LAURA REGINA ANTUNES PONTES

Impact of radiographic examination on diagnosis and treatment decision of caries lesions in primary teeth – The CARies DEtection in Children (CARDEC-01) trial

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À Deus, por sempre estar ao meu lado.

À minha família, por serem a estrutura mais firme que eu pude sempre me apoiar.

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"Põe mais um na mesa de jantar, porque hoje eu vou praí te ver e tira o som dessa TV pra gente conversar" (Marcelo Camelo)

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"Eu não vou mudar, não. Eu vou ficar são, mesmo se for só não vou ceder. Deus vai dar aval sim, o mal vai ter fim, e no final, assim, calado, eu sei que vou ser coroado rei de mim." (Marcelo Camelo)

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"É preciso força pra sonhar e perceber que a estrada vai além do que se vê"

Marcelo Camelo

ABSTRACT

Pontes LRA. Impact of radiographic examination on diagnosis and treatment decision of caries lesions in primary teeth – The CARies DEtection in Children (CARDEC-01) trial [thesis]. São Paulo: Universidade de São Paulo, Faculdade de Odontologia; 2019. Original Version.

The aim of this randomized clinical trial (RCT), the CARies Detection in Children (CARDEC-01) was to compare the detection and treatment of caries lesions in primary molars performed with clinical examination using visual inspection alone (VIS) and visual inspection associated with radiographic examination (RAD). Children aged from 3 to 6 years, who looked for dental treatment, were randomized into two groups according to the diagnostic strategy used for caries detection: VIS or RAD. Participants were diagnosed and treated according to the treatment plan related to each group, and they were followed-up for 24 months. In the participants allocated to the VIS group, new analysis was performed considering the results obtained with radiographic method (before-after study). For these children, different types of treatment indicated with each strategy were analyzed: no treatment need, non-operative treatment, and operative treatment. From a total of 2,744 dental surfaces, changes from "no treatment need" decided by visual inspection to "non-operative treatment" after radiographic evaluation occurred in 52 surfaces, and changes to "operative treatment" were observed in 46 dental surfaces. In addition, 50 surfaces had their treatment decision changed from “non-operative treatment” to “operative treatment” after radiographic evaluation. These changes were more frequent in children with higher caries experience and in proximal surfaces. Considering the RCT, the primary outcome was the number of new operative interventions during 2-years follow-up. Other secondary outcomes were also evaluated. The groups were compared through Mann-Whitney test, using intention-to-treat analysis. Then, 252 children were included and randomized, and 216 were followed-up for 2 years (attrition rate of 14.3%). Median (interquartile range) of number of surfaces that needed a new operative intervention (primary outcome) was 1.0 (0.0; 5.0) in the VIS group, and 2.0 (0.0; 5.0) in the RAD group ($p = 0.476$). With regard to secondary outcomes, children from RAD group had more restorations with repairs, and more surfaces restored since

the beginning of the study. Moreover, the RAD group presented a higher number of false-positive results than the VIS group ($p < 0.001$). A secondary analysis was performed with the data obtained in the RCT, considering the clinical course of dental surfaces from primary molars of the children included in the main study. For this, 4,383 proximal and occlusal surfaces of primary molars were diagnosed with visual inspection and radiographic method, and followed-up during 24 months to evaluate for the occurrence of a new operative intervention (a new caries lesion or restoration replacement). It was observed that the therapeutic impact of the radiographic method compared with the clinical examination performed alone was low. Furthermore, in the surfaces with discordant results between the methods, there were evidences of harms consequent to the therapeutic decisions made by the radiographic method, due to false-positive results, overdiagnosis and lead time bias. Thus, simultaneous association between visual inspection and radiographic method for caries detection in preschoolers brings more harms than benefits. Visual inspection performed alone is more beneficial for children, and therefore, should be indicated for the daily clinical practice.

Keywords: Diagnosis. Dental caries. Caries detection. Preschool children. Visual inspection. Radiography.

RESUMO

Pontes LRA. Impacto do exame radiográfico no diagnóstico e decisão de tratamento de lesões de cárie em dentes decíduos - CARies DEtection in Children (CARDEC-01) trial [tese]. São Paulo: Universidade de São Paulo, Faculdade de Odontologia; 2019. Versão Original.

O objetivo deste ensaio clínico randomizado (ECR), o CARies DEtection in Children (CARDEC-01) foi comparar a detecção e tratamento de lesões de cárie em molares decíduos, realizados com a inspeção visual isolada (VIS) e inspeção visual associada ao exame radiográfico (RAD). Crianças de 3 a 6 anos que procuraram atendimento odontológico foram randomizados em dois grupos, de acordo com a estratégia de diagnóstico usada para detecção de cárie: VIS ou RAD. Os participantes foram diagnosticados e tratados de acordo com o plano de tratamento relacionado ao grupo alocado, e acompanhados por 24 meses. Nos pacientes alocados no grupo VIS, uma nova análise foi conduzida considerando os resultados com o exame radiográfico (estudo de antes-depois). Para esses participantes, foram analisados os tipos de tratamento indicados em cada estratégia: nenhum tratamento operatório, tratamento não operatório e tratamento operatório. De um total de 2.744 superfícies, houve alteração de "nenhum tipo de tratamento" com decisão obtida pela inspeção visual, para “tratamento não operatório” após o exame radiográfico em 52 superfícies, e a mudança para decisão de “tratamento operatório” ocorreu em 46 superfícies dentárias. Além disso, 50 superfícies tiveram sua decisão de tratamento alterada de “tratamento não operatório” para “tratamento operatório” após avaliação radiográfica. Essas alterações foram mais frequentes em crianças com maior experiência de cárie e em superfícies proximais. Para o ECR, o desfecho primário foi o número de novas intervenções operatórias no acompanhamento de 2 anos. Outros desfechos secundários foram também avaliados. Os grupos foram comparados com o teste de Mann-Whitney, utilizando análise por intenção de tratar. Assim, 252 crianças foram incluídas e randomizadas, e 216 foram acompanhadas por 2 anos (taxa de atrito de 14,3%). A mediana (intervalo interquartil) do número de superfícies que necessitaram de uma nova intervenção operatória (desfecho primário) foi de 1,0 (0,0; 5,0) no grupo VIS e de 2,0 (0,0; 5,0) no grupo RAD (p = 0,476). Para os desfechos secundários, o

grupo RAD apresentou mais reparos nas restaurações e mais restaurações realizadas desde o início do estudo. Além disso, o grupo RAD apresentou maior número de resultados falso-positivos que o grupo VIS ($p<0,001$). Uma análise secundária foi realizada a partir dos dados do ECR, considerando o curso clínico das superfícies dentárias dos molares decíduos dos participantes no estudo. Para isso, 4.383 superfícies proximais e oclusais dos molares decíduos foram diagnosticadas com os métodos visual e radiográfico, e acompanhadas por 24 meses, para avaliação da ocorrência de uma nova intervenção operatória (nova lesão ou troca de restauração). Observou-se que o impacto terapêutico da radiografia comparado ao exame clínico realizado isoladamente foi pequeno. Além disso, nas superfícies em que houve discordância entre os métodos, houve evidências de danos consequentes das decisões terapêuticas obtidas pelo exame radiográfico por meio de resultados falso-positivos, sobrediagnóstico e viés de tempo de espera. Dessa forma, a associação simultânea do método visual e radiográfico para detecção de cárie em pré-escolares causa mais danos que benefícios. A inspeção visual realizada isoladamente é mais benéfica para crianças e, portanto, deve ser indicada para a prática clínica diária.

Palavras-chave: Diagnóstico. Cárie dentária. Detecção de cárie, Pré-escolar. Inspeção visual. Radiografia

LIST OF ABBREVIATIONS AND ACRONYMS

CARDEC	Caries Detection in Children
CI	Confidence intervals
CMP	Claudio Mendes Pannuti
CONSORT	Consolidated Standards of Reporting Trials
dmf-s	Decayed, missed of filled surface from primary teeth
DPR	Daniela Prócida Raggio
ECOHIS	Early Childhood Oral Health Impact Scale
ECR	Ensaio clínico randomizado
EMC	Edgar Michel Crosato
FMM	Fausto Medeiros Mendes
HR	Hazard ratio
ICDAS	International Caries Detection and Assessment System
IQ	Interquartile range
JSL	Juan Sebastian Lara
LCB	Lucila Bastos Camargo
LRAP	Laura Regina Antunes Pontes
MMB	Mariana Minatel Braga
OR	Odds ratio
PR	Prevalence ratio
RAD	Radiographic method
RCT	Randomized clinical trial
SD	Standard deviation
SPIRIT	Standart Protocol Items: Recommendations for Interventional Trials
TFN	Tatiane Fernandes Novaes
TG	Thaiz Gimenez
VIS	Visual method

PREFACE

This thesis is entirely based on a randomized clinical trial designed to compare two different diagnostic strategies for caries detection in preschool children. The clinical trial was registered in the platform clinicaltrials.gov, in March 4th, 2012, and the registration number is NCT02078453 and approved by Committee for Ethics in Research of School of Dentistry, University of São Paulo (Protocol number 02952612.4.0000.0075) (Attachment A). The thesis consists of two chapters (I and II) containing two papers published in international journals. The pre-print version of these two manuscripts are presented in the chapters. Another chapter (III) described the results of the main trial, that was submitted to publication. Finally, the 4th chapter (IV) contains the findings from a secondary analysis of the data of clinical trial. This paper is being reviewed by the co-authors, and it will be submitted for publication soon.

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IV. Pontes LRA, Lara JS, Novaes TF, Freitas JG, Gimenez T, Moro BLP, Maia HCM, Braga MM, Raggio DP, Mendes FM. 2019. Negligible therapeutic impact, false-

positives, overdiagnosis and lead time: reasons why radiographs bring more harm than benefits in the caries diagnosis of preschool children.

SUMMARY

1 INTRODUCTION

The diagnostic process is an important step for the clinicians, since they check the signs and symptoms present in order to understand the process of the disease, and to plan the best treatment for each patient in order to achieve a better prognosis.

Considering the diagnosis of caries lesions, clinical examination using visual inspection is the method with better acceptability by the children, it is easy and does not require expensive equipment (1). Moreover, visual inspection has presented high specificity; however, the method has presented a high frequency of missed lesions (false negative results), mainly at proximal surfaces (2). Thereby, clinical guidelines around the world have recommended the use of radiographic method associated with visual inspection for all patients seeking dental care, regardless of their clinical condition at the first visit (3-5). This association would be justifiable due to the increase in the sensitivity obtained with this association, in comparison when the visual inspection is performed alone.

However, association of diagnostic methods can also lead to errors and misleading decisions related to the treatment plan, often leading to more invasive and unnecessary treatment. The association of visual inspection and radiographs in the daily clinical practice can lead to conflicting results, such as a decision of operative treatment in a dental surface with no clinical signs of caries lesions that would justify a restoration, but with radiolucency in the radiographic image indicating the necessity for operative treatment. Considering the recommendation of the clinical guidelines (3-5), the strategy indicated is the simultaneous association, where a positive result in one of the methods is enough to classify the surface as decayed. This strategy provokes an increase in the net sensitivity (compared with the sensitivities obtained with each method alone), but with a collateral effect of decrease in the net specificity.

Utilization of diagnostic methods for all patients, even asymptomatic, has different effects than to use the methods related to the presence of some signs or symptoms (6). Moreover, it is necessary to evaluate the diagnostic strategies according the target diseases and populations that would be benefited from the results obtained with the diagnosis (7,8).

As regards the caries diagnosis process, the association of the methods was indicated based on results obtained in accuracy studies. There are no previous research showing that the radiographic is an indispensable method for all patients, mainly considering health benefits for the patients. A randomized clinical trial would bring the best and most robust evidence to evaluate the benefits of this simultaneous association of methods.

Considering this scenario, we pioneered the conduction of clinical trials on caries diagnosis strategies used in children. This first research, reported in this thesis, compared the diagnostic strategy for caries detection recommended by the clinical guidelines, that is the simultaneous association of visual inspection and radiographic method, with the diagnosis made using only visual inspection. This is the first randomized clinical trial comparing two diagnostic strategies for caries lesions detection in children, and possibly, the first one with this design considering the whole playing field of dentistry.

2 PROPOSITION

The general aim of this study was to investigate the impact of the radiographic examination as an adjunct method of visual inspection, in the detection of caries lesions in primary molars of preschool children, compared to the visual inspection conducted alone. To reach this objective, a randomized clinical trial was designed, and four chapters were written considering different aspects and data analyses. All chapters, however, are related to the main clinical trial, and they were reported according to four different specific aims, that were:

I) To describe the research protocol, methods and data analysis proposed, prior to the beginning of the study.
II) To conduct a before-after study in order to evaluate the impact of radiographic examination on changes in the treatment decision related to dental caries compared to treatment decision reached only by visual inspection.
III) To perform a randomized clinical trial comparing the diagnosis and subsequent treatment of caries lesions in primary molars performed with visual inspection alone and associated with radiographic examination in children seeking dental treatment. Oral health outcomes after two years of follow-up were compared between the diagnostic strategies.
IV) To evaluate, at dental surface level, the treatment performed and clinical course after two years of occlusal and proximal surfaces of primary molars, that were diagnosed by both visual inspection and radiographic methods.

The next four chapters were related to each of these specific aims abovementioned.

3 CHAPTER I: TRIAL PROTOCOL

CARies DEtection in Children (CARDEC-01): Impact of the radiographic examination on diagnosis and treatment decision of caries lesions in primary teeth: study protocol for a randomized controlled trial

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Abstract

Background: Although most clinical guidelines throughout the world indicate that clinicians take two bitewings for detecting caries lesions in primary molars of all children, evidence for this recommendation is essentially based on cross-sectional studies performed at laboratorial setting or using convenience samples. Benefits and impact of performing radiographs on diagnosis and treatment decision of caries lesions in primary teeth, mainly considering relevant outcomes for patients, have not been evaluated yet. Thus, the aim of this randomized clinical trial will be to evaluate the impact of performing radiographic examination adjunct to the visual inspection for detecting and making treatment decision regarding caries lesions in primary teeth compared with visual inspection performed alone. We will consider different outcomes related to children's health and welfare.

Methods: To reach this objective, 250 children aged 3 to 6 years who looked for dental treatment in our dental school will be randomly allocated in two groups according to diagnostic strategy used for caries detection: visual inspection performed alone or visual inspection associated to radiographic examination. Two trained and calibrated examiners will carry out the examinations and elaborate the treatment decision plan. Then, children will be treated and followed-up for 2 years, with evaluations after 12 and 24 months after the inclusion of children in the study. Children will also return after 6 and 18 months for reinforce the preventive orientations. Primary outcome will be the number of dental surfaces with dental treatment need in follow-up. Secondary outcomes will be the components of the primary outcome separately, as well as, proportion of false-positive results, the oral health-related quality of life, cost-efficacy, cost-adjusted per life years and number of new lesions in the first permanent molars.

Discussion: Our working hypothesis is that radiographic examination would actually exert little influence on patient-centered outcomes, and that visual inspection would be enough as diagnostic strategy for caries detection in primary teeth.

Trial registration: www.clinicaltrials.gov, NCT02078453. Registered 4 March 2015

Keywords: dental caries, diagnosis, visual inspection, radiographic method, randomized clinical trial

Introduction

Background

Visual inspection is a quick and easy method for caries lesions detection in primary teeth [1]. Moreover, the method has presented high specificity [2] and it is the unique method validated to assess caries lesions activity [3, 4]. For those reasons, it is routinely used in daily clinical practice [1].

Nevertheless, the method has not presented high sensitivity in detecting caries lesions, mainly at proximal surfaces [2]. To overcome this limitation of the visual inspection, many clinical guidelines used throughout the world have advised that dentists take 2 bilateral bitewing radiographs in children to detect missed caries lesions in primary molars [5-7]. The radiographic method is capable to increase the sensitivity of visual inspection in primary teeth, decreasing the number of false-negative results in occlusal [2] and proximal surfaces [2, 8].

However, the increase in the sensitivity usually occurs at expense of a higher number of false positive results. Considering the dental caries, this increase of false positives may not be good for two main reasons:

(1) The prevalence of non-evident caries lesions seems to be low in most populations. Thus, there would be a higher number or diagnostic errors using methods with low specificity than with low sensitivity;

(2) A false positive result would lead to an unnecessary operative treatment, while a false negative result could be followed-up and detected further with no consequences for the patient.

In addition, performing unnecessary operative treatment seems to be more costly than missing some caries lesions undetected by visual inspection alone [9].

Some studies have observed this trend of an increased number of false-positive results with the radiographic method [10-13]. However, the most of these studies considered the criterion validity of the methods; hence, they compared the results of the methods with the results obtained with a reference standard method. This type of research usually obtained the rate or correct diagnosis of the method, but it is not concerned with the benefits for the patients.

None study performed to evaluate the caries diagnosis strategies has ever evaluated important outcomes for the patients. A correct diagnosis is not necessarily a benefit for the patient. For instance, the detection of a caries lesion in a primary tooth near to its exfoliation is not good for the patient, because it would lead to unnecessary operative treatment. Therefore, studies that evaluate the benefits for the patients are essential to evaluate the actual utility of radiographic method to detect caries lesions in primary teeth. This reason motivates the realization of the present study.

Objective

The aim of the present protocol will be to evaluate the effect of caries lesions detection in primary teeth performed with the radiographic examination adjunct to the visual inspection on the occurrence of outcomes related to the oral health of children through a randomized clinical trial.

Trial Design

A randomized controlled clinical trial with two parallel arms will be designed. A group will be comprised by children who will receive the diagnosis and treatment decision planned with the visual inspection alone. Another group will be formed by children who will receive diagnosis and subsequent dental treatment planning using visual inspection associated with radiographic examination.

Methods

This article adheres to the guideline for randomized clinical trial protocols (SPIRIT). The SPIRIT checklist is described in the additional file 1.

Participants, interventions, and outcomes

Setting

The children will be randomly selected from a pool of enrolment forms of children (3 to 6 years old) who had sought dental treatment at our school. As we will select patients who looked for dental treatment, we can consider extrapolating the results to the dental office setting. This context is adequate since clinicians usually apply these diagnostic strategies in the daily clinical practice. The children will be separated by age groups (3 - 4 year-old and 5 – 6 year-old children).

Eligibility: Inclusion and exclusion criteria

The inclusion criteria will consider children:

- who sought dental treatment in our school;
- aged among 3 and 6 years.
- who have at least one primary molar in the mouth.

It will be excluded of the study:

- children whose parents refuse to participate of the research;

- children presenting behavior problems during the initial appointments.

Interventions

A first clinical examination will be performed to evaluate the teeth which are present in the mouth, as well as the caries experience using the World Health Organization criteria [14]. The children will be classified in subgroups according the age (3 and 4 years old or 5 and 6 years old) and according the caries experience (children with dmf-s lower or equal to 3, or children with dmf-s higher than 3).

If the child is eligible to participate of the study, bitewing radiographs will be taken from each side, including upper and lower primary molars (2 bilateral radiographs for each child), as recommended by different clinical guidelines throughout the world [5-7]. Complementary periapical radiographs will be also taken when necessary. Radiographs will be processed using the time / temperature method, in which the film stays in the revealing solution (Eastman Kodak, Rochester, USA) for 2 minutes at a temperature about 27 C [15], followed by a fixation time of 10 minutes in fixing solution (Eastman Kodak, Rochester, USA), and then by washing in water for 20 minutes [15]. The revealing and fixing solutions will be always new, placed at the begining of each period of clinical appointments, guaranteeing the quality of processing.

