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Randomized controlled clinical trial of resin infiltration in primary molars: 2 years follow-up

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ABSTRACT

Objective: The aim of this split-mouth, randomized, controlled clinical trial was to evaluate the efficacy of resin infiltration in controlling the progression of non-cavitated proximal lesions in primary molars after two-years follow-up.

Methods: Fifty healthy children presenting at least two primary molars with proximal lesion detected radiographically (in the inner half of enamel or the outer third of dentin) were included in the study. The proximal lesions were randomly allocated into resin infltration + flossing (test group) or flossing (control group). All patients received oral hygiene instructions for daily brushing with fluoride toothpaste (1100 ppmF) and flossing. The proportion of caries progression was compared using the McNemar test. The main outcome after 2-years, caries progression in the radiography was assessed by pair-wise reading by an independent examiner who was blind regarding the treatment.

Results: The sample comprised 28 (56%) girls and 22 (44%) boys with a defs of 7,3 (SD = 6,5), mainly of moderate (46%) to high (48%) caries risk. Results after one year were published previously. After 2-years, 29 (58%) patients were assessed. Caries progression was observed in 24.1% (7/29) of the test lesions, compared with 55.2% (16/29) of the control lesions (p = 0.012). The therapeutic effect was 31.1% and the relative risk reduction (RRR) was 56.3%. Eigth lesions from the control group and two lesions from the test group progressed to the inner third of dentin and were restored.

Conclusions: In conclusion, resin infiltration was more efficacious in controlling proximal caries lesions in primary molars than non-invasive approach alone. Clinical Significance: The results indicate that resin infiltration was an efficacious method in controlling proximal caries lesions in primary molars after 2 years, even in patients with high caries risk, reaffirming the results of 1-year follow-up.

1. Introducion

Dental caries is a multifactorial, biofilm-mediated and sugar-driven disease [1] with high prevalence in several countries [2]. In Brazil this reality is not different. At 5 years of age only 16.4% of the children were considered free of caries according to the last national survey. Among those with caries, the carious component represented 80.2% of the dmft index [3]. Non-operative strategies are the key measures to reduce caries prevalence, focusing directly on the factors modulating the disease including bioiflm control, use of fluoride dentifrice and diet orientation [4,5]. Non-cavitated lesions can be controlled without restorations [6,7], however, invasive measures are often necessary in the case of non-improvement of the quality of oral hygiene and consequent caries progression to cavitation [8].

In 2007 a new alternative emerged as an option for the treatment of non-cavitated proximal carious lesions, the technique of infiltration with low viscosity resin [9,10]. This micro-invasive treatment represents a alternative between the non-invasive procedures and the invasive restorative treatment. It is a highly fluid, light-curing, low viscosity resin which, after conditioning the tooth surface with a strong acid (15% HCl for 2 min) to erode the superficial layer of the enamel caries, penetrates into the carious lesion body. The resin creats a mechanic barrier that occludes the diffusion pathways of the acids derived from the fermentation of the biofilm, resulting in the control of caries progression [11–13].

The first clinical results of proximal caries infiltration with low

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viscosity resin were published in 2010. In Germany, a study was conducted with young adults [14] and in Greenland, with children [15]. These studies showed that resin infiltration was more efficacious in controlling incipient proximal lesions when compared to placebo or conventional non-operative treatment. The therapeutic effect was 30% in permanent and 38.4% in deciduous teeth after a follow-up of 18 and 12months, respectively. Several other studies were performed on permanent molars [14,16–20], but only few studies were published comparing infiltration with conventional non-operative treatment in primary molars. One study was carried out in Brazil [21] with high to moderate caries risk children and another one was done in New Zeland [22] with moderate to low caries risk children. These two studies showed after 1 year and 2 years follow-up that resin infiltration had a therapeutic effect of 211% and 20.8%, respectively.

More recently, systematic reviews on caries infiltration have been published and highlighted that this is a promising alternative to control proximal caries [23–25]. In permanent teeth, there is robust evidence that resin infiltration is more efficacious than non invasive treatment alone for arresting proximal carious lesions [26]. However, no solid conclusions can be drawn regarding primary teeth [27]. This systematics reviews suggested that more clinical trials with longer periods are necessary [23,24,27]. Therefore, the objective of this randomized controlled clinical trial was to evaluate the efficacy of resin infiltration in hampering proximal caries lesions in primary molars after a period of 2 years.

