



Bioactive Tricalcium Silicate-based Dentin Substitute as an Indirect Pulp Capping Material for Primary Teeth: A 12-month Follow-up

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Abstract: *Purpose:* The purpose of this study was to evaluate the clinical and radiographic outcomes of a bioactive tricalcium silicate [Ca_3SiO_5]-based dentin substitute and a light-activated calcium hydroxide [$\text{Ca}(\text{OH})_2$]-based liner as indirect pulp treatment (IPT) interventions for vital primary molars with carious lesions approaching the pulp. **Methods:** Eighty children, aged four to eight years old, with 160 bilateral primary teeth without signs or symptoms of irreversibly inflamed or degenerative pulp tissue were treated in a split-mouth design trial comparing IPT using Ca_3SiO_5 or $\text{Ca}(\text{OH})_2$. The teeth were treated and restored with a preformed crown in a single session and assessed clinically and radiographically for one, three, six, and 12 months. **Results:** Sixty patients with 120 treated molars completed the 12-month evaluations. The combined clinical and radiographic success rates were 98.3 percent (59 out of 60) for Ca_3SiO_5 and 95 percent for $\text{Ca}(\text{OH})_2$ (57 out of 60). No significant differences were found for success rates between the two study groups ($P>0.05$). The combined success rates for both groups was 96.7 percent. **Conclusions:** These results suggest that the indirect pulp treatment procedure with either a bioactive Ca_3SiO_5 -based dentin substitute or a $\text{Ca}(\text{OH})_2$ -based material may be considered a suitable treatment to achieve acceptable therapeutic results when applied on deeply carious primary teeth without degenerative symptoms. (Pediatr Dent 2017;39(5):377-82) Received March 2, 2017 | Last Revision July 6, 2017 | Accepted July 6, 2017

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The most important objective of pediatric dentistry treatment is the preservation of functional primary teeth until natural exfoliation through early and well-indicated pulp therapies.¹⁻³ Indirect pulp treatment (IPT) is a non-invasive vital pulp therapy procedure that involves the removal of only the softened, humid, necrotic, demineralized, and infected dentin layer; it intentionally leaves the deepest layer of the dentin intact over the pulp tissue.⁴ This is followed by the placement of a biocompatible liner and hermetic restoration to provide a seal against microleakage, without the need to reenter for the removal of residual caries.⁵⁻⁷ IPT is an appropriate treatment for symptom-free primary teeth with deep carious lesions but without signs of irreversible pulp inflammation.⁸⁻¹⁰ Radiographically, a deep carious lesion exhibits a radiodense zone that separates the demineralized dentin from the pulp.^{4,11}

IPT can avoid the progression of the carious lesion and reduce the risk of pulp exposure and further damage to the dentin-pulp complex without causing adverse reactions.^{1,12,13} In children, this conservative technique is considered a crucial part of the management strategy referred to as minimally invasive dentistry, which is employed for the control of carious lesions, particularly in uncooperative children.^{1,14,15} Together with the primary pulp-repair capacity, the IPT procedure permits the establishment of a microenvironment in which the cariogenic process is arrested and tertiary dentinogenesis can occur.^{2,9,12} In addition to its therapeutic properties, IPT pos-

sesses the following practical advantages^{2,16}: the affected tooth may be treated and restored in a single clinical visit, and the procedure is easier, more patient-friendly, and less expensive than other pulp treatments (e.g., direct pulp capping or pulpotomy).^{8,9}

A bioactive tricalcium silicate [Ca_3SiO_5]-based dentin substitute has recently been introduced and marketed as Biodentine.^{16,17} Different studies have demonstrated that this new generation biomaterial is a suitable indirect and direct pulp-capping agent for permanent teeth due to its biocompatibility with human and rat pulp cells and its capacity to induce odontogenic differentiation and reparative dentin formation in a very short time period.¹⁷⁻¹⁹ Due to these reasons, Biodentine represents an alternative for IPT with $\text{Ca}(\text{OH})_2$ in primary teeth for the maintenance of tooth vitality.

The purpose of this clinical trial was to assess and compare, clinically and radiographically, the success rate of indirect pulp treatment using as capping agents a bioactive Ca_3SiO_5 -based dentin substitute and a light-activated $\text{Ca}(\text{OH})_2$ -based liner on the dentin-pulp complex of primary molars with carious lesions approaching the pulp after one year of follow-up. The null hypothesis tested was that there would be no significant difference in the clinical/radiographic outcomes between the two IPT liners.