In addition, a questionnaire to evaluate the impact of oral health on the quality of life of the children at the baseline will be applied for the parents. The instrument used will be the Brazilian version of the Early Childhood Oral Health Impact Scale (ECOHIS) [16, 17]. Then, the participant will be randomly allocated in one of the two groups.

The groups will be defined according to the diagnostic strategy used for reaching the treatment decision related to dental caries in primary molars proposed for each child. The two groups are:

- Visual inspection alone: Treatment decision plan based on only visual inspection. The examiners will not receive the bitewings of these children to elaborate the treatment plan. They will only access periapical radiographs when necessary (to decide between endodontics or tooth extraction, for example), those radigraphs will be available after finishing the decision making process of the other teeth.

-Visual inspection plus radiographic: Treatment plan will be based on the visual inspection complemented by radiographic examination. The access to periapical radiographs is also permited in this case.

At the second clinical appointment, two different examiners will perform the examination and elaboration of the treatment plan. They will be trained and calibrated prior to the study. During the study, they will also be checked about their calibration after each 50 children included in the study.

Caries detection procedures

The visual inspection will be done according to the International Caries Detection and Assessment System (ICDAS) [18]. The children will be positioned in a dental chair, under illumination, and they will receive prophylaxis using rotating bristle brush and a pumice/water slurry. The examiners will use a dental mirror and a ball-ended probe for the examination. The teeth will be examined wet, and then, they will be air-dried for 5 s with a 3-in-1 syringe. The examiner will also evaluate the caries activity status if a caries lesion is present [19]. The condition and treatment decision of each dental surface will be recorded in an appropriate sheet.

In all cases, the clinical evaluation will be performed without know the experimental group of the participant. After that, the examiner will be informed about the enrolled group, and will plan the treatment with or without access the bitewing radiographs.

For the children allocated to the experimental group, the same examination procedure will be done, but considering both visual inspection and radiographic examination to reach the treatment decision. Radiographic evaluation will be performed using a light box.

The treatment plan elaborated according to the allocated group will be put in envelops that will be delivered for the dentists responsible to perform the dental treatment. At the first day of treatment, children will receive orientation of oral hygiene, dietary advice and an anamnesis will be performed with the parents of the children. Dentists will perform the dental treatment following the plan and according to predetermined protocols for each type of treatment.

Dental treatment protocols

The choice of the protocols of treatment is based on the best available evidence:

- Operatory treatments will be done with partial caries removal [20];
- High-viscosity glass ionomer cement will be used to restore cavitated active caries lesions in occlusal [21] or approximal [22] surfaces (score 4 of ICDAS or higher and/or lesions reaching the outer half of the dentin in the radiographic image);
- Resin modified glass ionomer cement will be used to restorations of lesions involving more than two surfaces[23];
- Treatment of non-cavitated active caries lesions with fluoride varnish [24].

- Orientation according prevention measures will be based on orientation of oral hygiene using fluoride dentifrice with 1000 to 1500 ppm of fluoride [25] and dietary advice [26];
- Endodontic treatment using iodoformed paste [27, 28];
- Dental extractions and other types of treatment.

The dentists responsible for the treatments will not receive the bitewings radiographs of the participants; they will only have access to periapical radiographs that may be useful for indirect pulp capping, endodontic treatment and extraction.

During the operatory interventions, the presence of soft or hard carious tissue or the absence of carious tissue will be evaluated in order to record possible false-positive diagnosis for dentine caries.

The time of all procedures and the used materials will be registered by an external examiner for the economic analysis. Time spent for each procedure including returning visits will be considered to calculate the direct and indirect costs.

The number of visits of each participant and the procedure done at each session, with their respective duration times will be also recorded. For the calculation of direct costs, we will consider the average of market prices of materials used in each procedure [29, 30]. Such values will be obtained by averaging different locations which sale the products in question and it will be updated during the study. For the calculations, indirect costs will be also considered, as described in previous studies [29, 30].

Follow-up visits

After the end of dental treatments, the children will be recalled after each 6 months for reinforce the preventive orientations concerning the diet and biofilm

control. Furthermore, the participants will be orientated to contact us in case of a new complaint. In this case, the additional treatment will be immediately made and registered.

After 12 and 24 months, the number of dental surfaces with dental treatment will be collected for all participants. For this, two different examiners, blinded in relation to the experimental group of the children, will evaluate the conditions and need of new operative interventions. They will record:

- dental surfaces with necessity of operative tretament (evident dentine caries - cavitated or not);
- restored dental surfaces with necessity of replacement (large failures, caries around restorations and the complete loss of the material will be considered);
- restored dental surfaces with necessity of repair (small failures);
- tooth with need of endodontic treatment or extraction (in both cases, summing 5 surfaces per tooth).

Children with treatment needs will be treated by one of our dentists. All children will receive hygiene and dietary instructions, and fluoride products will be applied according their necessities. After 24 months, the ECOHIS will be reapplied for the children.

Outcomes

The primary outcome will be the number of dental surfaces with operative treatment needs in the follow-up. This outcome is composed of several mutually exclusive factors: number of surfaces with new dentin caries lesions; number of restored surfaces with necessity of replacement; tooth with pain episode and/or necessity of endodontic treatment and tooth indicated for extraction.

The components of the primary outcome separately will be considered as secondary outcomes. Other secondary outcomes will be impact of oral health on quality of life, number of false-positive results, number of new lesions in the first permanent molars, cost-efficacy and quality adjusted life year.

Participant timeline

Recruitment will take place from April 2014 to December 2015. Each participant is enrolled in the study for about 25 months in total (1-month RCT – diagnosis and treatment, followed by a 24-months observational period). Details of the data collection schedule are summarized (Figure 1).

Sample size

For the sample size calculation, we based on the occurrence of the primary outcome: number of dental surfaces of primary molars with operative needs during the follow-ups and incidence data. Considering operative needs, we observed that the mean of new caries lesions after two years was 17.6 surfaces [31], around 10% of restoration failure of occlusal or occluso-proximal restorations in two years [32], 0.08 extracted teeth in two years, totalizing 0.2 surfaces [33] and 0.3 pain episodes in two years, totalizing one surface in two years [33].

Therefore, it would be expected a mean of 19 surfaces with treatment need in the visual inspection alone group. A difference of 5 surfaces with treatment need in the visual plus radiographic method group was considered as minimal clinically important difference. The standard deviation values expected for visual and visual plus radiographic groups were 15 and 10, respectively. Therefore, using a two-tailed test and considering a significance level of 5% and 80% of power, the minimum

sample size of children calculated was 103 per group. Anticipating an attrition rate of 80%, the final minimum sample size was 250 children for all study.

Recruitment

Recruitment is based on our School of Dentistry, which is a reference in caring for children who seek dental care.

Assignment of interventions

Allocation: Sequence generation

The participants will be selected from a pool of enrolment forms of children who looked for dental treatment in our school, using a sequence of random numbers generated by software. The randomization procedure will be done per blocks of the same size and stratified by age and caries experience groups.

Allocation concealment mechanism

We will use sealed, sequentially numbered, opaque envelopes, separated by each stratum. The randomization will be done after the inclusion of the child and after the radiographs. The group will be revealed for the examiners after the clinical examination.

Implementation

The examiner that will perform the first clinical examination will see and designate the allocation of each child using the opaque envelops. Then, she will

inform it only to the examiners that will perform the visual inspection and treatment plans.

Blinding (masking)

Children and their parents, as well as, the dentists responsible for the dental treatment and the examiners who will evaluate the outcomes during the follow-up will be blinded regarding the allocation group.

Data collection, management, and analysis

Data collection methods

Data collection and returning assessments will be made by researchers who have been trained in using ICDAS and also to look for new dental treatment needs. They will be blinded to group allocation and they will be the same examiners at all time-points for each participant in order to minimize inter-observer variability.

Data management

Clinic data will be entered directly into predetermined sheets. Data quality will be ensured by validation checks that include missing data, out of range values, illogical and invalid responses.

Statistical methods

For comparing the outcomes between two groups, Student's t test and Poisson regression analysis will be performed. With concern to the impact of Oral Health on quality of life, difference in the final and baseline scores will be compared

between the groups through Student's t test or Mann-Whitney test, depending of the normality of the distribution data.

Multivariate analysis will be carried out to investigate the influence of the radiographic examination on treatment decision. Time and treatment cost will be compared by Student's t test. Incremental cost-efficacy ratio will be used to compare the economic impact of both diagnostic strategies, considering both the initial examination and possible treatment and re-treatments during the study. The quality-adjusted life year (QUALY) will be also calculated in order to estimate the ratio of cost saved/spent by the use of the proposed diagnostic strategy. For all analyses, the level of significance will be set at 5%.

Monitoring

Data monitoring

As adverse events related to the detection of caries lesions and dental treatments are unlikely, there is no Data Monitoring Committee, and independent oversight of trial data collection, management and analysis is undertaken by FMM. The chief investigator (FMM) has overall responsibility for the study and is custodian of the data.

Harms

It is unlikely that our procedures will result in any adverse effects, beyond those listed as trial outcomes. These effects are usually expected in any conventional dental treatment performed in the pediatric dentistry clinical practice.

Auditing

Data entered will be subject to audition by the coordinator weekly, and data queries will be raised as necessary. Any divergence detected will be corrected and sistematically registered.

Ethics and dissemination

Research ethics approval

The present protocol was submitted and approved by the Ethical Committee of the School of Dentistry, University of São Paulo in 25/05/2012.

Consent or assent

The participants' parents or guardians will receive an informed consent prior to be included in the research. Only children who parents sign the consent will participate in the study.

Confidentiality

Participant confidentiality will be ensured using identification code numbers. Participant identifiable information will be stored in locked filing cabinets in a secure room. Medical information may be given only to dentist's team.

Access to data

Data generated as a result of this trial will be available for inspection on request to the coordinator.

Ancillary and post-trial care

After completing the study participants will continue to receive dental treatments, if needed, in our dental clinics.

Dissemination policy

Results will be reported in full through peer-reviewed journals, patient newsletters and website.

Discussion

We expect that this study provide the best scientific evidence for defining better diagnostic strategies used to detect caries in primary teeth. Considering the research architecture in diagnosis [34], the diagnostic studies have basic designs with increasing level of evidence for answering 4 basic questions in diagnostic research. The first three basic questions are responded through cross-sectional studies for method validation. Studies that address Phase 3 question are performed to test the method in target populations selected consecutively or randomly, reducing the chance of selection bias, which may overestimate the performance of diagnostic methods [35]. Several cross-sectional studies of accuracy has been published evaluating different methods of caries detection [36-38]. Nevertheless, we observed that most studies lack in evaluating clinically relevant aspects or patient-centered outcomes [39].

We observed in a recent published study that the additional tests do not bring great benefits to detect carious lesions in primary molars [12]. Since the introduction

of selection bias was minimized in this study, this is a strong evidence with respect to the detection of caries in primary teeth.

However, randomized clinical trials evaluating relevant outcomes for patients (Phase 4 questions) represent a higher degree of evidence in diagnostic the research. This type of study is conducted to evaluate if patients who undergo a diagnostic method fare better than untested patients [34]. As an example, we can cite the issue of mammography for breast cancer detection. The validity of mammography has been confirmed by cross-sectional studies that perform the biopsy as the gold standard [40]. However, it is known that the real benefit of performing mammography as a screening test in women between 40 and 50 years of age is small. This observation is because the test would avoid death from breast cancer in less than 0.01% of women under age 50 who underwent screening. Considering the problems of unnecessary treatment due to false-positive results, stress caused by the diagnosis of women who do not die from this disease (correct and incorrect diagnoses) and other problems, the risks outweigh the benefits of mammography in this age group [41]. This type of results can be only evaluated in randomized clinical trials because the validity studies do not deal with this aspect.

Until now, however, no randomized clinical trial was conducted to evaluate caries diagnosis strategies. With the expected results, we aim to achieve the refutation of the recommendation to conduct bitewing radiographs for detecting caries lesions, even in children without signs or symptoms, which is present in all protocols of clinical procedures worldwide. On the other hand, in case of favorable results obtained with the experimental group, we will confirm the benefits of strategies of caries detection advised by those clinical guidelines. To the best of our

knowledge, this is the first randomized clinical trial to evaluate diagnostic strategies for diseases related to oral cavity, considering the whole playing field of dentistry.

Trial status

This is an ongoing trial, which is still recruiting the participants at this moment. Figure 2 presents the CARDEC trial logotype. The CARDEC collaborative group* represents all persons involved at this trial or in other studies that are been conducted and are nested in the CARDEC-01 trial. The group is formed by researchers, dentists, graduate and undergraduate students and technicians. The detailed roles of each member and respective affiliations are described in the additional file 2.

At the moment of the submission of this manuscript, 225 participants have been included. Final results are expected to in the beginning of 2018.

List of Abbreviations

CARDEC- Caries Detection in Children; ICDAS - International Caries Detection and Assessment System.

Competing Interests

The author(s) declare that they have no competing interests

Authors' contributions

FMM, DPR, MMB, CMP and EMC contributed to the conception of this trial. FMM was responsible for its design. TFN is the trial coordinator and FMM is the principal

investigator. FMM and TG drafted the protocol. LRAP and TG are in charge of participants´ recruitment. TFN and JSL are examiners and responsible for treatment plans. LCB and DPR are responsible for organizing and monitoring dental treatments. All authors critically reviewed and approved the final manuscript as submitted. CARDEC collaborative group* staff is responsible for promoting, organizing and conducting all procedures related to the study. Members are graphic designers and secretaries that make the dissemination and organization of the clinical trial, dentists and assistants to perform dental treatment and orientations for all study participants.

Authors´ and collaborators information

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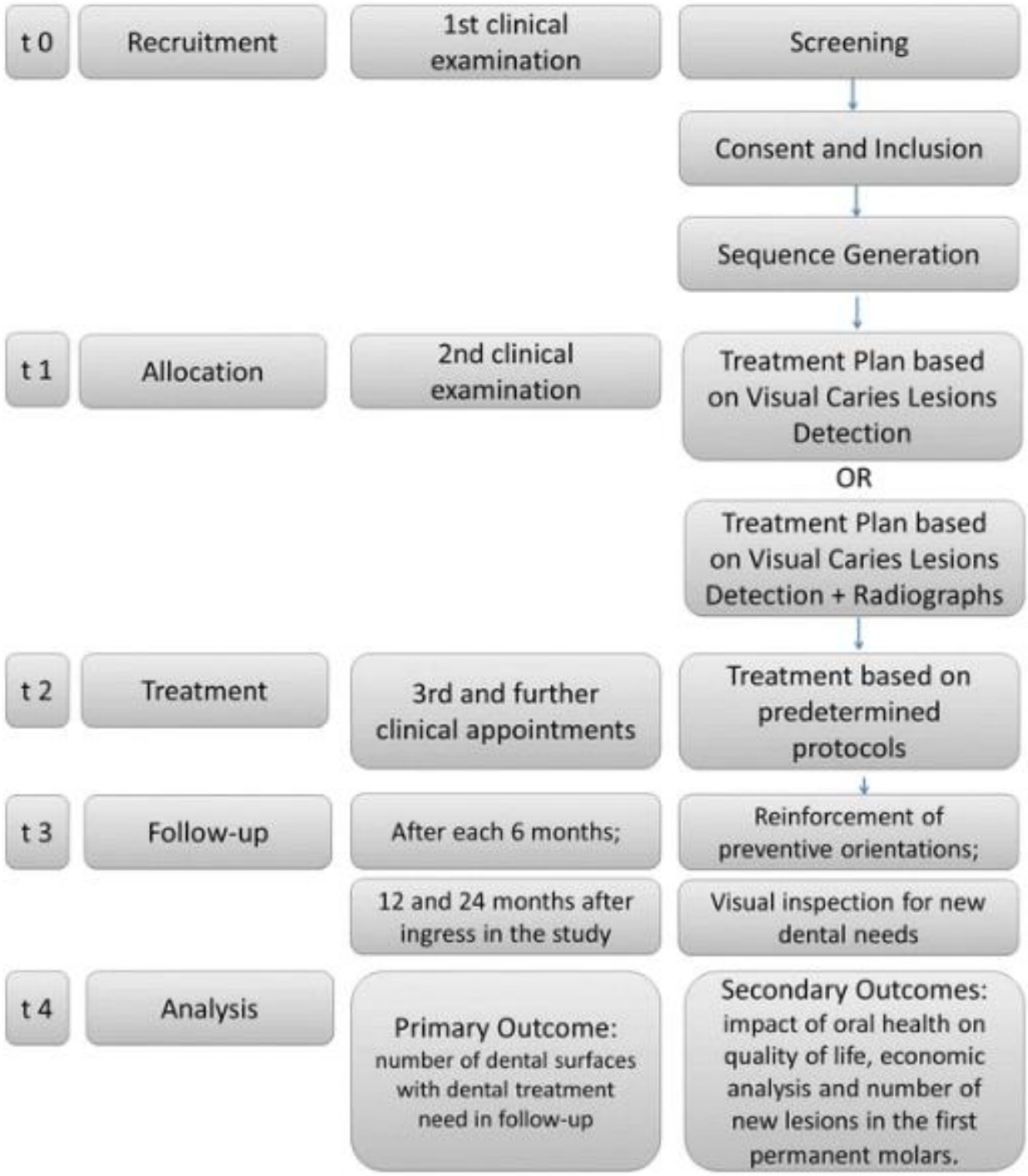
Figure Legends

Figure 1 – Timeline of study procedures.

Figure 2 – CARDEC trial logotype

Figure 1 - Timeline of the study procedures



Source: Author

Figure 2 - CARDEC trial logotype

Source: Author

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5 and 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6, 7, 8 and 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10 and 11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Additional file 2 - **CARies DEtection in Children (CARDEC) collaborative group**

***CARies DEtection in Children (CARDEC) collaborative group**

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4 CHAPTER II: BEFORE-AFTER STUDY

Impact of the radiographic method on treatment decisions related to dental caries in primary molars – a before-after study

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Abstract

Objectives To evaluate the impact of radiographic examination on changes of treatment decision related to dental caries compared to decisions guided by visual inspection alone in primary molars.

Materials and Methods 126 children aged 3-6 years who had sought dental assistance were randomly selected and examined by two calibrated examiners using visual inspection. A treatment plan regarding dental caries was generated based on this assessment. The same examiners then evaluated two bitewing radiographs, creating an additional treatment plan guided by concurrent assessment of both visual and radiographic methods. Occlusal and proximal surfaces of primary molars received a treatment decision as follows: (i) no treatment, (ii) non-operative treatment, and (iii) operative treatment. The frequency of changes in the treatment decision after radiographic examination was calculated, with subsequent Poisson multilevel regression analysis to evaluate variables influencing such changes.

Results Changes from 'no treatment' decided with visual inspection to 'non-operative treatment' after radiographic evaluation occurred in 52 surfaces (3.2%), and changes to 'operative treatment' were observed in 46 dental surfaces (2.8%). Furthermore, 50 surfaces (6.2%) had their treatment decision changed from 'non-operative' to 'operative treatment' after radiographic assessment. In addition, changes were significantly more frequent in children with higher caries experience, on proximal surfaces and in 1st primary molars.