2. Methods

This split-mouth controlled randomized clinical trial followed the CONSORT recommendations [28] and is registered in ClinicalTrials.gov (NCT01726179). Ethical approval was given by the ethical committee from the Federal University of Rio de Janeiro (65,726). Parents or guardians signed an informed consent.

2.1. Sample, Baseline data, Randomization and Intervention

This clinical trial was conducted on healthy children, between 5 and 9 year-old s in Rio de Janeiro, Brazil. Sample size was calculated based on the proportion of proximal caries progression observed in a previous split-mouth study with primary molars [15]. Assuming a progression rate of 23% of the test lesions and 62% of the control lesions, based on a two-sided test, considering a level of significance of 5% and power of 80%, a sample size of 25 individuals (25 lesions in each group) was required to complete the study. With the estimative of 30% of drop out, at least 33 individuals should be selected for the study.

Individuals were selected among the children attending the Pediatric Dental Clinic at the Federal University of Rio de Janeiro for routine dental treatment in 2013/2014. Children aged 5–9 years, presenting at least two pairs of adjacent primary molars with proximal contact were considered eligible (n = 130). After screening, 80 children were excluded due to systemic diseases, non cooperate behavior, primary molars supposed to exfoliate in less than two years, or proximal caries lesions showing obvious cavitation or clear sings of inactivity after tooth separation. Thus, 50 children fullfilled the inclusion criteria and had a pair of digital bitewing radiographs taken with individualized film-holders [21]. The digital radiographic images were stored using CliniViewTM software (Version 9.3.0). A experienced investigator scored the proximal caries lesions according to the radiolucency depth in: E1-radiolucency confined to the outer half of enamel, E2-radiolucency involving the inner half of enamel, D1-radiolucency in the outer third of dentin, D2-radiolucency in the middle third of dentin, and D3-radiolucency in the inner third of dentin [29]. Inclusion criteria required at least two primary molars with proximal lesions scored as E2 or D1 with an adjacent tooth surface sound or presenting a proximal lesion of less depth. Only one lesion per tooth was selected (Fig. 1).

At the first appointment, caries risk was assessed based on caries index [30], proximal plaque index [31], gingival bleeding index [32], dietary habits, and exposure to fluorides. The patient's caries risk was classified as low (up to 33%), moderate (from 34 to 66%) or high (more than 66%) based on the Cariogram model [33]. A single calibrated examiner assessed the clinical parameters and an assistant was in charge of interviewing parents regarding the remaining data of the caries risk form. All children received standard dental care in relation to their individual needs in the pediatric dental clinic.

Each child participated in the study with two proximal lesions: one for the control group (flossing) and one for the test group (resin infiltration + flossing). If more than two lesions were present, two of them were selected by chance. The number of elegible teeth were written on separate pieces of paper and put into a box and then two of them were drawn out of the box in a random manner. For the randomization into test or control group, the selected teeth were organized according to the sequence from tooth 55 to 65 in the upper arch and from 75 to 85 in the lower arch. The first tooth in the sequence was allocated by flipping a coin to test or control and the other tooth was automatically allocated to the other group [21]. Patients and their caregivers were instructed to floss once a day and brush with fluoridated toothpaste twice daily. The treatment (resin infiltration) of the test lesions was performed by a single trained investigator following the manufacture's intruction for the infiltration technique (low viscosity resin - Icon, DMG®, Hamburg, Germany).

2.2. Outcome and follow up

The main outcome was the proportion of caries progression assessed radiographically in the test group in comparison with the control group. Clinical assessment of proximal plaque, proximal gingival bleeding and dental caries was done at baseline, 6-months, 12-months, 18-months and 24-months by two trained examiners (intra examiner agreement for dental caries ranged from 90.2%, kappa 0.65, to 98.3%, kappa 0.75; and inter agreement from 90%, kappa 0.63, to 98.7%, kappa 0.81) and oral hygiene instructions were reinforced at each visit.