Methods

This study was conducted in accordance with the guidelines laid out in the Declaration of Helsinki, approved by the Ethics Committee of the Faculty of Dentistry (code CEI-FE-003-014), and registered at ClinicalTrials.gov (Identifier NCT02799927). The full trial protocol can be accessed at the *clinicaltrials.gov* web page.

The design was a randomized, split-mouth, clinical trial conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.²⁰ The sample comprised

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80 healthy children aged four years to eight years and 11 months who were recruited as non-probabilistic consecutive cases. The children were required to present at least one restorable primary first or second molar in each side of the mouth, affected by an occlusal, cavitated, active carious lesion in the deep dentin (with the lesion affecting equal to or greater than one half of the dentin on radiographic examination). Other inclusion criteria were negative spontaneous pain or sensitivity to palpation or percussion.⁸ Exclusion criteria were as follows: molars with abnormal mobility; spontaneous pain or fistula; radiographic findings, such as a carious lesion with no evidence of residual dentin in the pulp chamber or manifested pulp exposition, defined as extremely deep caries, in which primary/secondary dentin has been completely destroyed, with a massive formation of tertiary dentin²¹; internal root resorption or physiological root resorption greater than one-third; presence of periradicular/furcal radiolucent lesions; and occurrence of carious pulp exposure and bleeding during the operative procedure (in this case, the patient was eliminated from the trial). Participants were included in the study after parental acceptance through a signed informed consent.

Using the Pocock formula,²² sample-size estimation indicated a minimum of 80 patients (160 teeth), with a clinically meaningful difference effect size (ES) of 30 percent in the success rates between both IPT agents after one year of follow-up, with an α equal to 0.05 and a study power ($1-\beta$) of 80 percent and the expectation of a 20 percent dropout rate, in a two-tailed test. ES was determined based on the indexes proposed by Cohen (small, medium, and large ES values), in which an ES between small and medium (0.20 to 0.50) for two independent mean comparisons approximates the average size of observed effects.²³

Each tooth and treatment were randomly assigned by means of a two-stage block design, and opaque envelopes were used to achieve balance between the study groups in size; the first stage was employed to assign the tooth (left or right), and the second stage was used to assign the treatment. The test group was treated with a bioactive Ca_3SiO_5 -based dentin substitute (Biodentine, Septodont, Saint-Maur-des-Fosses, France), and the control group was treated with a light-activated $\text{Ca}(\text{OH})_2$ (plus calcium hydroxyapatite) liner (Ultra-Blend Plus, Ultradent Products, Inc., South Jordan, Utah, USA). The procedure was implemented by an independent assistant who was not involved in the study and who kept researchers and evaluators blinded until after the statistical analysis was performed. Operator blindness was not possible due to the visual appearance of both study materials.

IPT procedures were carried out by three residents in pediatric dentistry who received standardized training in the clinical setting with a pilot sample of 10 similar pediatric patients each. Study participants received local anesthesia and rubber dam isolation, which was disinfected, followed by the removal of carious peripheral dentin with a high-speed tungsten-carbide no. 3 bur and air-water spray. Then, only the infected soft dentin layer was carefully removed with a dentin sharp-edged sterilized hand excavator, based on hardness-tactile and visual criteria (hardness to probe), leaving the hard dentin adjacent to the pulp chamber ceiling so that the pulp tissue was not exposed. Cavity excavation was stopped when the remaining dentin over the pulp tissue showed increased resistance to manual instrumentation and was removed as dentin scales or chips, also termed leathery or firm dentin⁴; in the case of the

occurrence of an incidental pulp exposure after this step, the participant was eliminated from the study.

The next step involved placing the corresponding liner on the remnant carious dentin layer, following the manufacturers' instructions and according to the random assignment scheme. In the control group, the liner was cured under 20 seconds of light exposure. All treated molars were restored during the same IPT session with stainless steel preformed crowns (3M, St. Paul, Minn., USA) cemented with a glass ionomer cement. One week later (the between-intervention or waiting period), the same procedure was repeated in the opposite tooth with the other IPT agent.

One blinded experimental examiner performed clinical evaluations at baseline and at one, three, six, and 12 months, and radiographic evaluations were carried out at three, six, and 12 months. Clinical assessments included a record of the history of postoperative pain, sensitivity to percussion and palpation, mobility, and a visual examination of surrounding soft tissues (e.g., inflammation, edema, or fistula). Evaluated radiographic criteria were the presence of internal/external root resorption, periradicular/furcal radiolucent lesions, or periodontal space widening. Before the beginning of the study, the examiner was calibrated via the assessment of the intra- and inter-observer agreement by means of the Cohen kappa coefficient, and reliability rates of 0.74 and 0.81, respectively, were obtained.