Conclusions The impact of radiographic examination on changes in the treatment decision of primary molars made with visual inspection is modest. Changes are more frequent in children with higher caries experience and in proximal surfaces.

Clinical relevance The benefits of the radiographic method for detecting caries in children, as a protocol in the diagnostic process, seem to be overestimated; the impact of this method on changes in treatment decision made by visual examination alone is low. Radiographs could be, however, useful in particular conditions, such as in children with high caries experience.

Keywords: Dental caries; Caries detection; Visual inspection; Radiograph; Preschool children; Before-after study

Introduction

At present, the chosen strategy for caries lesion detection on primary teeth utilizes visual inspection complemented by radiographic examination [1-3]. This strategy is encouraged based on the accuracy properties of both methods. Although visual inspection presents high specificity, many false-negative results may occur with this method, particularly in the assessment of proximal surfaces. The net sensitivity can be increased through the combined use of different diagnostic methods, albeit at the expense of a net specificity decrease [4]. Consequently, most authors have recommended that visual inspection should be complemented by radiographic examination using two bitewings, even in children displaying no symptoms or visual signs of carious lesions [1-3, 5-7].

Whilst this diagnostic strategy does increase sensitivity values, a decrease in specificity in detecting occlusal and proximal caries lesions in primary teeth does occur [8, 9]. Although accuracy is an important property, other parameters should be tested to determine the true clinical value of diagnostic strategies [10-12]. For example, an improvement in diagnostic test accuracy would be useful for patients only when the strategy leads to changes in both diagnosis and management [11], and ultimately, if such changes benefit patients' overall well-being [13-15].

Ideally, the effects of a diagnostic strategy on patients' health should be evaluated using randomized clinical trials. However, these studies can be impractical due to the requirements for large sample sizes and long follow-up periods. An alternative design capable of assessing changes in treatment decision is the before-after study [13, 14]. The before-after design, an observational study by nature, utilizes a preliminary diagnostic test to assess a series of patients; a treatment management decision is recorded based upon the diagnosis reached from the test. The same patients are then subjected to an additional diagnostic method, offering practitioners the opportunity to revise their original decision. The impact of this adjunct test is then observed with consideration given to all changes from the initial diagnosis and management options [13-15].

Although more than one-hundred studies have evaluated the accuracy of different caries detection methods [6, 7, 16], few manuscripts have assessed changes in treatment decision with different methods [17-21]. Nevertheless, most of

these studies presented a high risk of bias associated to sample selection [17-20], or, focused only on the comparison of two scoring systems for visual inspection [21]. No previous study has evaluated changes in caries lesions management in primary teeth through comparison of visual inspection alone and with the radiographic method associated.

Therefore, the present before-after study, conducted with preschool children, aimed to evaluate the impact of radiographic examination on changes in treatment decision related to dental caries lesions compared to the treatment decision planned after visual inspection alone.

Materials and methods

Ethical concerns and participants' selection

This before-after study was approved by Committee for Ethics in Research of School of Dentistry, University of São Paulo (Protocol number 02952612.4.0000.0075); participants' guardians signed an informed consent prior to the participation of the children in the study. This research is nested within a clinical trial performed to test different strategies for caries diagnosis in children. The main clinical trial, CARies Detection in Children (CARDEC-1), is registered at Clinicaltrials.gov (NCT02078453), and its protocol was previously published [22].

Briefly, the above-mentioned clinical trial was designed to compare two different strategies for caries diagnosis in preschool children: examination performed with visual inspection alone, and with visual inspection adjunct to the radiographic method. After assessments, the examiners prepared treatment plans according to the diagnostic strategy used. The present before-after study included only those participants allocated to the visual inspection group. Initially, the examiners prepared treatment plans considering the evaluation made only by visual inspection. Following provision of the bitewing radiographs, examiners developed a second treatment plan with consideration given to both visual inspection and radiographic methods. This nested design was possible due to the acquirement of bitewings from all children enrolled in the larger clinical trial, although they had not been used for original plans

in the aforementioned clinical trial in the participants allocated to the visual inspection group.

For the entire clinical trial, we calculated the sample size and we reached a minimum of 250 children. Details of the sample size calculation were published elsewhere [22]. Therefore, approximately 125children would be eligible to be included in the present study. Participants were selected from a sample of children (3 to 6 years old), who had sought dental assistance at our dental school. To avoid selection bias, children were randomly chosen from a pool of enrolment forms, with no previous knowledge of their oral health condition.

The inclusion criteria were (i) children aged 3 to 6 years and (ii) with at least one primary molar with no evident signs of dental caries. First, a researcher (L.R.A.P) assessed children and classified them according to their age and caries experience, considering number of decayed, missed or filled surfaces on primary teeth (dmfs). Two bitewings were then taken on each child with 22 X 35 mm films, 0.3s exposure time (Kodak Insight, Eastman Kodak, Rochester, NY, USA), and X-ray machine (Spectro x 70, Dabi Atlante, Ribeirão Preto, Brazil), set at 70 kV and 8 mA.

Subsequently, each participant was randomly allocated to one of the two groups considering the main clinical trial, according to caries diagnosis strategy. For children allocated to the visual inspection group, the examiners prepared a treatment plan based on visual inspection alone, and then, another one based on the combination of both methods.

Caries diagnosis procedures

All children were assessed by one of two previously trained and calibrated examiners (T.F.N. and J.S.L.). The calibration procedures involved assessment of 20 children who was not included in the main study. Intra and inter-examiner was conducted, and the examiners reached kappa values higher than 0.80 prior to the beginning of the study.

After the training and calibration procedures, participants were visually examined using the International Caries Detection and Assessment System (ICDAS) [23]. This examination was performed in a dental chair under illumination, with no access to bitewings. Prior to the examination, teeth were cleaned with rotating bristle brush, pumice/water slurry and when necessary, dental floss. Examinations were conducted using a plane buccal mirror and a ball-ended probe. Initially, teeth were

assessed wet, and then, air-dried for 5 s using a 3-in-1 syringe. After visual inspection, the examiners registered the ICDAS scores [23] and caries lesion activity status [24] in both occlusal and proximal surfaces on primary molars. Based on this evaluation, each dental surface was scheduled to a treatment decision as follows: (i) no treatment, (ii) non-operative treatment, and (iii) operative treatment.

'No treatment' was decided for surfaces with no visual signs of caries lesions or with caries lesions classified as inactive. For surfaces presenting initial active caries lesions (scores 1 and 2), or active lesions with cavitation restricted to the enamel (ICDAS score 3), a decision of 'non-operative treatment' was reached. 'Operative treatment' was determined for surfaces presenting active caries lesions classified as ICDAS scores from 4 to 6.

The same examiner then assessed the bitewing radiographs to develop a new treatment plan, this time considering both visual and radiographic methods combined as recommended by clinical guidelines [1-3]. For the radiographic method, the examiners classified the surfaces in (0) with no radiolucency, (1) radiolucency restricted to the enamel; (2) radiolucency reaching the outer half of the dentin, and (3) radiolucency reaching the outer half of the dentin. Considering this classification, no treatment was decided in surfaces with no radiographic signs of caries lesions. For dental surfaces presenting radiolucency restricted to the enamel, a decision of non-operative treatment was made. Operative treatment was determined for surfaces presenting radiolucencies reaching dentin.

Data analysis

Descriptive analyses of the diagnosis for both occlusal and proximal surfaces of primary molars using visual inspection alone and in combination with the radiographic method, were conducted. For these analysis, results obtained with visual inspection performed with the ICDAS and an additional caries activity score system were categorized as follows: sound (score 0 from the ICDAS), initial active or inactive caries lesions (ICDAS scores 1 or 2), microcavitated active or inactive caries lesions (ICDAS score 3), dar shadow from dentin (score 4 of ICDAS), and extensive caries lesions (ICDAS scores 5 or 6). For the radiographic method, lesions were classified as follows: sound, enamel caries lesions, initial dentin caries lesions and advanced dentin caries lesions.

Frequency of changes on treatment decision after radiographic examination was also calculated. Changes could be from: (i) ‘no treatment’ decided with visual inspection, to ‘non-operative treatment’ after radiographic assessment; (ii) ‘no treatment’ decided with visual inspection to ‘operative treatment’ after radiographic assessment, or (iii) ‘non-operative treatment’ decided with visual examination, to ‘operative treatment’ after radiographic assessment.

Multilevel Poisson Regression analysis was conducted to evaluate whether variables influenced changes on treatment decision. Explanatory variables related to children were: sex (female, male); child’s age (3-4 year-olds vs. 5-6 year-olds); and caries experience (dmfs ≤ 3 vs. dmfs > 3). In relation to dental surfaces, evaluated variables were: type of surface (occlusal or proximal); tooth (1^{st} or 2^{nd} primary molar); dental arch (upper or lower); and mouth side (right or left). The main outcome was established as any change in treatment decision related to dental caries reached by visual inspection following radiographic evaluation. With this analytical approach, calculations of prevalence ratio (PR) values and respective 95% confidence intervals (95%CI) were performed. Univariate and multiple regression analyses were also carried out. Significance level was set at 5%, and data were analyzed using Stata 13.0 (Stata Corp, College Station, USA).

Results

A total of 126 children concluded all phases of the present study. From these, 59 (46.8%) were boys and 67 (53.1%) girls; 61 (48.4%) were 3-4 years old, and 65 (51.6%) 5-6 years old. Regarding dental caries experience, 56 (44.4%) presented dmfs from 0 to 3, and 70 (55.6%) had dmfs higher than 3. The dmfs mean (standard deviation) was 8.54 (11.17).

A total of 3,024 both occlusal and proximal surfaces of primary molars, were evaluated. From these, 112 presented restorations, 81 had pulpal involvement and 87 were indicated for extraction. Classification of other surfaces considering visual inspection alone and after the association with radiographic examination is presented in Table 1. A small percentage (<10%) of surfaces classified as ‘sound’ or with ‘initial caries lesions’ using visual inspection presented with dentin involvement in the

radiographic assessment. However, the majority of lesions with dark shadows (ICDAS 4), clinically observed, presented radiolucencies reaching dentin (Table 1).

Changes from ‘no treatment’, according to visual inspection alone, to non-operative or operative treatment after radiographic assessment were observed in 52 (3.2%) and 46 (2.8%) surfaces respectively. Furthermore, 50 surfaces (6.2%) with an initial decision of non-operative treatment at visual inspection changed to operative treatment after radiographic assessment (Table 2). Therefore, cumulatively, 148 (5.4%) primary molars surfaces, initially evaluated with visual inspection, had their treatment decision changed after radiographic examination.

Poisson Regression Analysis demonstrated that treatment changes were significantly more frequent in children with higher caries experience. Children with dmfs >3 presented around 2.3 times more changes than children with dmfs ≤3. Furthermore, proximal surfaces were more prone to have their treatment decision changed after radiographic examination in comparison to occlusal surfaces. On the other hand, 2nd primary molars presented 40% less changes than 1st primary molars (Table 3).

Discussion

Current guidelines encourage dental clinicians to perform caries lesion detection in children through combined visual and radiographic assessment [1-3]; however, these recommendations are mainly based on studies reporting diagnostic accuracy with the majority of studies presenting a high risk of bias, mainly in the selection of participants [6, 25]. From these studies, the impact of radiographic examination on decision making planned for dental surfaces remained unclear, especially in a random sample of children. Thus, we designed this before-after study including a representative and random sample of children seeking dental assistance to evaluate the magnitude of changes resulting from the addition of radiographic assessment to visual inspection alone. We observed a small frequency of changes (around 5%) in treatment decision made by visual inspection after radiographic examination in proximal and occlusal surfaces of primary molars.

The low frequency of changes seems to contradict recommendations to associate bitewings to visual inspection, particularly in children with no signs or symptoms of dental caries [1-3, 7]. Furthermore, the figures observed in this study regarding the impact on treatment decision were lower than those obtained in previous studies performed in primary teeth [17-20]. This discrepancy could be attributed to the fact that earlier studies were conducted in laboratory settings. The main strength of this current research, therefore, is the inclusion of a random sample of patients who sought dental treatment to evaluate the impact of the radiographic assessment on treatment decision when compared with that obtained after visual inspection alone.

Using this design, it was possible to minimize selection bias, since the distribution of caries lesions in the target population was not influenced. In this sense, it is clear that populations from different contexts and countries may show differences in the distribution and prevalence of caries lesions. However, such differences would not represent any inherent ‘bias’. The authors, therefore, strongly recommend that future studies investigating the accuracy of caries detection methods and/or using the before-after design use similar methods for participant selection to avoiding this type of bias.

Whilst we observed that surfaces classified visually as ‘sound’ or with ‘initial (non-cavitated) caries’ lesions presented dentin involvement on radiographs in around 3.5% of cases, the majority of ‘severe’ lesions (moderate and extensive caries lesions) detected by visual assessment showed dentin involvement on bitewings, which is normally expected. Hence, for surfaces classified as ‘sound’ or with initial caries lesions detected visually, the radiographic examination would have few benefits compared to visual inspection alone, since the prevalence of lesions reaching the dentin is low. In addition, radiographic examination can be deemed unnecessary for extensive caries lesions where visual inspection alone should be sufficient to decide on the best management approach. Periapical radiographs are still warranted for extensive lesions if there is a need to assess pulpal involvement, however, this is contextually separate from radiographic methods to assist in caries diagnosis and treatment planning.

Lesions with dark shadows (ICDAS 4) would benefit most from radiographic evaluation due to the presence of radiolucencies reaching dentin in the majority of cases. Similar findings were observed in previous research [26]. Based on this,

bitewings could be used as a sequential strategy, limited to these cases. Under this approach, clinicians could minimize false-positive diagnoses, consequently reducing unnecessary operative treatments.

Two previous studies, conducted in Swedish children, found that 33% and 48% of 5- and 9-year-old children, respectively, benefited from radiographic examinations. These figures were derived from the proportion of children who had at least one non-cavitated or cavitated lesion, detected only through radiographic examination [27, 28]. It is possible that many of these lesions could be false-positive results. Additionally, as the study was conducted in primary teeth, many 'true' lesions may not have progressed before natural tooth exfoliation. The latter scenario can be considered as overdiagnosis; occurring when clinicians reach true-positive results with no tangible benefits to the patients [29]. Both situations (false-positive results or overdiagnosis) are not desirable for children and parents due to the risk of overtreatment. In the present study, it was not possible to draw conclusions on the real benefits of the tested diagnostic strategies, since clinically important outcomes for children were not assessed. The assertion that the radiographic method is necessary for detecting caries lesions in primary molars as a protocol for all children relies on research focusing on the accuracy of diagnostic methods and studies without patient-centered outcome assessment [25]. Previous research has already questioned the benefits of radiographic examination and other adjunct methods [8, 9, 30], however, these papers again focused only on accuracy. Further studies evaluating clinically important outcomes for children are required; indeed, the main trial in which this study is nested aims to assess these outcomes [22].

Whilst the impact of radiographic examination on treatment decision in comparison to that made only by visual examination was low in the overall analysis, it was possible to identify some variables where these changes were more pronounced. Children with higher caries experience presented almost twice the changes than children with lower caries experience, possibly due to a higher probability of having carious lesions in the former group. Another plausible reason is the occurrence of cognitive bias, known as representativeness, as observed in a recently published study [31].

Furthermore, we observed a higher frequency of changes in proximal surfaces in comparison to occlusal surfaces. This result was expected based on previous research which showed that radiographs are more important for caries lesion

detection at proximal surfaces [5, 7, 9]. Changes in treatment decision were more frequent in 1st primary molars than in 2nd ones; the difficulties of visually assessing the distal surfaces likely increased the probability of missing lesions during visual inspection.

The small frequency of changes in treatment decision observed with the combined assessment of visual inspection and radiographic examination indicates that this strategy for caries detection in primary molars is not appropriate. However, and in accordance with our findings, radiographic examination may be useful in cases of teeth with an underlying dark shadow from dentin detected during the clinical examination. In addition, radiographic examination could be beneficial for the detection of proximal lesions on primary molars in children with high caries experience. Notwithstanding these conclusions, randomized clinical trials that compare different diagnostic strategies are required in order to determine the most appropriate diagnostic strategy for caries detection.

In conclusion, the impact of radiographic examination on treatment caries-related decisions in comparison to that made only by visual examination is low. However, changes to treatment decisions are more significant in children with higher caries experience and in proximal surfaces.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

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test different strategies for caries diagnosis in children. The main clinical trial, CARies Detection in Children (CARDEC-1), is registered at Clinicaltrials.gov (NCT02078453).

Informed consent: Participants' guardians signed an informed consent prior to the participation of the children in the study.