Digital bitewing radiographs were taken at baseline and repeated after 12 and 24-months. Pair-wise reading was assessed by one calibrated examiner, blind in relation to test and control lesions (intra and inter examiner realibility was 95.8%, kappa 0.90; and 90%, kappa 0.75, respectivelly), and in a randomized order, regardless of the participant number and group. Reproducibility of the examiner was reassessed based on duplicated readings. If any carious lesion progressed to D2 or D3 or to cavitation, it was referred to restorative treatment and was considered as progressed in the study.

2.3. Statistical analysis

Intra and inter-examiner realibility was assessed using percentage agreement and Kappa coeficient test. Data were analyzed in SPSS software (SPSS Inc., Chicago, USA-version 22). Descriptive analysis provided information about the different variables assessed in the baseline. Chi-square test and Mann-Whitney test were used to compare the baseline clinical paramaters between the evaluated sample and dropouts. The difference in the proportion of progressing lesions between test and control groups was analyzed descriptively and using the McNemar Test, and the therapeutic effect were calculate by the relative risk reduction (RRR) – efficacy – and also through absolute value [34]. The level of significance was set at 0.05.

3. Results

The sample comprised 50 children: 28 girls (56%), 22 boys (44%), with mean age of 6.2 (± 1.29) (ranging from 5 to 9 years), living in a fluoridated area. The caries risk based on Cariogram model [33] showed that 24 children had high risk (48%), 23 medium risk (46%)

