion F		Vidrion F + antibiotics		Total group		p values
	n	%	n	%	n	%	
1 month							
Yes	8	36.4	19	82.6	27	60.0	$p^{(2)} = 0.002^*$
No	14	63.6	4	17.4	18	40.0	
Total	22	100.0	23	100.0	45	100.0	
3 months							
Yes	6	31.6	22	95.7	28	66.7	$p^{(2)} < 0.001^*$
No	13	68.4	1	4.3	14	33.3	
Total[1]	19	100.0	23	100.0	42	100.0	
6 months							
Yes	4	21.1	20	90.9	24	58.5	$p^{(2)} < 0.001^*$
No	15	78.9	2	9.1	17	41.5	
Total[1]	19	100.0	22	100.0	41	100.0	
12 months							
Yes	2	12.5	17	85.0	19	52.8	$p^{(2)} < 0.001^*$
No	14	87.5	3	15.0	17	47.2	
Total[1]	16	100.0	20	100.0	36	100.0	

(*) Significant difference at 5%. (1) The difference in the values of n was due to the fact that one tooth has not been assessed. (2) Through the chi-square test.

We therefore recommend the use of GIC with antimicrobials in infected carious lesions, corroborating with other authors (3,5,7,8), who obtained good laboratorial performance with these products.

The treatment protocols for dental caries in dentistry are changing and the principle of complete removal (20,21) has been replaced by the partial removal of carious tissue (15,23). The fact that the clinical and qualitative radiographic analyses showed high success rates in both groups at all evaluations (Tables 1 and 2) leads to a discussion of the ideal limit for removing carious tissue. Increasingly, controlled clinical trials (3,16) and a laboratory study (3) suggest that less invasive measures are effective in controlling dental cavities,

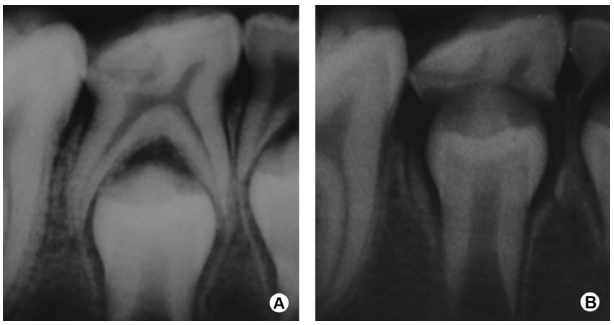

Figure 2. Radiograph of carious lesion in the primary mandibular right second molar (NSBS) at baseline (A) and 12-month follow-up period (B). A decrease of area of caries was observed at final evaluation.

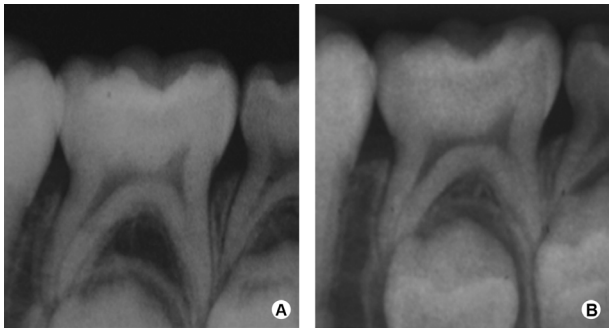

Figure 3. Radiograph of carious lesion in primary mandibular right second molar (NLG) at baseline (A) and 12-month follow-up period (B). A increase of area of caries was observed at final evaluation.

such as sealing infected dentin. Additionally, systematic reviews (3,4) report that the total removal of infected dentin is unnecessary for the treatment of dental caries and no scientific evidence has been produced demonstrating that the continued survival of this tissue is harmful. Since a large portion of the population has no access to dental services (24), adoption of simplified, effective strategies for arresting dental caries such as ART is of paramount importance.

Although the use of antibacterial GIC as a liner for deep cavities was not originally part of the ART technique (9), the adaptation of this technique should expand the population that can be provided this type of dental care and may reduce tooth loss, by increasing the applicability of ART. Therefore, the use of an antibacterial GIC is a promising option in public health and pediatric dentistry, contributing to the rationalization of dental practice. Additionally, new dental materials being developed *in vitro*, as a restorative GIC with the antibiotics ciprofloxacin, metronidazole and minocycline (GC; Fuji IX, Tokyo, Japan) (7) might simplify the operative steps used in this study.

Further clinical and laboratory studies should be conducted on the use of antibacterial GIC with other restorative materials in the primary and permanent dentition and comparisons with other antibacterial liners to prove the effectiveness of its routine use in dental practice.

The use of antibacterial GIC liner on infected dentin in atraumatic restorations proved satisfactory. This product is a useful, minimally invasive approach to primary teeth.

Resumo

Os materiais dentários com propriedades antibacterianas podem proteger os efeitos nocivos causados por bactérias cariogênicas. Este ensaio clínico controlado duplo-cego avaliou o desempenho do cimento de ionômero de vidro (CIV) associado à antibióticos no selamento da dentina infectada em restaurações atraumáticas de molares decíduos. O estudo envolveu 45 crianças (45 dentes) entre 5 e 8 anos de idade, de ambos os sexos, divididos em dois grupos: GC (n=22), onde as cavidades foram forradas com CIV convencional (Vidrion F) e GA (n=23), onde as cavidades foram forradas com Vidrion F contendo 1% de cada um dos antibióticos metronidazole, ciprofloxacina e cefaclor. Ambos os grupos foram restaurados com Ketac Molar Easymix. Molares com lesões de cárie na metade interna da dentina, sem danos pulpares clínicos ou radiográficos foram selecionados. Os pacientes foram avaliados clinicamente (presença de dor, fístulas ou mobilidade) e radiograficamente (área de cárie, região periapical e de furca dos dentes), após 1, 3, 6 e 12 meses. Para a análise estatística o Qui-quadrado ou Exato de Fisher foram utilizados com 5,0% de significância. GA (82,6-95,7%) obteve melhores resultados do que GC (12,5-36,4%) em todas as avaliações ($p<0,05$) e a diferença na taxa de sucesso foi de 46,2-72,5% maior para GA. O uso do CIV com antibióticos no forramento da dentina infectada foi satisfatório em dentes decíduos.

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