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Table 1. Relationship between diagnosis obtained with visual inspection and radiographic method in primary molars (n = 126 children)

Visual inspection	Radiographic examination Number of surfaces (%)				
	Sound	Enamel lesions	Initial dentin lesions	Advanced dentin lesions	Total
Sound	1470 (93.8)	52 (3.3)	34 (2.2)	11 (0.7)	1567
Initial active lesions	557 (80.0)	104 (14.9)	29 (4.2)	6 (0.9)	696
Initial inactive lesions	34 (97.1)	0 (0.0)	1 (2.9)	0 (0.0)	35
Microcavitated active lesions	86 (76.8)	11 (9.8)	12 (10.7)	3 (2.7)	112
Microcavitated inactive lesions	17 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	17
Dark shadow from dentin	2 (4.3)	5 (10.6)	33 (70.2)	7 (14.9)	47
Extensive caries lesions	10 (3.7)	7 (2.6)	58 (21.5)	195 (72.2)	270
Total	2176 (79.3)	179 (6.5)	167 (6.1)	222 (8.1)	2744

Table 2. Relationship between treatment decision related to caries lesions obtained through visual inspection and through radiographic examination in occlusal and proximal surfaces of primary molars

Visual inspection	Radiographic examination Number of surfaces (%)			Total
	No treatment	Non-operative treatment	Operative treatment	
No treatment	1521 (93.9)	52 (3.2)	46 (2.8)	**1619**
Non-operative treatment		758 (93.8)	50 (6.2)	**808**
Operative treatment			317 (100.0)	**317**
Total	**1521**	**810**	**413**	**2744**

Shaded cells represent changes in treatment decision after radiographic examination

Table 3. Descriptive and univariate analysis of the association among explanatory variables and changes in treatment decisions after radiographic examination compared to those initially made with visual inspection

Explanatory variables	Change in the initial treatment decision			
	No N (%)	Yes N (%)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)
Variables related to the child (n = 2744 surfaces in 126 children)				
Sex (ref.: Male)	1,211 (94.9)	65 (5.1)	1.00	**
Female	1,385 (94.3)	83 (5.7)	1.07 (0.66 to 1.75)	
Age (ref.: 3 to 4 yrs-old)	1,332 (95.0)	70 (5.0)	1.00	**
5 to 6 yrs-old	1,264 (94.2)	78 (5.8)	1.18 (0.73 to 1.91)	
Caries experience (ref.: dmfs ≤ 3)	1,294 (96.4)	48 (3.6)	1.00	1.00
dmfs > 3	1,302 (92.9)	100 (7.1)	2.37 (1.43 to 3.94) *	2.30 (1.39 to 3.79) *
Variables related to the dental surfaces (n = 2744)				
Surface (ref.: occlusal)	843 (97.6)	21 (2.4)	1.00	1.00
Proximal	1,753 (93.2)	127 (6.8)	2.72 (1.71 to 4.32) *	2.68 (1.69 to 4.25) *
Tooth (ref.: 1st molar)	1,271 (93.3)	92 (6.7)	1.00	1.00
2nd molar	1,325 (95.9)	56 (4.1)	0.60 (0.43 to 0.84) *	0.60 (0.43 to 0.84) *
Dental arch (ref.: inferior)	1,274 (94.2)	79 (5.8)	1.00	**
Superior	1,322 (95.0)	69 (5.0)	0.83 (0.60 to 1.15)	
Mouth side (ref.: right)	1,294 (94.2)	80 (5.8)	1.00	**
Left	1,304 (95.0)	68 (5.0)	0.85 (0.62 to 1.18)	
Total	**2,596 (94.6)**	**148 (5.4)**		

PR = Prevalence ratio; 95% CI = 95% confidence interval

dmfs = number of decayed, missed or filled surfaces of primary teeth

* association statistically significant ($p < 0.05$)

** variable not included in the multiple model.

5 CHAPTER III: MAIN RESULTS OF THE CLINICAL TRIAL

Caries detection in children (CARDEC-01): a two-year randomized clinical trial

5.1 ABSTRACT

The aim of this randomized clinical trial (CARies DEtection in Children 1 –CARDEC-1) was to compare the detection, and subsequent treatment, of caries lesions in primary molars performed with visual inspection alone (VIS) and associated with radiographic examination (RAD). Children aged 3 to 6 years were randomly assigned to two groups according to the diagnostic strategy used for caries detection on primary molars: VIS or RAD. Participants were diagnosed and treated according to the management plan, related to the allocated group. The primary outcome was the number of new operative interventions during the 2-year follow-up period. Secondary outcomes were: surfaces with new restorations, restorations with repair or replacement, restorations performed since the beginning of the study, among others. Groups were compared using Mann-Whitney test, and intention-to-treat approach was used. Initially, 252 children were included and randomized and 216 were followed-up after 2 years (14.3% attrition rate). The median value (interquartile range) of surfaces requiring operative treatment (primary outcome) was 1.0 (0.0; 5.0) for the VIS group children, and 2.0 (0.0; 5.0) for RAD group ones (p = 0.476). As regards the secondary outcomes, RAD children had more restorations replacement (p=0.038) and more restorations performed since the beginning of the study (p=0.038) in comparison to VIS children. Moreover, RAD group had higher number of false-positive results than VIS group (p<0.001). Other secondary outcomes did not present significant differences. In conclusion, simultaneous association of visual inspection and radiographic examination for caries diagnosis in primary molars of children who seek dental treatment does not provide additional benefits when compared to the diagnosis performed with the visual inspection alone.

Trial registration: www.clinicaltrials.gov (NCT02078453, registered in 4th March 2015)

Keywords: clinical trial, dental caries, radiography, primary teeth, diagnosis, children

5.2 INTRODUCTION

The choice of the best diagnostic strategy for caries lesions detection in children in daily clinical practice is still controversial. Although visual inspection is an indispensable method, since it is easy and inexpensive (1), clinical guidelines have recommended the use of bitewings as an adjunct method for all children (2-5).

This recommendation is based on the premise that visual inspection overlooks some lesions, mainly at proximal surfaces (6), and that simultaneous association with radiographic method for detecting caries lesions on primary molars increases the sensitivity (7). Increase of sensitivity actually occurs, however, at expense of a higher occurrence of false-positive results, and consequently, decreasing specificity (8,9).

For dental caries, false-positive results are undesirable, since the prevalence of non-evident caries lesions in primary molars is low (9,10). Besides, false-positives immediately lead to unnecessary treatment, while non-detected caries lesions could be followed-up and detected further, causing no harms to children. Although previous accuracy studies have observed these trends (8-10), they only consider right and wrong results compared to a reference standard, and that type of study does not consider long-term benefits for patients' oral health.

Ideally, a diagnostic strategy should be also appraised regarding the patients' health outcomes subsequent to diagnostic results and related treatments (11,12). The appropriate study design to evaluate such aspects is the randomized clinical trial, testing diagnostic strategies, in which subjects are randomly allocated to two or more diagnostic strategies, and management planning and subsequent treatment are conducted according to results obtained with the allocated diagnostic strategy. Afterward, relevant outcomes for patients' health may be evaluated (11-13). Many

randomized clinical trials evaluating diagnostic strategies for several medical disorders have been conducted (13,14), but no study related to dental conditions was found (14).

Therefore, in the absence of knowledge around the evaluation of diagnostic strategies through clinical trials on dental conditions, and facing the controversies at choosing the best strategy for caries lesion detection in children, we designed this randomized clinical trial to compare, the detection, and subsequent treatment, of caries lesions in primary molars performed with visual inspection alone and associated with radiographic examination, in children seeking dental treatment. Outcomes related to children's oral health after two-year follow-up were considered. This is the first of a series of randomized clinical trials, result of a pioneering initiative that intends to test different diagnostic strategies related to dental caries in children: CARies DEtection in Children (CARDEC) trials.

5.3 MATERIALS AND METHODS

5.3.1 Trial Design

This article was written in accordance with the CONSORT statement, and the CONSORT checklist is presented in figure 5.1. This study was designed as a two-arm, randomized, triple-blind, parallel-design trial with two years of follow-up. The study protocol was approved by the Local Research Ethics Committee (CAAE number 02952612.4.0000.0075) and registered on the ClinicalTrials.gov platform (NCT02078453). Moreover, the protocol was previously published (15) and it is described in the Chapter I. Minor changes to the methodology previously reported in the protocol are described in specific sections of the present manuscript.

5.3.2 Participants

Participants were assessed for eligibility from a pool of enrolment forms of children from 3 to 6 years of age who sought treatment at our dental school. Children with challenging behavior during their first appointment or whose guardians did not consent to participate, were excluded.

Once included, an initial clinical examination was performed to evaluate present teeth and caries experience (16). A pair of bitewings and periapical radiographs (when necessary) were taken to all included children before randomization, using 22X35 mm films (Kodak Insight, Eastman Kodak, Rochester, USA) and X-ray machine (Spectro X70, Dabi Atlante, Ribeirão Preto, Brazil), set at 70 kV and 8 mA. Radiographic films were manually processed by the time/temperature method.

A researcher (LRAP) who did not take part in other phases of the study was responsible for both the initial examinations and taking radiographs. Children were classified according to age (3-4 years old or 5-6 years old) and caries experience, considering the number of surfaces of decayed primary teeth, missed due to dental caries or filled (children with dmf-s ≤ 3 or with dmf-s > 3). All caries diagnostic procedures and treatments were conducted at a dental office setting.

5.3.3 Interventions

Interventions tested in this trial were strictly related to the diagnostic strategy for caries detection in primary molars, corresponding to the allocated group. Children were randomized to one of the groups, which was revealed to the examiners only before performing the caries detection procedures. One of two previously trained and calibrated examiners (TFN and JSL), conducted the dental examinations, in accordance with the trial groups:

1- Visual inspection group: Children were assessed using visual inspection alone. The caries assessment was conducted according to the International Caries Detection and Assessment System (ICDAS) associated with caries activity assessment. After that, treatment plan was elaborated.

2- Radiographic group: Children were examined using visual examination simultaneously associated with the radiographic method. Examiners conducted visual inspection using ICDAS and caries activity assessment. They also had access to the bitewings. Then, treatment plan was elaborated considering these methods used jointly.

The treatment plan designed according to the allocated group was stored in sealed envelopes. At treatment appointments, dental practitioners, unaware of child's group, received the treatment plan, with no access to the clinical examination records or bitewings. Treatments were strictly performed according to the envelope's treatment plan. Non-operative and operative procedures were carried out following protocols previously described for both groups (15). Once the treatments were finished, participants were oriented to return after 6 months, or if any intercurrence happened.

5.3.4 Follow-up examinations and outcomes

All participants were scheduled for a follow-up examination every 6 months until they completed 24 months after the last baseline treatment's appointment. Moreover, children's guardians were instructed to contact the research team whether they had noticed any treatment need.

At recalls, children received oral hygiene orientation advising the use of fluoride dentifrice (1000 to 1500 ppm F-) and dietary habits counseling. A trained and calibrated outcome appraiser (DPR), blinded to the allocated groups, conducted the examinations for assessing for the occurrence of the clinical conditions considered as outcome variables.

The primary outcome was the number of dental surfaces with operative treatment need on primary molars during follow-up. This was a composite endpoint including the number of primary molars surfaces with: (i) new caries lesions requiring restorative treatment (caries lesions with evident dentin involvement); (ii) restorations performed at the baseline that needed replacement (large failures, caries around restorations, and complete loss of material); (iii) and teeth (5 surfaces) with endodontic treatment need; or (iv) extraction.

The number of primary molars surfaces with new caries lesions and the number of restored surfaces needing replacement (analyzed separately), were both considered as secondary outcomes. Other secondary outcomes were the need of small repairs on restorations, number of cavitated caries lesions on first permanent molars, and number of primary molars submitted to endodontic treatment or extraction. Reports of pain episodes were also recorded. All outcomes were previously specified in the published study protocol (15).

A secondary outcome that was not considered in the initial protocol was posteriorly included for analysis. This is the total number of restorative procedures, including placed restorations at baseline and during follow-up, also including replacements. The decision to assess this variable was based on the premise that this information could influence the treatment costs based on different diagnostic strategies.

Additional secondary outcomes proposed in the protocol related to oral health-related quality of life and economic analysis will be further explored due to their particular nature.

5.3.5 Sample size

Sample size calculation was based on the primary outcome. For this, a mean of 19 and a standard deviation (SD) of 15 surfaces with treatment need was estimated for the group submitted to the visual inspection alone, and a difference of 5 surfaces (SD=10) as minimal clinically important difference for the radiographic group. Considering a two-tailed test, 5% level of significance and 80% power, and anticipating an attrition rate of 20%, the final sample size was 250 children (125 in each group). Details of the sample size calculation can be found elsewhere (15).

5.3.6 Randomization

Participants were randomly assigned to visual Inspection or visual inspection associated with radiographic method groups with 1:1 allocation rate. The random allocation sequence was generate using the website www.sealedenvelopes.com. Randomization was stratified by age and caries experience, in blocks of eight.

The generated sequence was closed in opaque envelopes numbered sequentially according to children's strata. Envelopes were opened sequentially and once the children was seated at the dental unit and had received dental prophylaxis prior to dental examination. Bitewings were only provided to the examiner for children allocated in the radiographic group.

A researcher (LRAP) was responsible to enroll participants, conducting the initial examinations and taking all radiographs. She was also responsible to assign children to trial groups.

5.3.7 Blinding

This was a triple-blind study. As bitewings were taken for all included children, participants and their parents were blinded concerning the allocated group. The care providers who performed the dental treatments were also blinded, as they were not aware about which diagnostic strategy had been used for treatment plan. The outcome assessor was also blinded in relation to the allocation group. In contrast, the researcher responsible to enroll participants in the study and the examiners who conducted the baseline dental examinations and treatment plans were not blinded.

5.3.8 Statistical methods

All quantitative variables were first submitted to D'Agostino-Pearson and Levene tests to check on the normality and homogeneity of variances, respectively. As these

assumptions were not reached, statistical comparisons were conducted using non-parametrical tests, and data were presented as mean, SD, median and interquartile range (IQ).

Intention-to-treat analyses were used. Missing data from participants who dropped-out were handled by conditional multiple imputation considering the children's age, caries experience, trial group and data collected in previous follow-up recalls (if these data were available).

First, similarities between the two groups at baseline for variables such as sex, child's age, and caries experience were evaluated using chi-square test. Quantitative variables were also compared using Mann-Whitney test. Data obtained at baseline between children who had finished the study and children who had dropped out were also compared.

Subsequently, Mann-Whitney tests were conducted comparing groups in relation to variables collected after the end of the initial treatment as follows: number of surfaces of primary molars that did not receive any type of treatment, surfaces submitted to non-operative treatment, surfaces that were restored at the beginning of the study, number of false-positive results, number of primary molars submitted to endodontic treatment or molars that were extracted. False-positive results were considered for surfaces assigned to operative treatment, but that did not present dentin carious tissue after opening.

The primary outcome (number of new operative interventions on primary molars within the follow-up period) assessed alongside 2 years was compared between the groups using Mann-Whitney test. The same statistical procedure was used for the secondary outcomes. Proportion of children of each group reporting pain within the follow-up period was compared through chi-square test.

We used two statistical packages, Stata 13.0 (Stata Corp, College Station, USA) and MedCalc 18.6 (Medcalc Software bvba, Ostend, Belgium). The level of significance was set at 5%.

5.4 RESULTS

From 252 randomized children, 216 were followed-up until the end of the study (follow-up rate of 85.7%), being 106 from the visual inspection group (82.8%) and 110 from the radiographic method group (88.7%), with no difference between the groups (p = 0.182). In addition, no significant differences were observed for other variables when comparing participants and children who had not finished the study (Table 5.1). Three children (two from visual inspection group and one from radiographic group) did not receive the interventions since they did not attend subsequent appointments. No children crossed over to the other group during the trial. The study flow chart is presented in Figure 5.1.

Children were included from February 2014 to November 2015, and all treatments were finished until February 2016. The recalling phase was completed in January 2018. We did not notice any significant difference between groups for any variables at baseline (Table 5.1).

Regarding to the initial treatments performed according to two diagnostic strategies, children allocated to the visual inspection group had significantly more surfaces of primary molars that did not received any type of treatment (Table 5.2). On the other hand, children allocated to the radiographic group presented 10 times more surfaces with false-positive results in comparison to children submitted to visual inspection alone. Similarities between groups were observed for other variables (Table 5.2).

In relation to the primary outcome, although mean values were similar for both groups, the median indicated that children allocated to the visual associated with radiographic method group tended to have more new interventions; however, no statistically significant difference was observed (Table 5.3).

There were no significant statistical differences between groups regarding number of surfaces with new caries lesions, number of surfaces with restorations' repairs, caries lesions in the 1st permanent molars, teeth with endodontic treatment or extracted within the follow-up period (Table 5.3). In contrast, children allocated to the simultaneous association of visual and radiographic method diagnostic strategy had a higher need of restoration's replacement and significantly more restored surfaces since the beginning of the study, and during the follow-up period, in

comparison to children submitted to visual inspection alone as their diagnostic strategy (Table 5.3).

No harms or unintended effects specifically related to the diagnostic strategy were reported. Twenty-three (18.8%) children from visual inspection group and/or their caregivers and 30 (24.2%) from the radiographic group reported having pain episodes (p = 0.342). The causes of pain, however, varied. From the pain reports, it was noticed that most of them were related to the exfoliation process of primary teeth, and only 9 could be associated to dental caries in the primary molars (4 from visual inspection group children and 5 from radiographic group ones). Other adverse episodes were not reported.

5.5 DISCUSSION

The currently recommended diagnostic strategy for caries lesion detection in daily clinical practice by clinical guidelines is the simultaneous association of visual inspection with radiographic assessment for all patients at different ages (2-5). Nevertheless, such recommendation has been based on accuracy studies, and the evaluation of the true clinical value of diagnostic tests should not be limited to their accuracy. The impact on patients' health outcomes must also be investigated through randomized clinical trials (11,12,17). Our study is the first randomized clinical trial comparing two diagnostic strategies for caries lesions detection in primary teeth, and probably, the first one with this design considering the whole playing field of dentistry.

Previous accuracy studies for caries detection in children have observed that the association of methods did not have advantages (8-10). In our study, we compared children allocated to the strategy recommended by the clinical guidelines against using visual inspection alone, considering the occurrence of new operative interventions after two years of follow-up. This primary outcome was chosen since it is considered that patients, once finish their dental treatments, would like to keep their teeth with no new treatment needs for as long as possible.

For this particular matter, no differences were observed between strategies. Thus, simultaneous association of visual inspection with radiographic methods for caries detection in children for treatment plan did not provoke less new interventions

compared with visual inspection alone. Given this similarity and based on the principle of parsimony, caries lesions detection in all preschool children as part of the diagnostic process and before the performance of dental treatments, should be based on visual inspection alone.

The analyses of secondary outcomes reinforce this recommendation. We hypothesized that children submitted to a combination of visual inspection with a subsequent radiographic assessment for caries lesion detection would receive more restorations; and consequently, more restoration failures could occur in the follow-up. On the other hand, children diagnosed only with visual inspection would have a higher number of missed caries lesions, and therefore, new treatments would be necessary in the follow-up. Although secondary analyses should be interpreted with caution, our first hypothesis was proved, since we observed more restorations alongside the study and more restorations replacements in the children allocated to the radiographic group. However, children submitted to visual inspection alone did not show a significantly higher number of new restorations within the follow-up period, rejecting our second assumption. In fact, we observed that radiographic examination had a low impact on changes in the treatment decision made by the visual inspection alone in a before-after study published earlier (18), probably due to the low prevalence of non-evident caries lesions requiring operative treatment in primary molars, as previously observed (9,10).

Authors who advocate the use of radiographs as protocol for caries detection have stated that bitewings would allow to detect caries lesions before an operative intervention is needed (3-5). Nevertheless, our results contradict this observation, at least for primary molars, as the number of surfaces indicated for non-operative treatment was similar between the groups. Moreover, no differences were observed in the occurrence of new lesions within the follow-up period. Another important finding is the higher number of false-positive results on children belonging to the radiographic method, which is in accordance with accuracy studies (6,7).

Given the above, we observed that the management of caries lesions based on the simultaneous association of visual inspection with the radiographic method as a detection strategy is a more invasive approach than when this process is conducted only by visual inspection, bringing no benefits for children. This observation is only possible by conducting randomized clinical trials, that is the main strength of our research. Conversely, clinical trials are committed with internal validity, limiting

generalizability of obtained results. Another limitation is that our findings are restricted to primary molars.

Recommendations for clinical practice, as result of this investigation, focus primarily on the use of visual inspection alone as strategy of choice for caries detection and treatment planning. Bitewings, however, could be considered, but in a sequential association, being helpful at choosing the best treatment approach (i.e. non-operative vs. operative treatment) for some lesions detected by visual inspection. This association is more in line with the minimum intervention dentistry approach. However, this strategy should be tested through a randomized clinical trial.

In conclusion, the simultaneous association of visual inspection and radiographic examination for caries lesions detection in primary molars does not avoid new operative treatments when compared to the visual inspection alone. Consequently, visual inspection must always be used for caries lesion detection in children to make an appropriate management decision making.