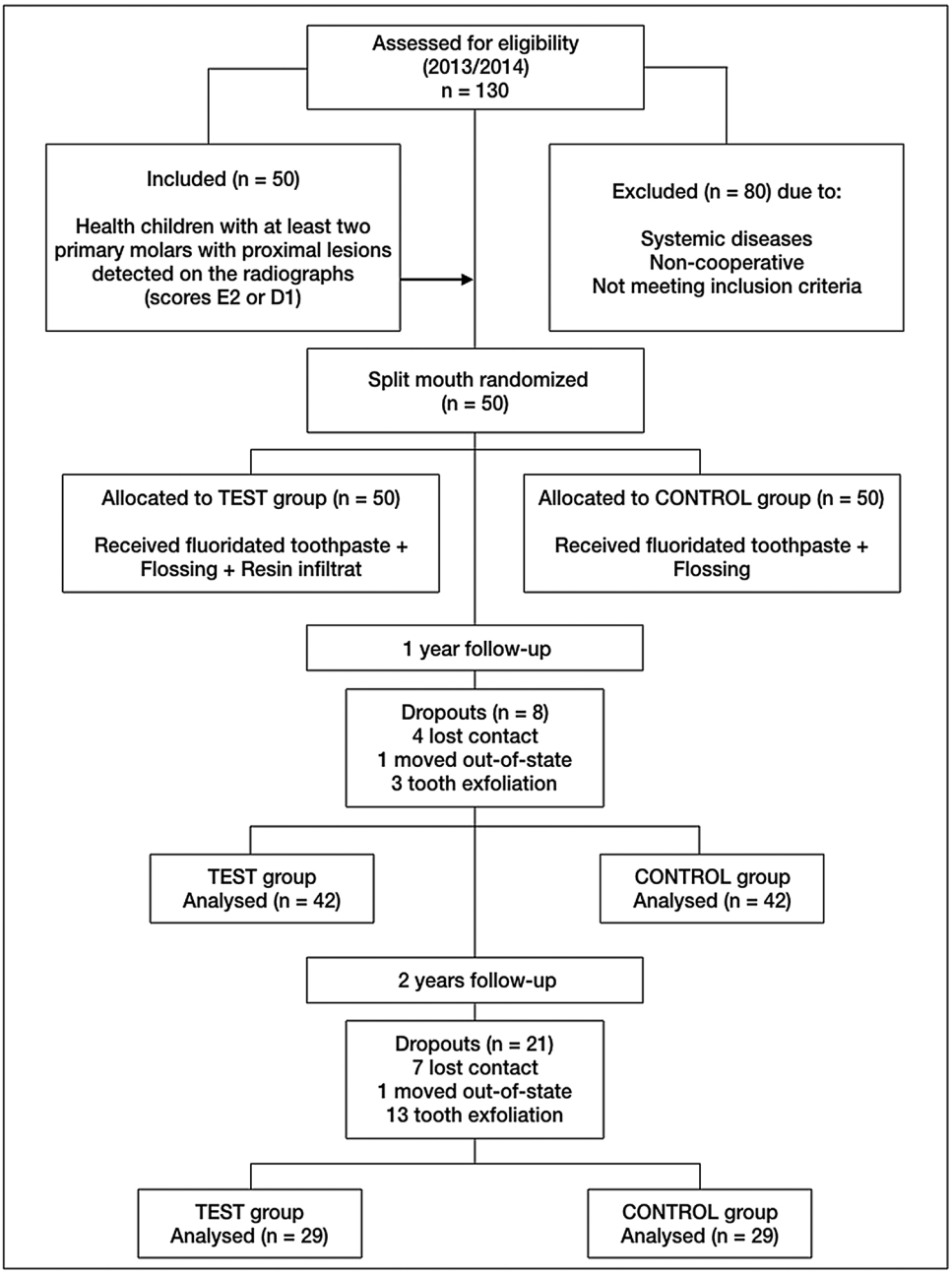

Fig. 1. Study flow diagram.

and 3 low risk (3%). Table 1 shows the data of the full sample at baseline, 1-year and 2-years follow-up and the dropouts during this period. No significant difference was observed in the baseline data between dropouts and those who completed 1-year and 2-years follow up, except for the mean age. As one of the reasons for dropout was the exfoliation of the teeth, it somehow explains the higher baseline mean age among the dropouts. The difference in the baseline mean age is justified by the fact that the older children were more prone to have one of the teeth exfoliated. Plaque and gingival bleeding were present in most of the proximal selected sites (test and control) at baseline and also at the recall (2-years).

Table 2 shows baseline data of tooth/tooth surface and radiographic score of the full sample, 2-years sample and dropouts. At baseline, from the test lesions, 30 (60%) were in the distal of first molars, 16 (32%) were in the mesial of second molars, and 4 (8%) were in the distal of second molars. From the control lesions, 22 (44%) were in the distal of first molars, 18 (36%) were in the mesial of second molars, and 10 (20%) were in the distal of second molars. After 2 years, dropout rate was 21/50 (42%). The proportion of E2 and D1 lesions and the distribution according to tooth/tooth surface remained similar to baseline.

The significant difference between test and control lesions regarding the proportion of caries progression persisted in the second year of follow up (Fig. 2). After 2 years, 55.2% (16/29) of the control lesions and 24.1% (7/29) of the test lesions progressed ($p = 0.002$). In 10 patients (34.5%) only the control lesions progressed, in 6 (20.7%) patients both control and test lesions progressed, and in one patient only the test lesion progressed. The therapeutic effect (absolute value) was 31.1% and the relative risk reduction (RRR) was 56.3% meaning that resin infiltration enhanced caries arrestment in comparison to the control group.

Table 3 shows how control and test lesions behaved in the first and in the second year of the study. In the test group, caries progression were seen from E1 to D1 and from D1 to D2. Only in the control group, progression from E2 straight to D2 was seen both in the first and in the

Table 1
Baseline variables at baseline of the full sample (n = 50), patients evaluated after 1 year (n = 42) and after 2 years (n = 29), and dropouts (n = 21).

Baseline variables	Baseline	1 year			2 years		
	Full sample	Sample	Drop-outs	p	Sample	Drop-outs	p
	n = 50	n = 42	n = 8		n = 29	n = 21	
Age	6.2 (± 1.29)	6.7 (± 1.3)	7.6 (± 1.1)	0.03[c]	6.28 (± 1.1)	7.62 (± 1.1)	0.00[c]
Girls	28 (56%)	23 (54.8%)	5 (62.5%)	0.72[b]	14 (48.3%)	14 (66.7%)	0.25[b]
Boys	22 (44%)	19 (45.2%)	3 (37.5%)		15 (51.7%)	7 (33.3%)	
Proximal Plaque (%)	62.9%(± 28.2)	60.6 (± 27.8)	75.2% (± 29.1)	0.15[c]	56.6% (± 27.8)	71.6% (± 27.0)	0.06[c]
Proximal GB (%)	38.1% (± 19.6)	38.0 (± 19.3)	37.2% (± 21.7)	0.92[c]	35.1% (± 15.5)	41.7% (± 23.8)	0.43[c]
Caries Index[a]	7.3 (± 6.5)	7.8 (± 7.2)	8.7 (± 7.7)	0.71[c]	8.45 (± 7.1)	5.71 (± 5.3)	0.12[c]
Caries Risk							
Low	3 (6%)	3 (7.1%)	0 (0%)		1 (3.4%)	2 (9.5%)	
Medium	23 (46%)	18 (42.9%)	5 (62.5%)	0.68[b]	13 (44.8%)	10 (47.6%)	0.65[b]
High	24 (48%)	21 (50.0%)	3 (37.5%)		15 (51.8%)	9 (42.9%)	