Treatment outcome was considered a success or a failure according to some of the criteria employed during the participant-selection step, such as the presence of pain, sensitivity to palpation or percussion, abnormal mobility, gingival fistula, or the presence of periradicular/furcal radiolucent lesions and pathological external or internal root resorption. The presence of any clinical/radiographic sign or symptom of irreversible pulpitis or necrosis was recorded as a failure, and the affected tooth was subsequently either pulpectomized or extracted.

Only one cavity per half-mouth was included in the analysis. The data were recorded and subjected to statistical analysis using SPSS 15.0 software for Windows (IBM Corp., Armonk, N.Y., USA). First, a descriptive analysis was carried out with frequencies and percentages of participants and treated molars. Then, inferential testing was planned; because the result variable was measured dichotomously (success/failure) in related samples, a McNemar test for paired nominal data was performed but only for treated molars that were present at the end of the follow-up period; P -values were reported, and all significant differences were expressed as 95 percent confidence intervals (95 percent CI; α equals 0.05).

Results

The recruitment period for eligible children was five months. IPT procedures were initially planned for 94 patients (mean age equals 6.79 ± 1.01 years old; range equals 4.1 to 8.9 years old); 14 of these were excluded due to radiographic contraindications for the IPT procedure in at least one molar. Among the remaining 80 patients who were initially treated, four of them did not return to the planned second treatment to apply the opposite material, according to the randomization schedule, and 16 did not complete the follow-up and were eliminated. A total of 60 patients finished the 12-month follow-up period; there was a 25 percent dropout rate (they did not present for subsequent treatment or control appointments). Therefore, 120 treated primary molars were included in the final analysis: 37

maxillary first molars (31 percent), 40 mandibular first molars (33 percent), 24 maxillary second molars (20 percent), and 19 mandibular second molars (16 percent). The Figure describes the participant progress throughout the clinical trial.

After 12 months of follow-up, the combined final clinical/radiographic success rate of the IPT treatment for both groups was 96.7 percent, with no statistically significant difference in success rates between the two dentin liners studied (59 out

of 60, 98.3 percent for Biodentine and 57 out of 60, 95 percent for Ultra-Blend Plus; $P=0.86$; 95 percent CI for the difference equals 0.11 to 2.9). In the experimental group (Biodentine), one maxillary first molar was associated with spontaneous pain and exhibited abnormal mobility, swelling, and a gingival abscess, together with the presence of an obvious furcal radiolucency and pathological external root resorption. In the control group (Ultra-Blend Plus), three primary molars (two