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Table 5.1 - Baseline demographic and clinical characteristics of the participants randomized to the groups related to the diagnostic strategy used for caries detection in primary molars (N = 252), and also considering the participants who were followed-up until the end of the study and who have dropped-out

Baseline characteristics	**Participants randomized**			**Participants included**		
	Visual	**Radiographic**	**p ***	**Analyzed**	**Drop-outs**	**p ***
Categorical variables	**N (%)**	**N (%)**		**N**	**N**	
N total	**128 (50.8)**	**124 (49.2)**		**216**	**36**	
Groups						0.182
Visual				106	22	
Radiographic				110	14	
Sex			0.313			1.000
Male	60 (47.6)	66 (52.4)		108	18	
Female	68 (54.0)	58 (46.0)		108	18	
Child´s age			0.707			0.758
3 to 4 yrs-old	62 (49.6)	63 (50.4)		108	17	
5 to 6 yrs-old	66 (52.0)	61 (48.0)		108	19	
Caries experience			0.920			0.959
dmf-s = 0 a 3	57 (50.4)	56 (49.6)		97	16	
dmf-s > 3	71 (51.1)	68 (48.9)		119	20	
Quantitative variables	Mean (SD)		p **	Mean (SD)		p **
Age (years)	4.89 (0.99)	4.92 (0.94)	0.795	4.90 (0.97)	4.91 (0.95)	0.933
Decayed surfaces	7.29 (10.52)	6.92 (10.59)	0.950	7.06 (10.29)	7.39 (12.10)	0.914
Surfaces missed due to dental caries	0.12 (1.24)	0.54 (3.18)	0.058	0.29 (2.26)	0.53 (3.17)	0.745
Filled surfaces	1.08 (2.38)	0,84 (1.76)	0.810	0,97 (2.15)	0,92 (1,81)	0.971
dmf-s	8.45 (11.11)	8.31 (11.74)	0.909	8.30 (11.28)	8.83 (12.26)	0.801

* calculated by chi-square test.
** calculated by Mann-Whitney test
dmf-s = number of surfaces of primary teeth decayed, missed due to caries or filled. SD = Standard deviation

Source: Author

Table 5.2 - Number of surfaces of primary molars of children allocated according to the initial treatment performed (N = 252), decided by respective diagnostic strategy used for caries detection in primary molars (trial groups)

Diagnostic strategy (trial groups)	Visual		Radiographic		p **
	Mean (SD)	Median (IQ)	Mean (SD)	Median (IQ)	
Surfaces with no initial treatment done	20.3 (10.1)	22.0 (11.5 – 29.0)	17.8 (10.2)	18.0 (9.5 – 26.5)	0.046
Surfaces with non-operative treatment	9.9 (6.1)	9.5 (6.0 – 13.5)	10.0 (6.2)	10.0 (6.0 – 15.0)	0.692
Surfaces restored at the beginning of the study	3.3 (4.7)	1.0 (0.0 – 5.0)	4.1 (5.0)	2.0 (0.0 – 6.0)	0.065
False-positive results *	0.04 (0.26)	0.0 (0.0 – 0.0)	0.48 (1.17)	0.0 (0.0 – 1.0)	<0.001
Teeth submitted to endodontic treatment	0.30 (0.81)	0.0 (0.0 – 0.0)	0.28 (0.70)	0.0 (0.0 – 0.0)	0.852
Teeth extracted	0.23 (0.62)	0.0 (0.0 – 0.0)	0.22 (0.61)	0.0 (0.0 – 0.0)	0.929

* Obtained from surfaces restored
** derived by Mann-Whitney test
SD = Standard deviation; IQ = interquartile range

Source: Author

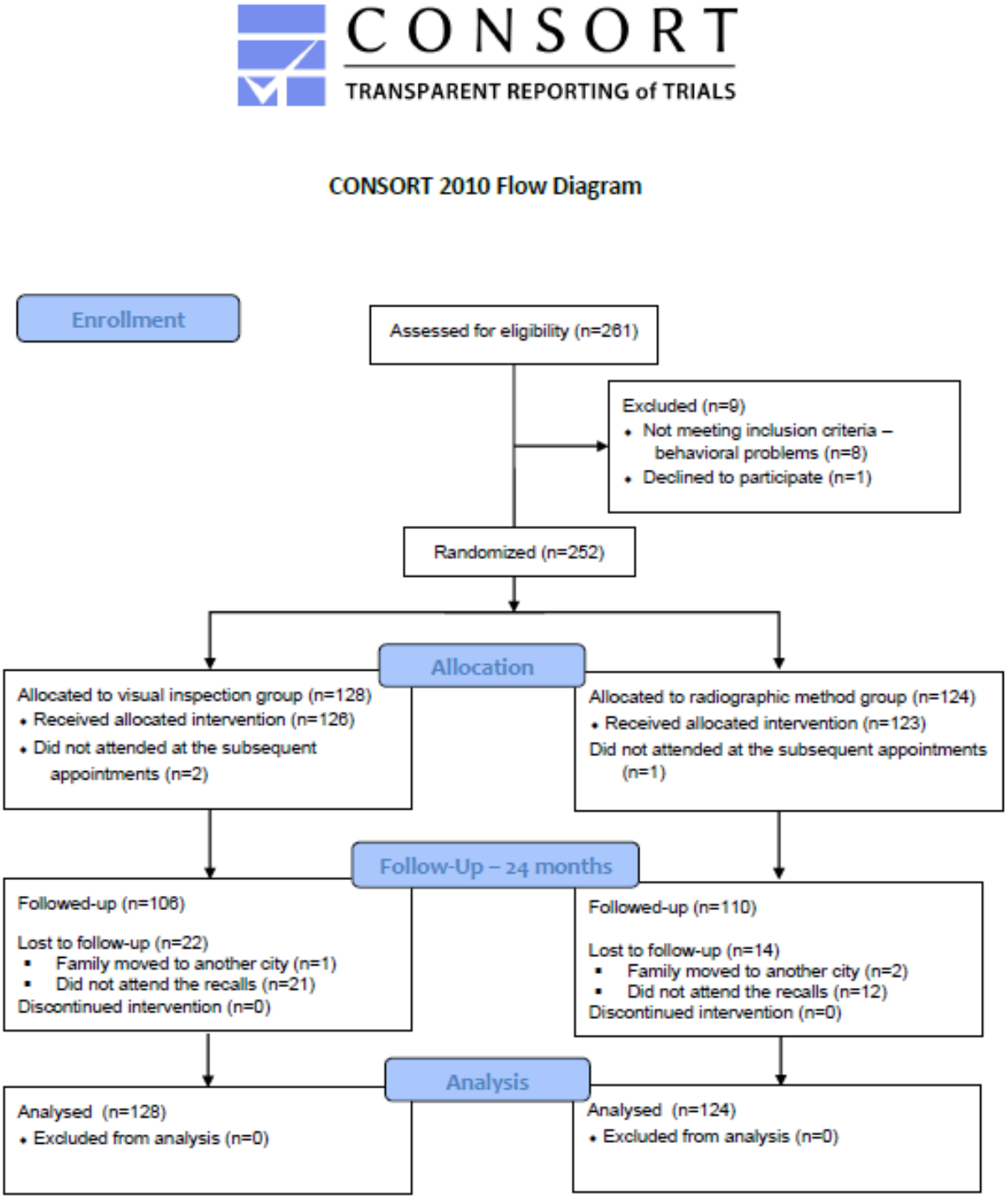
Table 5.3 - Intention-to treat analyses with all randomized children (N = 252) considering number of surfaces that needed new interventions during the follow-up (primary outcome) and other secondary outcomes according to the groups related to the diagnostic strategy used for caries detection in primary molars

Diagnostic strategy (trial groups)	**Visual**		**Radiographic**		**p ***
	Mean (SD)	**Median (IQ)**	**Mean (SD)**	**Median (IQ)**	
Primary outcome					
Surfaces with new operative interventions	3.4 (5.5)	1.0 (0.0 – 5.0)	3.2 (4.1)	2.0 (0.0 – 5.0)	0.476
Secondary outcomes					
Surfaces with new caries lesions	0.8 (1.6)	0.0 (0.0 – 1.0)	0.7 (1.2)	0.0 (0.0 – 1.0)	0.858
Surfaces with replacement of restorations	1.2 (3.6)	0.0 (0.0 – 1.0)	1.3 (2.2)	0.0 (0.0 – 2.0)	0.038
Surfaces with repair of restorations	1.7 (3.2)	0.0 (0.0 – 2.0)	2.0 (3.8)	1.0 (0.0 – 2.0)	0.412
Surfaces with restorative procedures since the beginning of the study	5.3 (8.1)	3.0 (0.0 – 7.0)	6.1 (6.3)	5.0 (1.5 – 9.0)	0.038
Caries lesions in the 1st permanent molars	0.16 (0.51)	0.0 (0.0 – 0.0)	0.17 (0.54)	0.0 (0.0 – 0.0)	0.939
Teeth with new endodontic treatments	0.05 (0.25)	0.0 (0.0 – 0.0)	0.03 (0.18)	0.0 (0.0 – 0.0)	0.775
Teeth extracted during the follow-up	0.16 (0.51)	0.0 (0.0 – 0.0)	0.19 (0.49)	0.0 (0.0 – 0.0)	0.258

* calculated by Mann-Whitney test.
SD = Standard deviation; IQ = interquartile range

Source: Author

Figure 5.1 - Study flowchart regarding participants enrolled, followed-up and analyzed



Source: Author

6 CHAPTER IV: THERAPEUTIC IMPACT STUDY

Negligible therapeutic impact, false-positives, overdiagnosis and lead time: reasons why radiographs bring more harm than benefits in the caries diagnosis of preschool children

6.1 ABSTRACT

Objectives: To evaluate the treatment performed and the clinical course during two years of follow-up of dental surfaces from deciduous molars diagnosed (and consequently treated) by two different strategies: diagnosis made by clinical examination alone or associated with radiographs.

Design: A secondary analysis of a two-arm randomized clinical trial with two parallel groups related to the diagnostic strategy for caries detection of preschool children.

Setting*:* Dental office setting

Participants: 216 children (3 to 6 years old) who looked for dental treatment in the pediatric dentistry clinics of a dental school

Interventions: All dental surfaces were diagnosed by visual inspection and after, through radiographic assessment. The treatment was made according to the results obtained with visual inspection performed alone or to the results obtained with a simultaneous combination of visual inspection and radiographic methods, considering the randomization of the main trial. The same treatment protocols were used for both groups.

Main outcome measures: In the present study, dental surfaces (the unit of analysis) with no necessity of restoration, or that were restored at the beginning of the study were followed-up for two years. The treatment decision was made according to the allocated group. The outcome for this study was the occurrence failure during the follow-up, characterized by a new operative intervention or a restoration replacement.

Results: 4,383 proximal and occlusal surfaces of deciduous molars in 116 preschool children were diagnosed and treated according to the diagnostic strategies abovementioned, and then, they were followed-up for 24 months. Considering all types of treatments (no treatments, non-operative and operative treatments), radiographic method changed the initial decision made by visual inspection in about 30% of the surfaces. However, most disagreements occurred in the initial lesions; radiographs tended to underestimate these type of lesions. Considering lesions that required operative treatment, discordances between the methods occurred in less than 5% of all surfaces. In the cases of discrepancy, treatments decided by the results obtained with radiographs were not more successful compared to the treatments made considering only the visual inspection. Actually, use of radiographs in the diagnostic strategy for caries detection in children bring more harms than benefits due to the ccurrence of false-positives, overdiagnosis and lead time bias.

Conclusions: Simultaneous association of visual and radiographic method for caries detection in preschool children causes more harms than benefits. Visual inspection conducted alone is more beneficial for children at the pediatric dental office setting, and therefore, should be indicated for the daily clinical practice.

Trial registration: clinicaltrials.gov platform: NCT02078453, registered in 4 th March 2015

6.2 INTRODUCTION

The current paradigm related to diagnosis in health care is the early, even presymptomatic, detection of the diseases (1-4). In this way, asymptomatic people are encouraged to attend at regular health checkups in order to keep their well-being (2).

Nevertheless, this movement of making more and earlier diagnosis has a collateral effect: many people are considered sick, even though these diseases would not actually cause any problem for them during their lifetime (5). This is defined as overdiagnosis; persons who are diagnosed with diseases that would not cause any symptoms and harms, or would not be the cause of death of these persons (5-7). This issue is being extensively investigated in adults' health care (7), but the occurrence of overdiagnosis have also raised awareness in Pediatrics (6,8).

The same trend can be observed in dental care practice. People are advised to visit the dentist in recall intervals varying from 3 to 24 months (9-11), although the effectiveness and ideal interval of these regular checkups is still unclear (10,11). Moreover, early diagnosis of different oral health problems has been proposed (12, 13), especially for dental caries (9,14-17).

Dental caries, also knowing as dental decay, is a preventable non-communicable disease mediated by the biofilm formed on the dental surfaces and modulated by the diet, mainly fermentable carbohydrates. It is a dynamic process consisting of alternating periods of demineralization and remineralization; when the net mineral loss is predominant during a period of time, an initial caries lesion becomes clinically detectable. With the progression of the disease, caries lesions of different stages, from initial lesions restricted to the enamel to deep caries exposing the pulp can affect children, adults and elderly (15,18,19). Dental caries is the most prevalent oral health condition (20) and consistently causes negative impact on quality of life in all age groups (21). As regards the childhood, untreated dental caries in deciduous teeth affects around 500 million children, being the most prevalent chronic disease at this age group (22).

Currently, the diagnostic strategy for caries lesions detection indicated in most clinical guidelines is the clinical examination simultaneously associated with the radiographic method (9,17,23-26). Visual inspection must be performed in all patients

at the beginning of the treatment, and the method presents high specificity for the detection of caries lesions that need some type of treatment. However, clinical examination tends to overlook many caries lesions requiring operative treatments, mainly at occlusal and proximal surfaces of posterior teeth (26,27).

Due to this low sensitivity, radiograph has been indicated as an adjunct method of clinical examination. The first argument for this recommendation is that radiographic method increases the sensitivity of the visual inspection used alone; therefore, many lesions that need operative treatment and were missed during the clinical examination would be detected (17,23,26). Other advantage would be the early detection of caries lesions before the cavitation. Consequently, these lesions could be treated non-operatively, avoiding more invasive treatment (9,17,24-26). In both situations, a simultaneous diagnostic strategy is indicated. This simultaneous combination of visual inspection and radiographic methods, however, has been challenged by studies conducted in representative samples, mainly for the detection of caries lesions in deciduous teeth (28,29).

Other possibility is the use of radiographs in a sequential combination with visual inspection (29-31). In this way, the method would be used to confirm a positive result obtained with visual inspection, increasing the certainty on the real necessity of an operative treatment. Nevertheless, the utility of the radiographic methods used in the caries diagnosis strategy has been tested only with accuracy studies, most of them with a high risk of selection bias (26,27). No previous research has investigated the benefits of the caries detection methods evaluating patient-centered outcomes through a longitudinal evaluation.

Therefore, the use of radiographs for caries detection, mainly in children, is controversial. As observed in other fields of health sciences, the tendency of early detection of many diseases can bring more harms than benefits for the patients. While a very small number of patients would benefit from early detection of some life threatening diseases, many others would suffer anxiety and adverse effects of the unnecessary treatment of a problem that would never bother these people (6-8, 32, 33). Additionally, this excess of diagnosis has an obvious economic impact for most stakeholders (5-7,33). Thus, diagnostic strategies for prevalent and disabling diseases, such as dental caries, should be tested through randomized clinical trials in order to strength the evidence on their use in daily clinical practice.

Considering this scenario, we pioneered the conduction of clinical trials on caries diagnosis strategies used in children. This initiative, named CARies DEtection in Children (CARDEC) trials, began with a randomized clinical trial testing two different diagnostic strategies (and subsequent treatment) for caries detection in deciduous teeth of preschool children: visual inspection performed alone or simultaneously combined with radiographic method. The main trial compared the participants for the occurrence of new operative interventions during a two-year follow-up (34), and the results are presented in the previous chapter (Chapter III). In this present study containing secondary analysis of the data of the main trial, we aimed to evaluate the treatment performed and clinical course after two years of individual occlusal and proximal surfaces of deciduous molars of the children, that were diagnosed by both visual inspection and radiographic method.

6.3 MATERIAL AND METHODS

6.3.1 Trial design

The present study is a secondary analysis from a randomized clinical trial carried out to investigate diagnostic strategies for caries detection in preschool children. This report was written following the directions of the Consolidated Standards of Reporting Trials (CONSORT) statement and the CONSORT checklist is presented as a supplemental file (Appendix A). The main clinical trial, named CARies DEtection in Children-1 (CARDEC-01), had the protocol approved by the Research Ethics Committee of the School of Dentistry of University of São Paulo (CAAE number 02952612.4.0000.0075), and it was registered on the ClinicalTrials.gov platform (NCT02078453). Moreover, the protocol was previously published (34) and it is presented in the Chapter I.

In short, the CARDEC-01 study is a two-arm, randomized, parallel design clinical trial with two years of follow-up comparing two different diagnostic strategies for caries detection in children aged from 3 to 6 years: caries detection, and subsequent treatment, conducted using only visual inspection (VIS group), and caries

detection and dental treatment performed through the simultaneous association of visual inspection and radiographic method (RAD group). For the latter strategy, a positive result obtained with one of the methods would classify the surface as decayed, considering initial or more advanced caries lesions.

In the main trial, the unit of analysis for the primary and all secondary outcomes was the children. The primary endpoint was the number of new operative interventions performed in the deciduous molars during the two-years of follow-up, a composite outcome including treatment of new caries lesions, replacement of restorations, endodontic treatment or extraction. Other secondary outcomes were evaluated. The results regarding the primary and most secondary outcomes obtained in the CARDEC-01 study will be published elsewhere and are presented in the Chapter III. Data related to oral health-related quality of life and economic analysis will be further analyzed and published separated.

In the present study, secondary analyses were performed considering the dental surface of deciduous molars as the unit of analysis. The dental surfaces were clustered on deciduous molars, which were clustered in the children. This 3-level cluster structure was considered in all analyses. These analyses have not been predetermined in the protocol (34).

6.3.2 Participants

Children from 3 to 6 years old, whose parents looked for dental treatment in the School of Dentistry of the University of São Paulo, São Paulo, Brazil, were eligible to participate in the study. Parents who did not agree with the participation of their children, or children who did not assent to take part in the study or with problems in the behavior during the first appointments were excluded.

A researcher (LRAP), responsible for the enrolment of the participants, conducted initial dental examinations and taking two bitewings in all included children. Other periapical radiographs were also taken, when necessary. All procedures, including diagnosis and subsequent dental treatments, were conducted at the dental office setting.

6.3.3 Interventions

The interventions performed were related to the diagnostic strategies which the participants were allocated. The trial groups were VIS and RAD groups, as described before.

One of two trained and calibrated examiners (JSL and TFN) conducted the diagnostic procedures. The assessments were carried out in a dental chair under artificial light. Teeth were previously cleaned with rotating bristle brush, pumice/water slurry and dental floss. For the visual inspection, teeth were examined with the aid of a plane buccal mirror and a ball-point probe. The examiners evaluated each dental surface, first wet, and then, air-dried for 5s, and they classified them using the International Caries Detection and Assessment System (ICDAS) associated with the activity assessment (35,36).

The radiographic method was conducted evaluating two bitewings, taken with 22X35mm films (Kodak Insight, Eastman Kodak, Rochester, USA) in an X-ray machine (Spectro X70, Dabi Atlante, Ribeirão Preto, Brazil) set at 70 kV and 8 mA. Films were manually developed, and the examiners evaluated the images in the backlit screen with no magnification.