[a] Nyvad score system (Nyvad et al. 1999) at tooth surface level, considering only active caries lesions (both primary and permanent teeth); GB: gingival bleeding.
[b] Fisher exact test was used to compare distribution between sample and drop-outs.
[c] Mann-Whitney test used to compare indices between sample and drop-outs.

Table 2
Baseline data of tooth/tooth surface and radiographic score of the full sample (n = 50 pairs of lesions), 2 years sample (n = 29 pairs of lesions) and dropouts (n = 21 pair of lesions).

	Baseline		2 years		Dropouts		
	Test	Control	Test	Control	Test	Control	p
	n	n	n	n	n	n	
Tooth Surface							
1° Molar/Distal	30	22	16	13	14	9	0.14*
2° Molar/Mesial	16	18	12	13	4	5	0.11**
2° Molar/Distal	4	10	1	3	3	7	
Radiographic scores							
E2	35	41	19	22	16	19	0.53*
D1	15	9	10	7	5	2	0.27**
Total	50	50	29	29	21	21	

Fisher exact test was used to compare distribution between sample and drop-outs in the *test group and in the **control group.

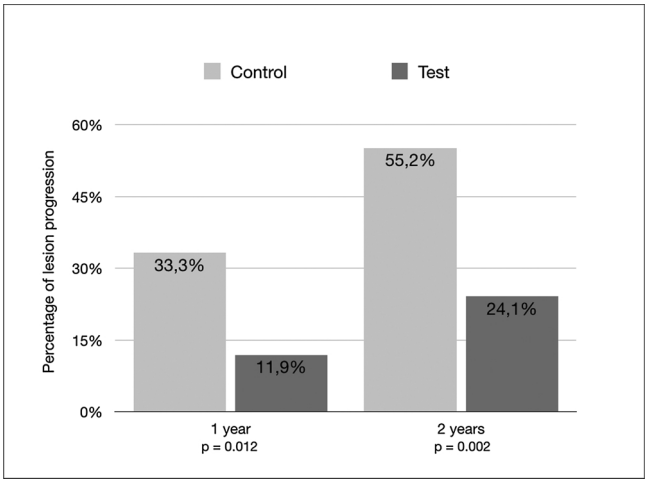

Fig. 2. Percentage of caries progression after 1 year (n = 42 pairs of lesions) and 2 years (n = 29 pairs of lesions) among Test (infiltrated) and Control (not infiltrated) groups. P values were calculated by McNemar test.

second year of follow-up.

4. Discussão

According to this clinical trial, progression of proximal caries lesions in primary molars was inhibited by resin infiltration. The significant

Table 3
Radiographic assessment of caries progression after 1 and 2 years of follow-up among test and control lesions.

Group	After 1 year			After 2 years		
	n/score at baseline	n	score	n/score at baseline	n	score
Test	30/E2	28	E2	19/E2	16	E2
		2	D1		3	D1
	12/D1	9		10/D1	6	
		3	D2		4	D2
Control	35/E2	25	E2	22/E2	11	E2
		6	D1		7	D1
	7/D1	3		7/D1	2	
		4	D2		4	D2
		4			5	

Note: dropouts due to lost of contact or exfoliation of the test or control teeth: 8 patients/pairs of lesions (16%) after 1 year; 21 patients/pairs of lesions (42%) after 2 years.

lower number of progression to deep dentin lesions among infiltrated lesions after two years indicates that resin infiltration was able either to arrest or to slow the caries process. Two previous trials have also reported that resin infiltration was efficacious in reducing caries progression of proximal lesions in primary molars [15,22]. Differently from the present study that evaluated the additional effect of resin infiltration over brushing and flossing instructions, the two previous trials included fluoride varnish application to both control and test lesions.