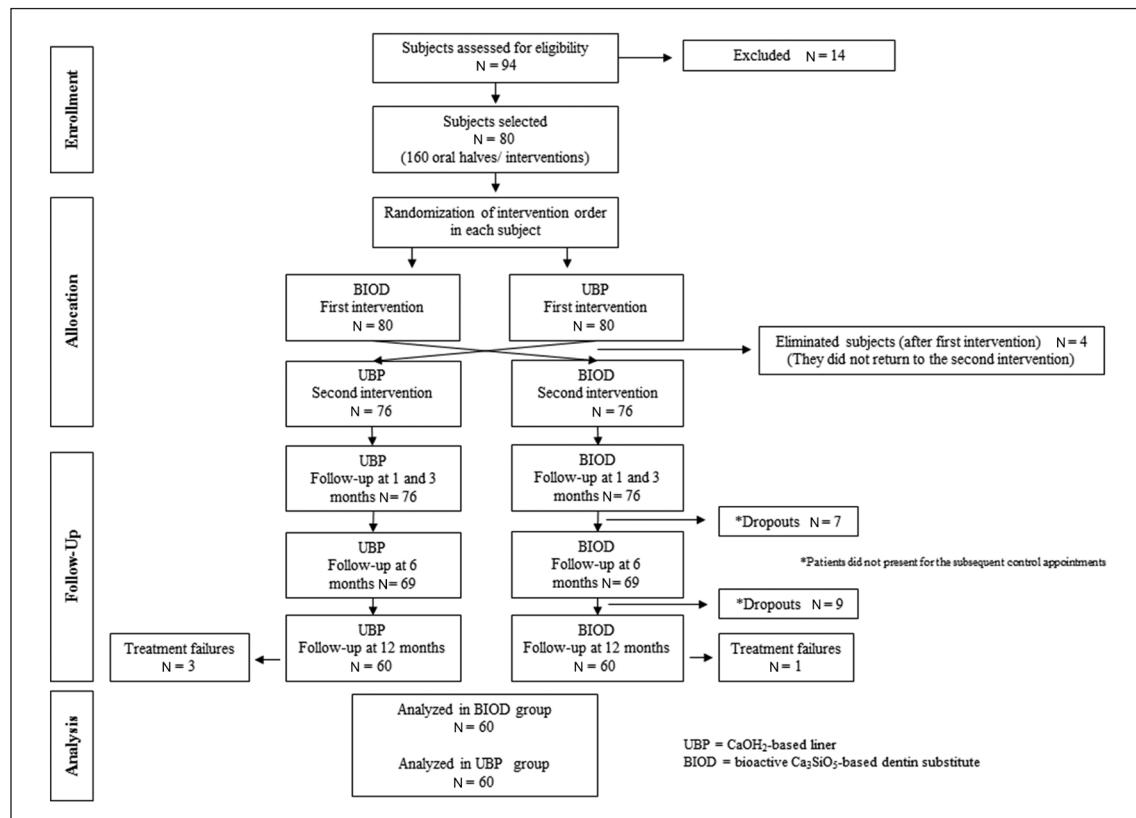


Figure. Patient flow through the clinical trial.

* UBP=CaOH₂-based liner; BIOD=bioactive Ca₃SiO₅-based dentin substitute; S=success; F=failure; IPT=indirect pulp therapy.

† Four patients did not return to the second intervention.

‡ Seven patients were lost during follow-up.

§ Nine patients were lost during follow-up.

Table 1. OUTCOMES OF INDIRECT PULP THERAPY (IPT) PERFORMED WITH A BIOACTIVE CA₃SiO₅-BASED DENTIN SUBSTITUTE AND A Ca(OH)₂-BASED LINER AFTER UP TO 12 MONTHS OF FOLLOW-UP, ACCORDING TO THE PARTICIPANT'S AGE GROUP*

Age group (years)	No. of IPTs initially performed in patients who received both interventions (N=76 per group [†])	Follow-up at 1 and 3 months (N=76 patients)				Follow-up at 6 months [‡] (N=69 patients)				Follow-up at 12 months [§] (N=60 patients)			
		UBP		BIOD		UBP		BIOD		UBP		BIOD	
		S	F	S	F	S	F	S	F	S	F	S	F
4	13	13	0	13	0	12	0	12	0	11	0	11	0
5	17	17	0	17	0	15	0	15	0	12	1	13	0
6	19	19	0	19	0	16	0	16	0	14	0	14	0
7	13	13	0	13	0	13	0	13	0	9	1	9	1
8	14	14	0	14	0	13	0	13	0	11	1	12	0

mandibular first molars and one maxillary second molar) were considered failures due to the same clinical reasons; only one of these molars exhibited radiographic anomalies (a periradicular lesion throughout the mesial root). All failures occurred between six and 12 months after treatment (Table 1); there were no significant differences related to dropouts or the number of treatment failures among the three resident operators. No exfoliations of treated molars or other adverse events were reported during the follow-up period. According to these results, the null hypothesis could not be rejected. Both materials were found to be equally effective for the IPT of primary molars.

Discussion

The results obtained in the present clinical trial indicate that both dentin liners—the bioactive Ca_3SiO_5 -based dentin substitute and the $\text{Ca}(\text{OH})_2$ -based liner—exhibited similar clinical/radiographic success rates in IPT procedures in selected primary teeth after one year of follow-up. These findings corroborate the outcomes from previous similar studies, which were found after an extensive review of current literature confirming that: (1) IPT is a less invasive technique that does not require extensive carious dentin excavation; and (2) in deeply carious primary teeth, IPT is a preferable alternative to pulpotomy when the pulp tissue is correctly diagnosed as normal or reversibly inflamed.^{1,3,8,10,11,13,15}

Despite the high overall success rates (between 78 and 99 percent) and the positive clinical, radiographic, and histologic/bacteriologic findings reported in long-term studies on primary teeth, the IPT technique has not yet been widely recognized by the pediatric dentistry community worldwide.^{2,5,8,12,14,24,25} The use of IPT in the primary dentition remains controversial among clinicians. This lack of consensus can be explained by the observation that only a few high-quality, randomized clinical studies have been conducted and published that provide solid evidence, with encouraging results, on the usefulness and practicability of IPT in carious primary teeth.^{2,7,26-32}

Three factors should be considered for explaining the high success rates achieved in this and other studies: (1) a precise diagnosis of the pulp status⁸; (2) the removal of only the infected dentin layer and cariogenic bacteria from the remaining carious dentin layer³²; and (3) an adequate marginal seal provided by the chosen restorative material.