For the children allocated to the VIS group, the examiners conducted the examinations through visual inspection, and they elaborated a treatment plan based on this evaluation. No specific treatment was decided for dental surfaces of deciduous molars classified as sound (score 0 of the ICDAS). The same decision was made for inactive caries lesions. For active caries lesions scored from 1 to 3 of the ICDAS, a decision of non-operative treatment was reached. Moreover, lesions classified as scores from 4 to 6 of ICDAS were indicated for operative treatment. After the planning of dental treatments made by visual inspection, the bitewings were disclosed for the examiners, and then, they classified the proximal and occlusal surfaces of deciduous molars according to the radiographic images, elaborating a new treatment plan. The dental treatment, however, were made considering the first management plan. Differences between two treatment plans made in the children allocated to the VIS group were analyzed in a before-after study, published elsewhere (37), and described in the Chapter II.

In the RAD group, the examiners received the bitewings before the clinical examination, and evaluation of both methods were used for the caries diagnosis and elaboration of the treatment plan. As a simultaneous strategy was used, a positive result in any method would be sufficient to classify the surface as decayed. Considering the radiographic images, no radiolucency present in the radiographic image leaded to a decision of no treatment necessary. Dental surfaces with radiolucency restricted to the enamel were indicated for non-operative treatment, and surfaces with radiolucency reaching the dentin were indicated for operative treatment. In case of discordances between the visual inspection and radiographic methods, the most severe classification was considered.

Surfaces with no treatment need did not receive any specific treatment. Non-operative treatment in our study was performed using 22,600 ppm fluoride varnish (Duraphat, Colgate-Palmolive, Waltrop, Germany) on the decayed surfaces. Operative treatment was conducted with partial caries removal and restoration using high-viscosity glass ionomer cement. Detailed treatment protocols were earlier described in the Chapter I and in a previous publication (34).

6.3.4 Outcomes

The primary and secondary outcomes of the main trial were related to children. In the present study, this secondary analysis focused on dental surfaces of deciduous molars, and only the surfaces of the deciduous molars that did not received operative intervention or that were restored at the beginning of the study were included. Surfaces with old restorations, or teeth submitted to endodontic treatment or extraction were excluded in the analysis. Moreover, we only considered proximal and occlusal surfaces of deciduous molars.

Therefore, the outcome considered for the present study was the occurrence of a new operative intervention in these surfaces, performed during the follow-up. This variable could be (i) a new restoration due to a new caries lesion during the follow-up, (ii) a replacement of restoration, or a (iii) surface from a tooth submitted to endodontic treatment or (iv) submitted to extraction during the follow-up.

Children were scheduled to return every 6 months after the end of the dental treatment for two years, and the outcome was assessed by an independent assessor (DPR). The parents were also orientated to return if they have noted any treatment need.

6.3.5 Sample size, randomization, and blinding

Sample size was calculated considering the primary outcome of the main trial, and the minimum sample size calculation estimated a number of 250, anticipating an attrition rate of 20%. Details were previously published (34), and were presented in the Chapter I.

For the randomization, an allocation rate of 1:1 between the groups was used. The random sequence was generate using the website www.sealedenvelopes.com, in block of eight numbers, stratified by child's age (3 and 4, or 5 and 6 years old) and caries experience (number of surfaces from deciduous teeth decayed, missed or filled – dmf-s from 0 to 3, or children with dmf-s > 3).

The sequence generated was closed in opaque envelopes numbered sequentially according to the strata. The envelopes were opened only after the dental cleaning, with the children positioned in the dental chair prior to the diagnostic assessment. Bitewings were taken from all children, but they were initially disclosed to the examiners only for the children allocated at the RAD group.

This study was triple-blind. Children and parents were blinded according to the allocated groups. Furthermore, the dentists who performed the dental treatments according to the pre-determined treatment plans (care providers) and outcome assessor were also blinded in relation to the diagnostic strategy used in each child. The person responsible to enroll the participants and the examiners, contrariwise, were not blinded.

6.3.6 Data analyses

First, we built a decision tree representing the treatment plan made using the visual inspection and then, the radiographic method. After, we represent the treatment actually performed for each possible combination of results, and the outcome (success or failure) after the follow-up. A failure was considered as the necessity of a new operative intervention during the follow-up. In the first decision tree, we recorded all possible treatments performed in the beginning of the study: no treatment required, requirement of a non-operative treatment, or a surface requiring a restoration (operative treatment). The actual numbers and frequency values in relation to all dental surfaces included were calculated for each step in the decision tree. Moreover, respective 95% confidence interval (95%CI) values of each frequency were calculated using an approach appropriate for the cluster nature of the data (38). This decision tree permitted the evaluation of the therapeutic impact of different associations between visual and radiographic methods used for caries detection in the deciduous molars of the children, considering all types of treatment possible. The option for deriving the probabilities in relation to the total number of surfaces was because the use of natural frequencies tended to be interpreted more accurately (39), and these figures give a more real understanding regarding the impact of each diagnostic result and subsequent treatment performed.

Another decision tree was drawn, but now only considering the decision for operative treatments. Also, actual numbers, frequencies in relation to the total of included surfaces and respective 95%CIs adjusted by the cluster were recorded. In this analysis, besides the therapeutic impact of the association of methods in the decision for operative treatment, we also figured out the number of false-positive results obtained with both methods, and we estimated the overdiagnosis made by radiographic method in surfaces classified as sound by the clinical examination. Comparisons between failure rates occurred in specific conditions were performed using multilevel logistic regression analysis, considering three levels: dental surfaces (1^{st} level), deciduous molars (2^{nd} level), and children (3^{rd} level). When we used this approach, odds ratio (OR) values and respective 95%CIs were derived. Moreover, this decision tree permitted the evaluation of the frequency of situations that were benefitted by the radiographic method.

For the investigation of the factors associated with the occurrence of a new operative intervention (outcome variable) during the follow-up, we also conducted multilevel logistic regression analysis. The main exposure variable was the different combination of the results obtained with visual and radiographic method for the dental surfaces. First, OR values and 95%CIs of all explanatory variables were calculated in univariate analysis.

Then, multiple regression analyses were performed following the structure of a conceptual framework previously elaborated (Figure 6.1). This framework included the main explanatory variable (results from the caries diagnostic procedures) and the outcome (new interventions during the follow-up), some confounding variables (child's age, caries experience, type of deciduous molar and type of dental surface) and a possible mediator (performing or not the restoration at the beginning of the study). A first multiple model was built including all confounders; then, a second multiple model was derived adding the mediation variable.

Additionally, we carried out a mediation analysis to evaluate if performing a restoration in dental surfaces with a negative result obtained with the visual inspection, but that was positive through radiographic evaluation, could exert a mediation effect on the occurrence of failures. In this analysis, regression coefficients and standard errors were derived using multilevel logistic regression analysis, adjusted by the confounding variables. To evaluate the statistical significance of the mediation effect, we used the Sobel test.

Finally, to investigate the possibility of occurrence of lead time bias, survival analysis considering multiple-failure-time was conducted only in the surfaces diagnosed as negative by visual inspection, but as positive by radiographic method. For these surfaces, restorations were conducted in children allocated to the RAD group in the beginning of the study. In the children allocated to VIS group, however, the surfaces were not restored at the baseline, and they would only be treated if an evident caries lesion was noted during the follow-up. For the survival analysis, the time 0 for each surface was adjusted as the birth date of the children. Then, the first event was always determined as the first restoration performed in the dental surface, and the time when this restoration was performed was recorded. The subsequent failures were due to restoration failures. The main explanatory variable was the conduction of the restoration at the beginning of the study or not. The method for analysis was Cox regression using conditional risk set model and Efron's method for

handling ties, and the hazard ratio (HR) and respective 95% CI were calculated. The data was presented in a time-to-event graphic.

The conceptual framework was built in the DAGitty website (www.dagitty.net). The statistical analyses were conducted using two statistical packages: Stata 13.0 (Stata corp. College Station, USA) and MedCalc 18.5 (MedCalc software bvba, Ostend, Belgium). The level of significance was set at 5% for all analyses.

6.4 RESULTS

6.4.1 Characteristics of the participants and dental surfaces included

Initially, 252 children were included from February 2014 to November 2015. From these children, 216 were followed-up until 24 months (attrition rate of 14.3%). Considering the groups of the main trial, 106 children allocated to the visual inspection group and 110 from the radiographic method group finished the study (p =0.108, by chi-square test). Full data of the main trial will be published elsewhere and is presented in the Chapter III, including the flow chart and data of the participants at the baseline.

For the present study, we only considered occlusal and proximal surfaces of deciduous molars that did not receive any type of treatment, or were submitted to non-operative or restorative treatment at the beginning of the trial. Teeth that presented old restorations or that received endodontic treatment or extraction at the baseline were excluded. Therefore, we analyzed 4,383 dental surfaces (66.7% of proximal and 33.3% of occlusal surfaces) in 1,461 molars, being 720 first (49.3%) and 741 second (50.7%) deciduous molars of 214 children. From these children, 108 (50.5%) were male and 106 (49.5%) were female, 107 (50.0%) were 3 or 4 years old and 107 (50.0%) were 5 or 6 years old. Moreover, 97 (45.3%) children had a number of decayed, missed or filled dental surface from deciduous teeth (dmf-s) from 0 to 3, and 117 (54.7%) children presented a dmf-s higher than 3.

6.4.2 Caries detection and treatment conducted considering all types of treatments

In the figure 6.2, we observed the decision tree showing the diagnosis and subsequent dental treatment performed first with visual inspection and then with the adjunct radiographic method. We noticed that both methods were coincident in the diagnosis for most surfaces (almost 70% of all surfaces). Considering sound surfaces, initial and more advanced caries lesions in the assessment, radiographic method underestimated the diagnosis and treatment decision made by visual inspection in around 25% of the surfaces, and in 4.5% of the surfaces, the radiographic method overestimated the treatment decision (Figure 6.2). The underestimation occurred mainly in surfaces with initial caries lesions according to the visual inspection, but that the radiographies did not show any radiolucency (Figure 6.2, pathway a).

We found only 121 dental surfaces (less than 3% of all surfaces examined) classified as sound by the visual inspection, but with a radiolucency in enamel or dentin in the radiographs (Figure 6.2, pathway a). This situation has been advocated as one of the advantages in taking bitewings in the clinical practice, since non-operative treatments could be performed to avoid the caries lesion progression and cavitation. From these 121 surfaces, non-operative treatment was performed in 41 surfaces, while 64 surfaces did not receive any type of treatment (16 surfaces were restored). Besides the low occurrence of this situation, the frequency of failures (cavitation during the follow-up) of the untreated surfaces was 18.8%, while failures in the surfaces submitted to non-operative treatment occurred in 19.5% (OR = 1.05; 95%CI = 0.35 to 3.09) (Figure 6.2).

6.4.3 Caries detection related to the decision for operative treatment

The decision tree presented in the Figure 6.3 is related to the diagnosis made by different strategies in relation to the decision of operative treatment performed in the occlusal and proximal surfaces of deciduous molars. This emphasis is due to the

assertion that the radiographs are useful to detect caries lesions missed by the visual inspection, that is the main reason claimed to justify the use of radiographic method for all children at the beginning of the treatment. When we considered the indication for operative treatment in dental surfaces of deciduous molars, the vast majority of surfaces presented results coincident between both methods (more than 96%) (Figure 6.3). Discordances were observed in only 3.7% of the dental surfaces assessed; in around 2.8% (Figure 6.3, pathway b), radiographs indicated operative treatment more frequently than the visual inspection. In around 1.0%, however, bitewings did not show radiolucency in surfaces classified as decayed by the visual inspection method (Figure 6.3, pathway a).

Therefore, considering the results that would be reached with the use of simultaneous association of methods changes in treatment decision, from non-operative with visual inspection to operative treatment with radiographic method, would occur only in 121 surfaces (Figure 6.3, pathway b). From these surfaces, 65 were not restored, and 23 failed (35.4%). Other 56 surfaces were restored, and 22 restorations (39.3%) needed to be replaced during the follow-up. Comparing these frequencies, no significant differences were observed (OR = 1.10; 95%CI = 0.12 to 10.43).

On the other hand, if the results of the diagnostic methods had been considered in a sequential association, where the bitewings would be used to confirm a positive result obtained with visual inspection, 42 dental surfaces would have not been indicated for operative treatment due to absence of caries lesions at the radiographic images. From these surfaces, 41 were restored, and the failure rate was 19.5% (8 restorations replaced during the follow-up) (Figure 6.3, pathway a).

6.4.4 Occurrence of false-positive results

In the figure 6.3, we can also observe the occurrence of false-positive results obtained with the caries detection methods. A false-positive result was recorded when the dental surface was indicated for operative treatment, but when the clinician performed the cavity opening, an independent assessor observed the absence of

carious tissue in the dentin. Therefore, all surfaces classified as false-positive results were restored.

We observed a total of 45 surfaces with false-positive results (1.02% considering all surfaces included in the study). From these surfaces, 25 (55.6% of all false-positives) were diagnosed as positive for both methods (Figure 6.3, pathway a). In 3 surfaces (6.7% from the false-positives), the decision for operative treatment was reached only by visual inspection (Figure 6.3, pathway a), and in 17 (37.8%) surfaces, the result was positive only with radiographic method (Figure 6.3, pathway b).

6.4.5 Evidence of overdiagnosis

Occurrence of overdiagnosis was estimated in surfaces indicated for operative treatment by the caries detection methods, but that were not restored and did not progress during the follow-up. As the main clinical trial was designed to compare the diagnostic strategy considering the simultaneous association between visual inspection and radiographic examination with the visual inspection performed alone, we had only 4 dental surfaces positively diagnosed by visual inspection that were not restored due to failure in following the treatment plan. Three of these surfaces progressed in the subsequent two years (Figure 6.3, pathway a), indicating a low probability of overdiagnosis made by the visual inspection.

On the other hand, we had 65 dental surfaces with an indication of operative treatment through the bitewing images, but that were not restored (Figure 6.3, pathway b). From these 65 surfaces, 42 (64.6%) surfaces did not need any operative treatment during the follow-up (Figure 6.3, pathway b). This value is an estimative of overdiagnosis with radiographic method in dental surfaces of deciduous molars with non-obvious clinical signs of caries lesions.

6.4.6 Factors associated with the necessity of new operative interventions during the follow-up

According to the multilevel logistic regression analysis, when the radiographic method detected caries lesion requiring operative treatment that were missed by the visual inspection, the occurrence of failures was significant higher than when both methods detected the lesions (Table 7.1). On the other hand, when the visual inspection detected these types of lesions, but radiographic method did not confirm this finding, the occurrence of new operative treatments during the follow-up was similar to when both methods detected the lesions (Table 7.1). Obviously, when both methods were coincident in classifying a dental surface as sound (not requiring operative treatment), the occurrence of new treatments was significantly lower than when both methods detect caries lesions requiring restorations. These trends were observed in the univariate analysis, as well as in the multiple analysis adjusted by possible confounding variables. Moreover, when we added a possible mediator in the multiple model, the same trend was observed (Table 7.1).

For situations of caries lesions supposedly requiring operative treatment, that were not detected by the visual inspection but that presented radiolucency reaching the dentin in the radiographic images, it would be expected a higher frequency of new operative interventions. Part of these failures could have been due to restorations needing replacement, and another part could have been due to the occurrence of new caries lesions missed by the visual inspection. Therefore, to evaluate if the restoration performed at the baseline could exert some influence on the occurrence of new interventions during the follow-up in these situations, we conducted a mediation analysis. With this analysis, we observed a significant and direct effect between the result obtained in the diagnostic strategy and the occurrence of new operative interventions (Figure 6.4a). This effect, however, remained significantly after the inclusion of the mediator in the model, and the Sobel test indicated that the mediation effect of performing a restoration at the baseline was not statistically significant (Figure 6.4b). This fact was probably due the similar failure rates found in the surfaces that were not restored and those that were restored: 35.4% of surfaces needed a restoration needed a new restoration during the follow-up, and 39.3% of restorations needed to be replaced, respectively.

6.4.7 Evidence of lead time bias

Despite the similar failure rates comparing non-restored and restored dental surfaces with caries lesions detected only by radiographic method, this detection made by radiographic method could indicate the occurrence of lead time bias. To evaluate this possibility, we performed survival analysis using Cox regression for multiple-failure-time data considering these 121 surfaces that had caries lesions detected only by the radiographic method. Considering the t0 as the birth date of the children, we obtained a HR = 9.92; 95% CI = 5.78 to 17.02, $p < 0.001$, indicating a higher probability of failures for dental surfaces restored at the beginning of the study. This trend can be clearly observed in the figure 6.5. We observed that 34 surfaces restored at the beginning did not have failures during the study. However, other 18 dental surfaces restored at the beginning of the study failed 22 times during the follow-up. Considering the surfaces not restored at the beginning of the study, 42 surfaces remained with no obvious lesions after 24 months (overdiagnosis made by radiographic method). Other 23 surfaces were restored, and these restorations failed in 12 occasions (Figure 6.5). This analysis reflects the occurrence of lead time bias when the treatment is decided by the simultaneous strategy of caries lesions detection using visual inspection and radiographic method.

6.4.8 When radiographs brought real benefits in the caries diagnosis of preschool children

Despite the problems previously described, the diagnosis made by the radiographic method associated with the visual inspection could have presented some benefits.

In our study, 8 teeth were submitted to endodontic treatment during the follow-up. From these, in 5 teeth, caries lesions requiring operative intervention were detected by both methods, and they were restored at the baseline. One tooth was restored based on the diagnosis made by the radiographic method, and this restoration failed and the tooth was subsequently submitted to endodontic treatment.

In the remaining 2 teeth, the endodontic treatment was necessary because the caries lesions progressed until reaching the pulp during the follow-up. These lesions, both in proximal surfaces, were overlooked by visual inspection, but radiolucency was presented in the bitewings. Therefore, these 2 teeth (corresponding to 6 dental surfaces) would benefit from the diagnosis made by the simultaneous association with radiographic method.

Moreover, 10 teeth were extracted due to reasons related to dental caries. Two of these teeth were extracted after failure of the endodontic treatment (already considered in the previous paragraph). In 5 teeth, both methods detected the presence of caries lesion and they were restored at the baseline. In the other remaining 3 teeth, presence of caries lesions was not observed by both methods. Thus, considering the extracted teeth in our sample, radiographic method would not have therapeutic impact compared with the visual inspection performed alone.

Radiographic method would also be beneficial in the caries diagnosis procedure performed in preschool children when the visual inspection presented false-positive results that were not confirmed by the radiographs. This situation happened in 3 surfaces (Figure 6.3, pathway a). In other dental surfaces, the decision for operative treatment was due to a positive result (true positive) observed through the visual inspection, but the radiographic method did not have any radiolucency. In 8 of these surfaces, the restorations needed to be replaced at the follow-up (Figure 6.3, pathway a).

Therefore, considering these possible situations above reported, real benefits of the radiographic method could be observed in 17 dental surfaces (0.39% of all 4,383 surfaces included in the study).

Other situations could also be considered as advantages of the radiographic method, although these benefits are not too evident. In 23 dental surfaces, no operative treatment was decided by the visual inspection method, while the radiographs had presented positive results (Figure 6.3, pathway b). However, these surfaces presented new caries lesions during the follow-up (17 surfaces) or were submitted to endodontic treatment, as described previously (6 surfaces). The benefit in these 17 surfaces is not too clear because, this occurrence could be charactrrized as lead time bias, as described before.