The overall caries progression in the study of Ekstrand et al (2010) [15] was two times higher than in the study of Foster-Page et al (2017) [22] and in the present study after one year [21]. Besides the high caries risk of the majority of the sample, another reason might be the fact that around two thirds of the lesions were already reaching the dentin (score D1) at baseline while in the present study and in the study of Foster-Page et al (2017) [22] most of the lesions were in the inner half of enamel (score E2) at baseline. It is well documented in the literature that proximal caries lesions progress significantly more once the dentin is reached [35]. It has also been observed by the present study and by previous trials that resin infiltration tends to be more efficacious in E2 lesions than in D1 lesions [17,22]. In the present study, the infiltrated lesions that progressed to the middle third of dentin (D2) were

already D1 when the treatment was done. It is worthy mentioning that some of these D1 lesions might present microcavitations not detected neither radiographically nor clinically that could contribute to a higher progression rate. Once a cavitation is present the efficacy of resin infiltration is compromised [36]. A modified infiltrant with micro filler particles might be able to overcome this limitation and extend the indication of resin infiltration to small proximal cavitations. The first in vitro results were promising [37].

In the study of Foster-Page et al (2017) [22], patients presented low or moderate caries risk while in the present study caries risk was mainly moderate or high. Despite of that, the proportion of progression was quite similar in the two studies both after one year and two years follow-up, particularly for the test lesions. Control lesions progressed slightly more in the present study, resulting in a higher therapeutic effect.

In the present study, each patient participated in the study with only two proximal lesions, one for the test treatment and one for the control treatment. Hence, individual risk factors for caries progression such as dietary and oral higyene habits were equally influencing both test and control lesions. The randomization strategy guaranteed no significant differences between test and control lesions regarding type of tooth, tooth surface and radiographic depth at baseline.

One limitation of the present study was the sample size. Although the sample fitted the sample size calculation as explained previously [21], the dropout of 16% (8/50) after one year increased to 42% (21/50) after two years. The main reason was the lost of patients due to tooth exfoliation. Along the two years follow-up 16 (32%) patients were lost because one (test or control) or both teeth (test and control) exfoliated. Such a high number of tooth exfoliation was not expected as the mean age of the children at baseline was 6.2 (± 1.29) years. In the study of Foster-Page [22] the mean age at baseline was 8.0 years and the percentage of dropouts due to tooth exfoliation was lower than 17%. Probably because in the present study the first primary molar represented 60% of the sample while in the study of Foster-Page more than 75% of the sample was represented by the second primary molar that exfoliates later.

Despite the relatively high dropout rate, it was possible to detect a significant difference between test and control lesions after two years follow-up with a better result for the test lesions in accordance with the previous trials in primary teeth [15,22]. Regarding permanent teeth, the benefit of resin infiltration to the controlling of proximal caries lesions has been reported by several studies [14,16–18,20,26]. As a microinvasive strategy to control caries, resin infiltration enables to avoid or to postpone invasive intervention preserving tooth structure. Besides being a safe [15,18,21] and well accepted technique by children [21,22], if resin infiltration is able to slow down the progression of proximal caries it might be enough to avoid drilling and filling primary teeth once they have a limited life-time in the mouth.

Another important aspect related to the decision between non-invasive, micro-invasive or invasive treatment is the cost-effectiveness. However, data on the cost-effectiveness of resin infiltration in comparison with other treatment options are still scarce. Considering a proximal caries lesion in permanent posterior tooth in the scenario of the German healthcare setting, both non- and micro-invasive therapy are less costly than invasive treatment. Although the micro-invasive treatment is generally more costly than non-invasive therapy, it is more effective [26]. Further cost-effectiveness analyses are required considering primary teeth and the healthcare scenario of different countries.

In conclusion, after 2 years follow-up, resin infiltration was more efficacious in controlling proximal caries lesions in primary molars than non-invasive approach alone, based on oral higyene intructions every 6 months, in children with moderate to high caries risk. Future clinical studies on the micro-invasive treatment for proximal caries in primary molars should include cost-effectiveness analysis.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Declaration of Competing Interest

Authors RCJ and IPRS declare no conflict of interest. Authors MMA and VMS received research grant from DMG, Hamburg, Germany. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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