Pulp vitality diagnosis. The diagnostic process for determining pulp vitality to select a correct case must be based on a careful preoperative clinical examination (e.g., history of pain or and other symptoms) and radiographic examination, bearing in mind that up to 50 percent of deep carious lesions may have pulp involvement, although no clinical symptoms are present.^{8,30,33}

Removal of only infected dentin. There are no objective clinical parameters to determine how much carious dentin should be removed during IPT. However, several microbiological studies have suggested excavation of only the superficial dentin layer during the IPT.^{30,32,34} This layer is called the infected dentin; it is a soft, yellow, humid, necrotic, and demineralized tissue characterized by partially degraded collagen fibrils that cannot be remineralized, and it contains the majority of cariogenic bacteria (mainly aerobic, anaerobic, lactobacilli, and *Streptococcus mutans*)³² and their toxic metabolic products.^{2,15,35,36} Regarding this information, some authors have mentioned that IPT provides successful outcomes, regardless of the use of capping materials; that is, IPT may be considered a non-material-dependent technique.^{5,12} Even inert

materials, such as wax or gutta-percha, have demonstrated the inactivation of active carious lesions.^{14,28,37} The second layer ("affected but not infected dentin") is significantly harder and less permeable and consists of undamaged, more compact, and organized collagen fibrils found very close to the pulp that are susceptible to remineralization.

Restorative material after IPT. According to Oliveira et al.,³⁸ a decrease in cariogenic biofilm activity may affect dental mineral loss, causing the inactivation of the dental caries process. Therefore, a well-made cavity margin seal is crucial for increasing the probability of a successful IPT procedure in primary teeth.^{5,8} An adequate seal prevents the infiltration of pathogenic bacteria and isolates the affected dentin from the oral environment.^{25,32,38} Promising survival rates have been shown, even in cavitated lesions treated without the removal of any carious tissues but with an appropriate seal (e.g., stainless steel crowns), such as with Hall's technique.³⁹ Residual bacteria on the carious dentin are not viable or are unable to proliferate beneath an adequate restoration, due to a lack of availability to the substrate or nutrient influx for cell metabolism.^{14,28,36,40}

In the present study, $\text{Ca}(\text{OH})_2$ (plus calcium hydroxyapatite) was selected as the control intervention because of its well-recognized alkaline biocompatible properties, antimicrobial effects, and reduced dentin contamination and because of its remineralizing ability on the remaining dentin-pulp complex^{8,11,32,33}; however, this material has demonstrated some drawbacks, such as low resistance to resorption, deficient antimicroleakage capacity, poor bonding to dentin, and mechanical instability.²⁵ Despite these inconveniences, $\text{Ca}(\text{OH})_2$ has exhibited satisfactory clinical success rates, both in the present and other previous trials (more than 90 percent),^{5,8} as an IPT capping material in primary teeth.

Bioactive Ca_3SiO_5 -based dentin substitutes have been shown to be an appropriate agent for direct pulp capping in permanent teeth, due to their superior physical/mechanical properties compared with $\text{Ca}(\text{OH})_2$, and have demonstrated dentinogenic capacity and excellent sealing ability. Tricalcium silicate's main component induces odontoblast proliferation and differentiation and, subsequently, new reparative dentin.¹⁶⁻¹⁸ The bioactive Ca_3SiO_5 -based dentin substitute, Biodentine, has been launched as an advancement over $\text{Ca}(\text{OH})_2$ and MTA because of its potential ability to form a mineralized tissue bridge, for example, in pulpotomized primary teeth.⁴¹ Despite the cost, this relatively new regenerative biomaterial needs to be tested in clinical and animal models to confirm its therapeutic properties.⁴¹

Some limitations observed during the performance of the present study were as follows:

The chosen one-year follow-up period for participants for clinical and radiographic observation was considered adequate based on previous reports. In the systematic review from Coll et al.,¹⁰ only IPT clinical studies with a follow-up of at least 12 months were selected in their final analysis. Additionally, Rosenberg et al.² determined the effectiveness of IPT in primary teeth to be greater than 96 percent after one year of follow-up, provided the cases were carefully selected and an adequate marginal seal was placed. Al-Zayer et al.⁵ reported an estimated one-year clinical survival probability of between 93 to 98 percent in IPT with $\text{Ca}(\text{OH})_2$ or resin modified glass ionomer performed on primary posterior teeth. Menon et al.³¹ reported a "good" clinical and radiographic formation of reparative dentin, with a significant increase in thickness six months after the IPT with mineral trioxide aggregate or TheraCal in 22 primary molars. Similar results were reported by