Other situation is concerned the restored surfaces that presented a positive result with the radiographic method but a negative one through visual inspection. In

our sample, 19 surfaces with these characteristics have not failed. This is not a clear benefit since part of these lesions could be cases of overdiagnosis.

Therefore, considering an optimistic estimative of the benefits of the radiographs for caries detection in deciduous molars, a total of 53 (6 + 3 + 8 + 17 + 19) dental surfaces (1.21% of all surfaces examined) possibly would have benefits from radiographic method used in association with the visual inspection.

Although proximal surfaces have been pointed as the type of surface that would have more benefits with the use of radiographs, a similar trend was observed compared to the total sample. At proximal and occlusal surfaces, possible benefits of radiographic method were also observed in 1,21% and 1.81% of these surfaces, respectively. The decision trees related to the decision for operative treatment divided by proximal and occlusal surfaces are presented as supplemental material (Appendix B and C).

6.5 DISCUSSION

The present diagnostic strategy for caries detection in children recommended by the clinical guidelines is the simultaneous association between clinical examination and radiographic method (9,17,23–26). Nevertheless, this recommendation is based on accuracy studies, since visual inspection has presented low sensitivity (27), and radiographs tend to increase this sensitivity (26). However, most of these accuracy studies were conducted at laboratory setting or present a high risk of selection bias (26,27). Previous accuracy studies performed in representative samples of children who looked for dental treatment, that is the target population for these diagnostic methods, have observed that radiographs indicated for all patients is not too useful (28,29).

Because of this controversy, we designed a randomized clinical trial comparing the diagnostic strategy combining the results of visual inspection and radiographic method and the use of visual inspection alone (34). Considering the primary outcome, that was number of new operative interventions, we did not observe statistical significant differences between the strategies. Moreover, children allocated to the RAD group received more restorations during all study and had more false-

positive results than children diagnosed and treated according to the visual inspection alone. These data are presented in the Chapter III.

In the present study, we performed a secondary analysis to evaluate the clinical course of all occlusal and proximal surfaces of deciduous molars that were diagnosed using both methods, but treated according to the allocated group. This is the main strength of our study. With this analytical approach associated to the study design, we could evaluate the therapeutic impact of the radiographic method on the visual inspection, and to compare the success of treatment made based on visual inspection alone or combined with radiographs assessment. Moreover, we could estimate the overdiagnosis, mainly with radiographic method, and a possible occurrence of lead time bias.

With regard to the therapeutic impact, we observed that the diagnosis and treatment decisions made with radiographic method did not change the majority of diagnosis and treatments decided with visual inspection alone. Considering all types of treatments (non-operative or operative), the diagnosis reached with the radiographic assessment would change the treatment decision in less than 30% of all surfaces. Moreover, most discrepancies (almost 25%) were in initial caries lesions, corroborating previous observations that visual inspection is more accurate than radiographic method at this threshold (26,27), and that the radiographs tend to underestimate this type of lesions (15,40). Therefore, considering the simultaneous association of the methods, the results obtained with radiographs would not change the classification made by visual inspection. This finding contradicts the authors who advocate the use of radiographs to detect caries lesions before the cavitation, since most initial lesions were not observed in the bitewings (9,17,24-26).

This argument, however, could be valid for lesions with no cavitation, but with radiolucency present in the enamel or in the initial third of dentin. Less than 3% of all surfaces were classified as sound by visual inspection, but presented radiolucency in radiographs. Moreover, in these surfaces, non-operative treatment performed according to the radiographic result was not more successful than the surfaces that did not receive any type of treatment. Therefore, use of radiographs for early detection of caries lesions before the cavitation did not present any advantages comparing with the visual inspection performed alone.

Other reason for the incorporation of the radiographs in the diagnostic strategy for caries detection in children is because this method would detect lesions requiring

operative treatment that were overlooked in the clinical examination. Our findings found a discordance between the methods in less than 4% of the surfaces regarding the decision of an operative treatment for proximal and occlusal surfaces of deciduous molars. Considering the simultaneous association, differences would be observed in 2.7% of the surfaces. If the radiographs, contrariwise, were used to confirm the positive results obtained in the visual inspection (sequential association), a therapeutic change occurred in about 1% of all surfaces.

Therefore, we observed a negligible therapeutic impact of the radiographs on the decision made using visual inspection alone. Taking into account the principle of parsimony, this finding would already be sufficient to do not recommend the radiographs in the diagnostic strategy for caries detection in children. In addition, we must consider the hazards of the ionizing radiation in children, since they are more sensitive to these effects than adults (41). Other problem is concerned the costs. We will deal with the economic aspects related to this study hereafter.

However, other possible harms of the radiographs were evaluated. An expected harm that was confirmed in our study was related to the occurrence of false-positives (42). Radiographic method and the simultaneous association with visual inspection has presented lower specificity than the visual inspection performed alone in several accuracy studies (26,28,29,31). Although most false-positive results were coincident between the methods, a higher number of dental surfaces had false-positive results exclusively with the radiographic method (17 surfaces) than with visual inspection (3 surfaces).

Other strength of our study is that, for the first time, the overdiagnosis with the use of radiographic method for caries lesions detection was appraised. This estimation was possible because we did not perform operative treatment in some dental surfaces classified as sound by the visual method, but that presented radiolucency reaching the dentin in the bitewings. We found that around 65% of dental surfaces of deciduous molars with no clinical signs of cavitated caries lesions but with radiolucency in the radiographic images were overdiagnosed, at least considering a period of two years.

Dental surfaces with no clinical signs of caries lesions requiring operative treatment would not be restored considering the evaluation made only by the visual inspection. These lesions, however, could progress, and a restoration would be necessary afterwards. On the other hand, if these surfaces had a radiolucency

reaching the dentin, and the treatment had been based on the simultaneous association of visual and radiographic method, restorations would be performed at the beginning of the study, and these restorations could fail during the follow-up. To evaluate if the operative treatment could reduce the failure due to the progression of the lesion, we conducted a mediation analysis. However, performing the restoration at the beginning of the study did not influence the failure rate of the dental surfaces with this combination of results (negative in the visual inspection but positive through the radiographic evaluation).

In fact, the failure rates were similar between the surfaces restored or not restored. However, a possible lead time bias could occur in the dental surfaces restored earlier because the result obtained with the radiographic method (42). When we conducted survival analysis for multiple failures, considering the first restoration as the first event, and a necessity of restoration replacement as further events, we observed that performing the restoration due to a positive result obtained with the radiographic method is a clear example of lead-time bias. This situation would only be beneficial if the failure rate of restorations was lower than the occurrence of new lesions in non-restored surfaces. However, the frequency of failures in the restorations made at the baseline was similar to the frequency of surfaces with new caries lesions during the follow-up. Therefore, the simultaneous association of visual inspection and radiographic method anticipated the operative treatment, charactering the occurrence of lead-time bias.

In very few cases, however, the results obtained with the radiographic assessment presented benefits. In 143 dental surfaces that presented discordant results between the methods in the decision for operative treatment, we estimated that 53 surfaces possibly benefited from radiographic method. Nonetheless, in view of several possibilities of harms reported before, this low number of dental surfaces benefited by the radiographs does not justify the incorporation of the method in the diagnostic strategy for caries detection of children in the daily clinical routine.

Nevertheless, our findings should be interpreted with caution, since the examiners and care providers were experienced and trained clinicians, and the study was conducted following the well-controlled characteristics of the clinical trials. Further pragmatic studies should be carried out to increase the external validity of our results. Moreover, our findings can be extrapolated only for caries detection in deciduous teeth. The performance of diagnostic strategies for caries detection

considering oral health outcomes for patients in other age groups should be further tested in longitudinal studies.

In conclusion, use of radiographs in the diagnostic strategy for caries detection in children brings more harms than benefits, and the reasons for these findings are related to the low therapeutic impact, as well as the occurrence of false-positive results, overdiagnosis and lead time bias. Visual inspection brings more benefits taking into account the clinical course of the dental surfaces of deciduous molars. Therefore, the clinical guidelines related to caries care (9,17,23,24) should revise their recommendations regarding caries diagnosis in children.

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The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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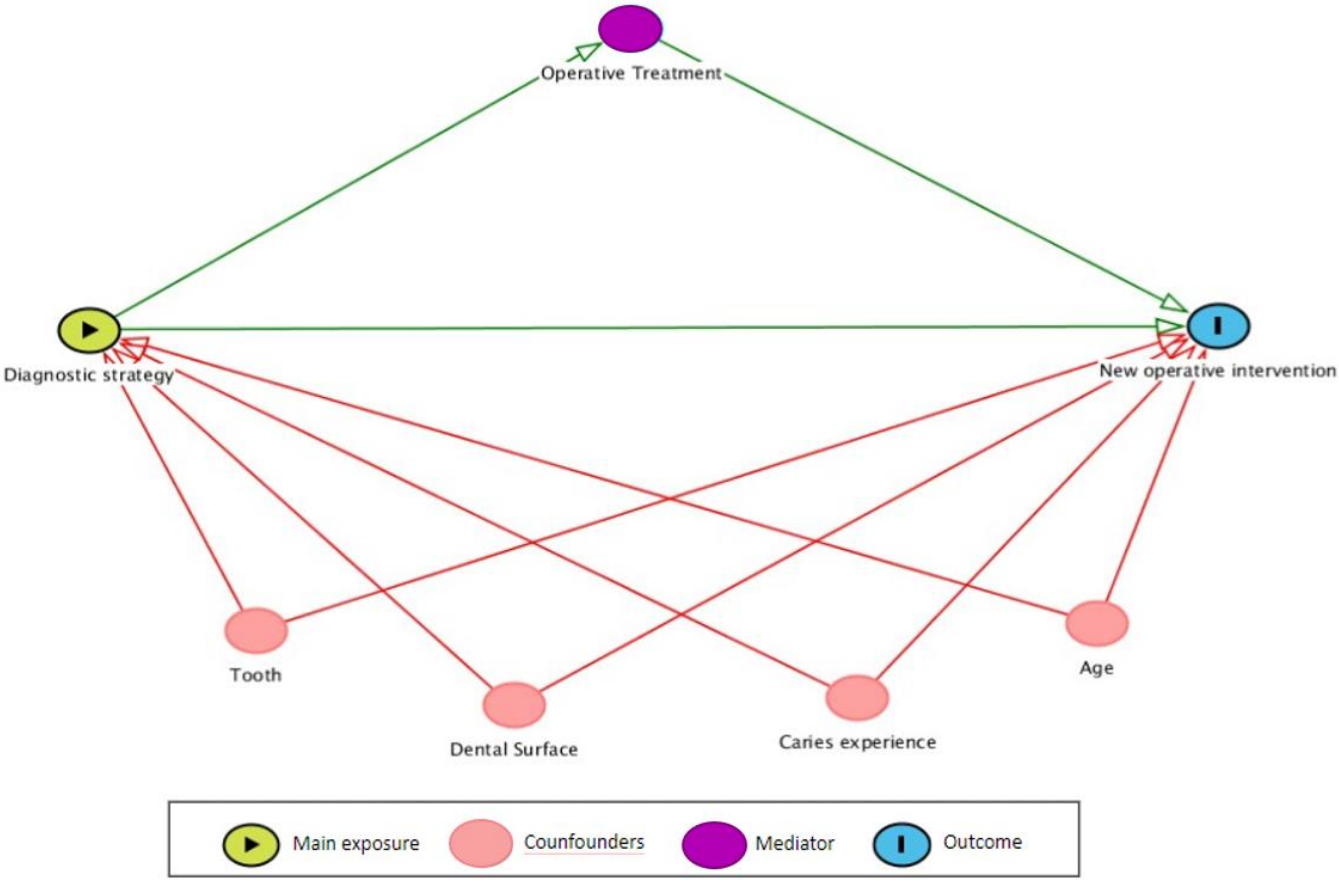
Table 6.1 – Multilevel logistic regression considering the results from different diagnostic strategies for decision to restore the dental surfaces and occurrence of a new operative intervention during the follow-up

Explanatory variables	Univariate analyses	Multiple model 1 **	Multiple model 2 ***
	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Adjusted OR (95%CI)
Diagnostic results			
Vis: positive; Rad: positive	1.00	1.00	1.00
Vis: positive; Rad: negative	0.78 (0.20 to 3.04)	0.85 (0.21 to 3.36)	0.85 (0.21 to 3.39)
Vis: negative; Rad: positive	4.52* (1.95 to 10.49)	6.12* (2.54 to 14.77)	8.62* (2.72 to 27.33)
Vis: negative; Rad: negative	0.09* (0.05 to 0.14)	0.13* (0.07 to 0.21)	0.23* (0.06 to 0.97)
Treatment performed			
Non-restored	1.00		1.00
Restored	11.43* (7.28 to 17.92)		1.87 (0.49 to 7.16)
Dental surface			
Proximal	1.00	1.00	1.00
Occlusal	1.91* (1.41 to 2.59)	1.28 (0.90 to 1.83)	1.29 (0.90 to 1.84)
Type of tooth			
1st molar	1.00	1.00	1.00
2nd molar	0.52* (0.33 to 0.81)	0.55* (0.34 to 0.90)	0.55* (0.34 to 0.90)
Caries experience			
dmf-s = 0 to 3	1.00	1.00	1.00
dmf-s > 3	8.71* (4.20 to 18.06)	5.35* (2.50 to 11.44)	5.37* (2.50 to 11.54)
Child's age			
3 or 4 years old	1.00	1.00	1.00
5 or 6 years old	0.69 (0.33 to 1.43)	0.43* (0.21 to 0.85)	0.42* (0.21 to 0.85)

OR = Odds ratio; 95%CI = 95% confidence intervals; Vis = Visual inspection method; Rad = Radiographic method; dmf-s =number of dental surfaces from primary teeth decayed, missed or filled.
* association statistically significant ($p < 0.05$)
** Multiple model 1 included only the confounding variables according to our predetermined conceptual framework.
*** Multiple model 2 included confounding variables and treatment performed as a possible mediator for failure occurrences

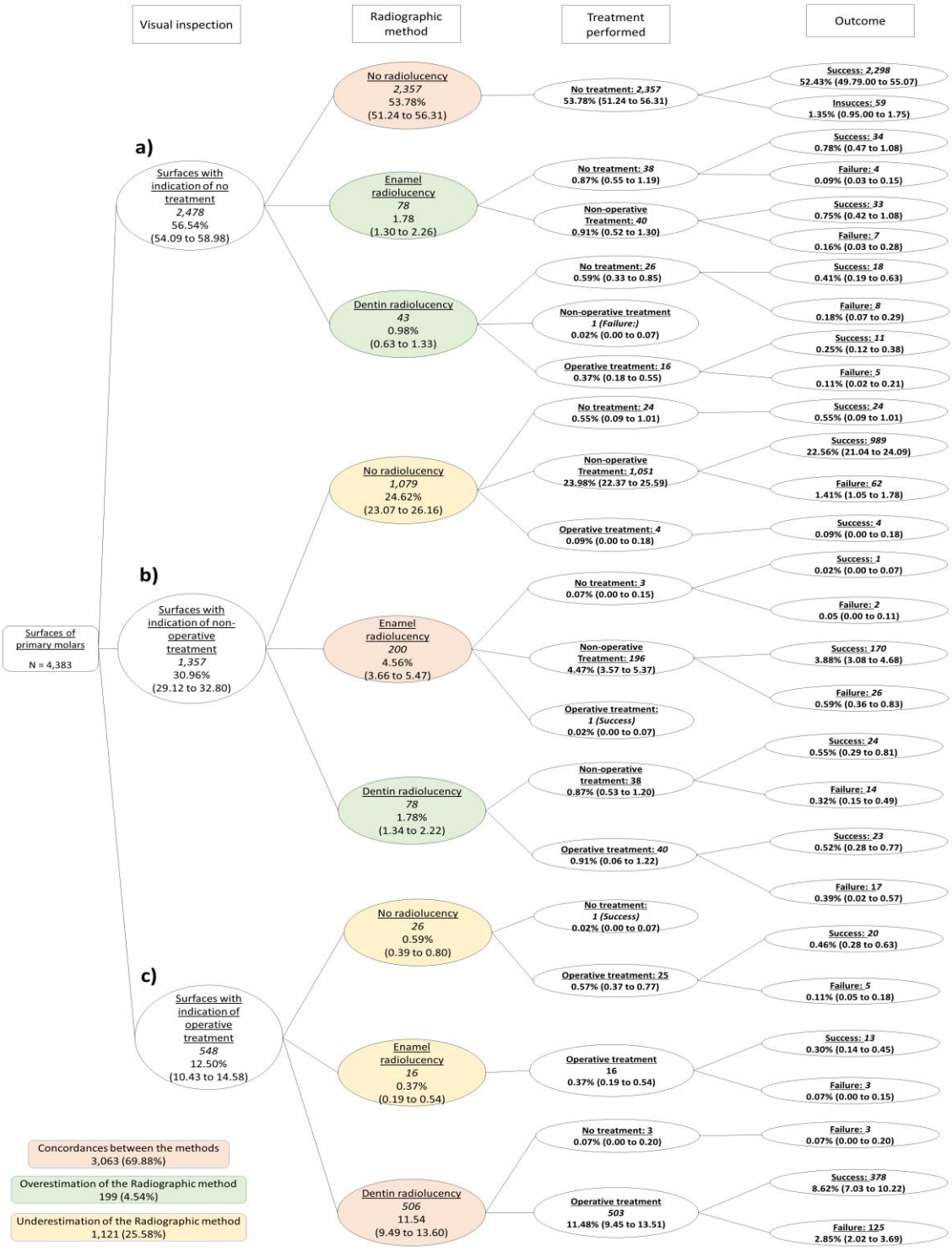
Source: Author

Figure 6.1 – Conceptual framework built to perform the multilevel logistic analysis to evaluate the influence of the results obtained with different diagnostic strategies on occurrence of new operative treatments during the follow-up