Oliveira et al.,³⁸ who detected radiolucent zones, over a seven-month period, that were suggestive of mineral gain in the remaining dentin. Maltz et al.³² re-opened sealed lesions six to seven months after treatment, and the dentinal tissue exhibited increased radiographic density and a significant decrease in bacterial counts; also, in their clinical trial with microscopic analysis, Bressani et al.³⁷ concluded that IPT in primary teeth exhibited favorable characteristics of color, consistency, and contamination of the remaining dentin three months after the procedure.

The rate of dropout during the follow-up period was high; despite this, the results generated can be considered clinically useful for pediatric dentistry specialists, because the final number of analyzed cases was still significant. Additionally, this dropout rate was similar between both study groups due to the methodological split-mouth design employed, which is appropriate in comparative studies in pediatric dentistry clinical research for comparing two interventions assessed simultaneously on the same participants.⁴² However, it is necessary to emphasize that there are different strategies for preventing dropouts throughout the course of a clinical trial. Researchers should use approaches to keep the study participants engaged in the study, including incentives, visit reminders, e-mails or newsletters, and intermittent phone calls to monitor pediatric patient status.⁴³

Regarding the experience level of the operators in this clinical trial, who were postgraduate students/practitioners, we considered that this factor exerted little effect on the observed IPT success rates when the cases were properly selected; it would be expected that more experienced practitioners would achieve more successful treatments.⁵ In this study, the three operators were all trained and standardized in the IPT performance and under the close supervision of qualified pediatric dentists, thus reducing the bias variability among operators and obtaining reproducible outcomes.

The failures observed in the present study are probably explained by inappropriate case selection. This could be due to the difficulty in the assessment of pulp vitality through clinical/radiographic data and child/parent reports of symptoms. Farooq et al.²⁴ mentioned other additional variables that may influence IPT outcomes, mainly the primary molar location in the dental arch. In their retrospective study, Al-Zayer et al.⁵ found that first molars, specifically maxillary molars, were more likely to fail than second molars. This difference may be explained by root anatomy, size, and the restorability of primary first molars. However, in the present study, the influence of this variable was not detected. Another potential limitation to be considered is the fact that a spoon excavator was employed to remove the infected dentin tissue, because sometimes it is easy to excavate a large bulk of softened dentin and cause a very small, not clinically evident, pulp exposure.⁴

In long-term studies, IPT has shown higher success rates than pulpotomy, with fewer potential side effects, and it does not affect the normal exfoliation pattern or the succedaneous tooth structure.^{3,7,10,24,28} According to the findings from a recent meta-analysis, IPT in primary teeth has a 94.4 percent success rate at 24 months.¹⁰ However, formocresol pulpotomy continues to be used to treat primary teeth with reversible pulpitis, despite the harmful effects reported, including genotoxicity and carcinogenicity.⁷ Moreover, it has been reported that pulpotomy increases the risk of displacing dentin residuals into the radicular pulp tissue, diminishing its repair capacity.⁴⁴

Due to these reasons, we suggest that the IPT procedure be considered a first option for the treatment of vital primary

teeth with deep carious lesions during the decision-making process in the pediatric dentistry clinical setting. Although more high-quality clinical trials are necessary, the IPT procedure has been shown to be a simple, less invasive, patient-friendly, practical approach for asymptomatic grossly carious primary teeth, with excellent clinical/radiographic outcomes, particularly for children who are uncooperative or who live far from the university clinic or practitioner's office.¹⁰

Conclusions

Based on this study's results, the following conclusions can be made:

1. The combined clinical and radiographic success rates were 98.3 percent for bioactive Ca_3SiO_5 -based dentin substitute and 95 percent for $\text{Ca}(\text{OH})_2$.
2. The combined success rates for both groups was 96.7 percent.
3. There was no significant difference between success rates of indirect pulp treatments performed with a bioactive Ca_3SiO_5 -based dentin substitute or $\text{Ca}(\text{OH})_2$ after one year of follow-up, in the management of deeply carious primary teeth with no clinical/radiographic signs or symptoms of irreversible pulp inflammation or pulp degeneration.

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