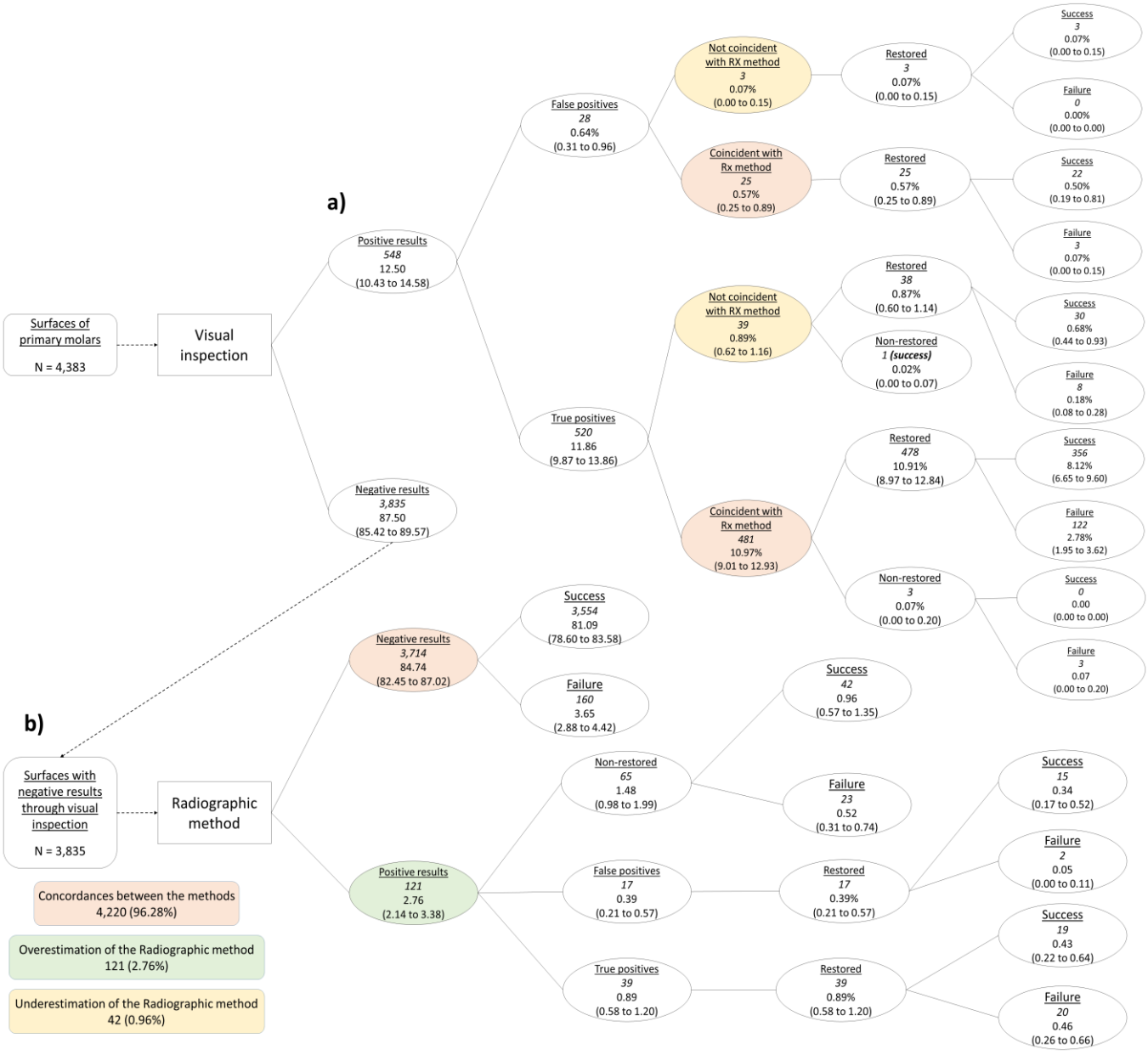
Source: Author

Figure 6.2 – Decision tree considering the caries lesions detection and subsequent treatment performed (no treatment, non-operative and operative treatment) performed first with visual inspection and then with adjunct radiographic method in occlusal and proximal surfaces of primary molars. Italicized numbers indicate the number of surfaces. The regular numbers indicated the frequency in relation to the total number of surfaces, and figures in parenthesis are the 95% confidence intervals adjusted by the cluster



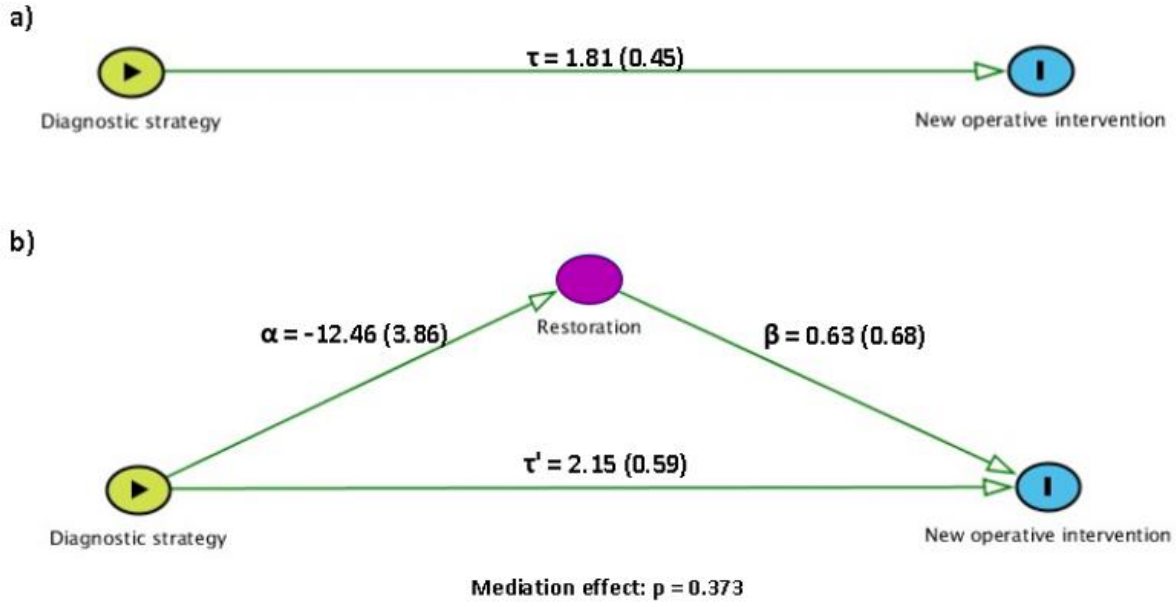
Source: Author

Figure 6.3 – Decision tree for the decision of operative treatment in occlusal and proximal surfaces of primary molars decided first by visual inspection and then with adjunct radiographic method. Italicized numbers indicate the number of surfaces. The regular numbers indicated the frequency in relation to the total number of surfaces, and figures in parenthesis are the 95% confidence intervals adjusted by the cluster



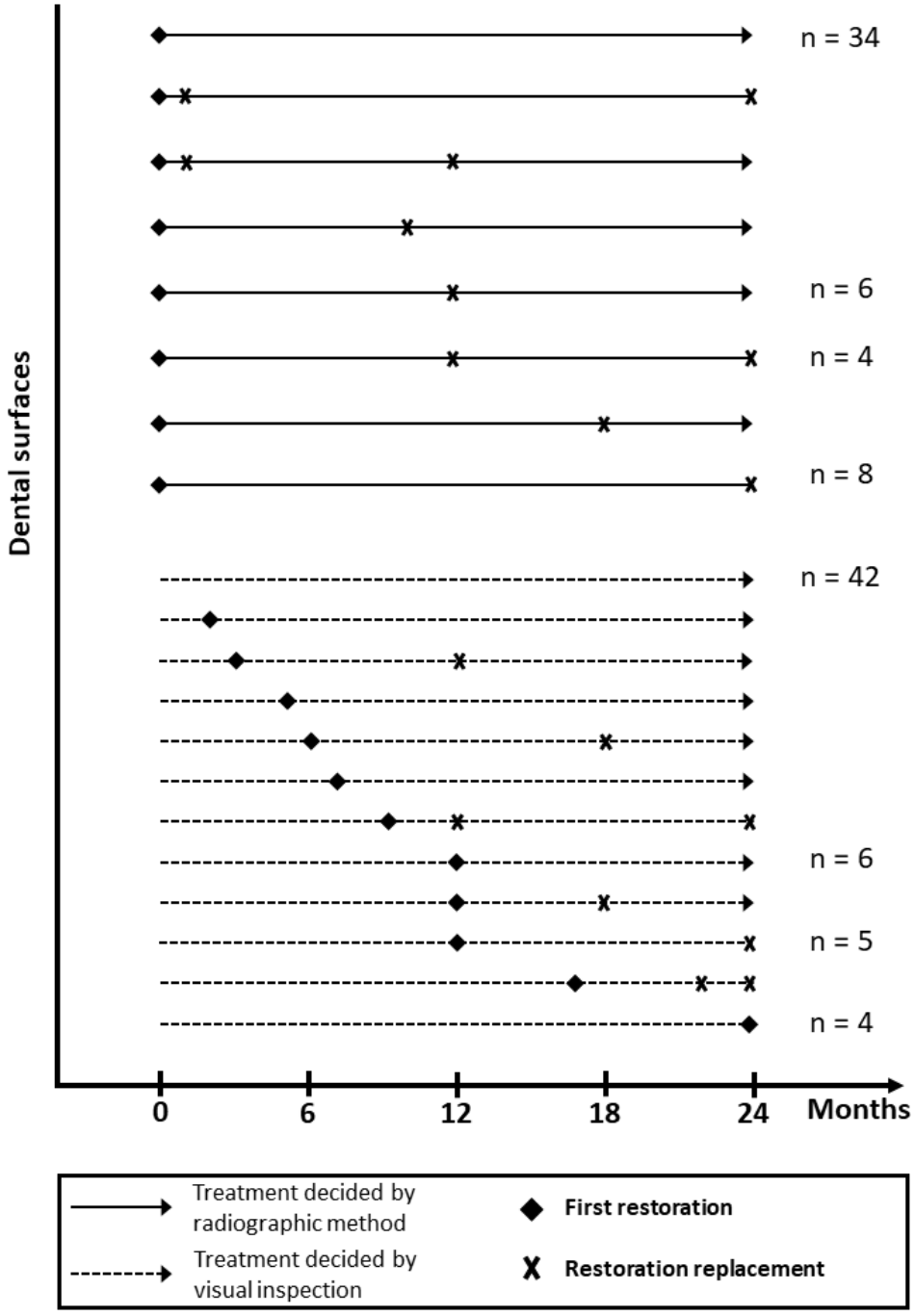
Source: Author

Figure 6.4 – Mediation analysis to evaluate if performing a restoration mediates the occurrence of new operative interventions in the surfaces where caries lesions were missed by visual inspection but detected by radiographs (a: direct effect; b: mediated effect). Numbers represent the multilevel logistic regression coefficients (standard errors) adjusted by type of teeth, dental surface, caries experience and child's age. P value was derived through Sobel test



Source: Author

Figure 6.5 – Time-to-event analysis for the surfaces with caries lesions detected only by radiographic method considering their clinical course (n = 121). Each arrow indicates a dental surface with a negative result through visual inspection, but positive result with radiographs. When N is indicated, there were more than one surfaces following the same clinical course



Source: Author

APPENDIX A – Checklist CONSORT - Consolidated Standards of Reporting Trials

CONSORT 2010 checklist of information to include when reporting a randomised trial*

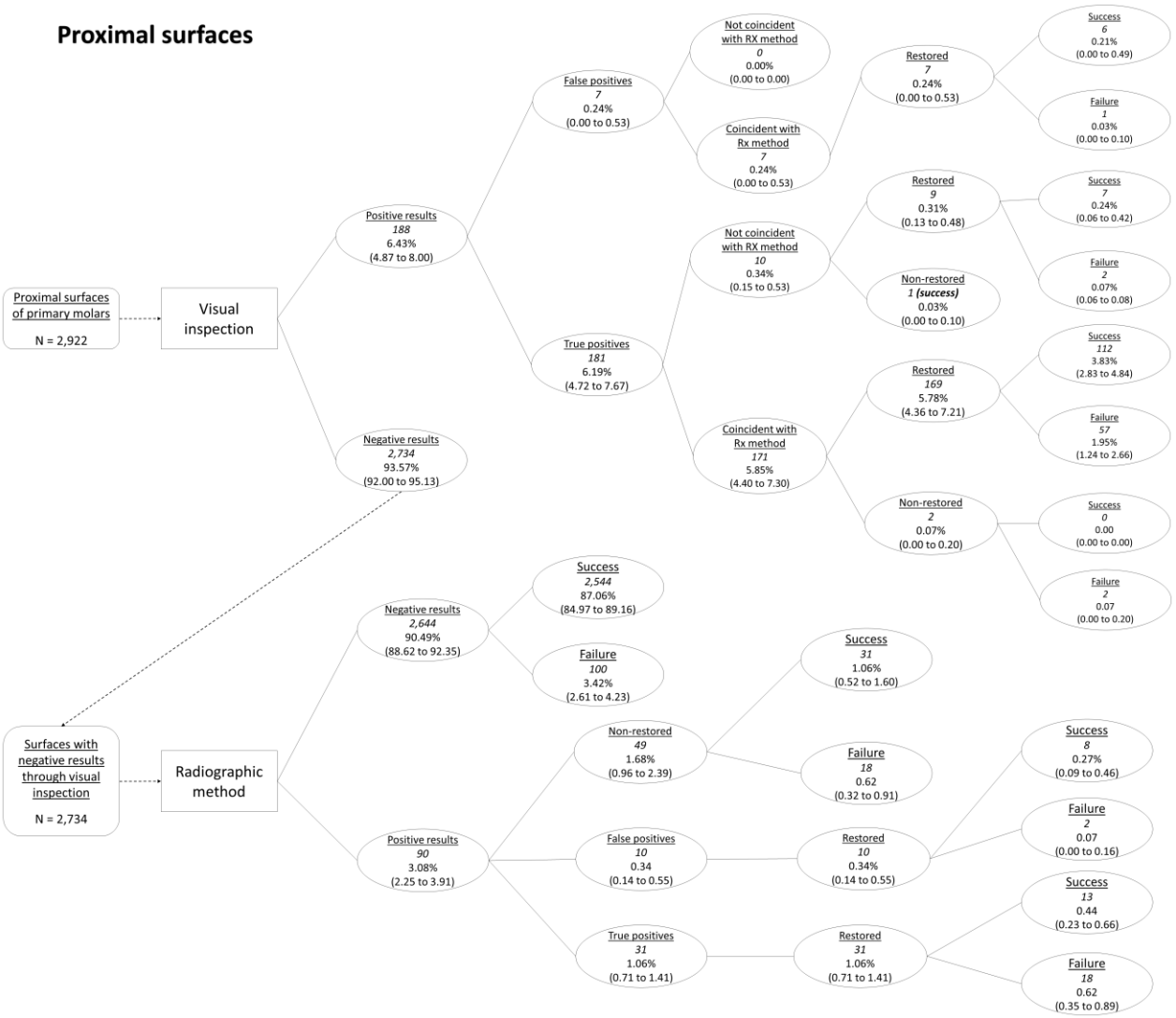
Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	P. 1 – Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	The JDR does not allow structured abstracts. However, all information is included in the abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	P. 3 and 4
	2b	Specific objectives or hypotheses	P. 4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	P. 4 and 5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	P. 5
Participants	4a	Eligibility criteria for participants	P. 5
	4b	Settings and locations where the data were collected	P. 5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P. 6 and 7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	P. 7 and 8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	P. 8
Sample size	7a	How sample size was determined	P. 8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	P. 9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P. 9

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P. 9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	P. 9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	P. 9
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P. 10 and 11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	P. 11 and Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	P. 11 and Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P. 11
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 11 and figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 2 and 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P. 12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P. 15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P. 15 and 16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	P. 13 and 14
Other information			
Registration	23	Registration number and name of trial registry	P. 2 and 5

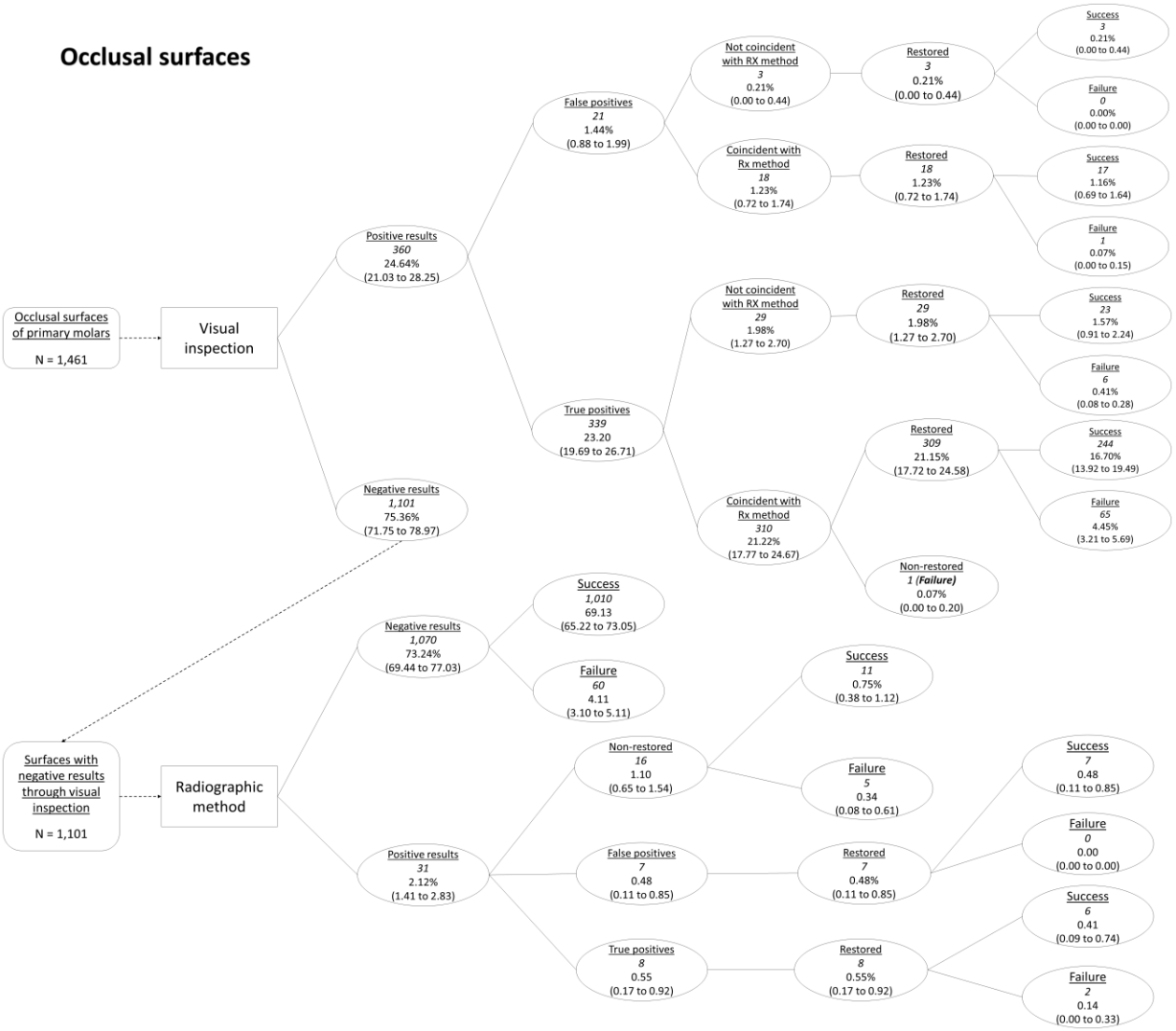
Protocol	24	Where the full trial protocol can be accessed, if available	P. 5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P. 16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

APPENDIX B – Decision tree related to the decision for operative treatment in proximal surfaces



APPENDIX C – Decision tree related to the decision for operative treatment in occlusal surfaces



7 FINAL CONSIDERATIONS

Analyzing all the data collected in the presented chapters, we realized that the use of bitewing radiographs simultaneously associated with the visual examination does not benefit the health of the patients. First, we observed that the therapeutic impact of the association is low, since most treatment decisions are coincident by both methods. Furthermore, radiographs lead to more false-positive results than visual inspection.

Moreover, we found that the use of radiographs does not contribute to best accuracy and prognosis. Also, diagnosis made by radiographs would indicate operative treatment of dental surfaces that would not bother the children and their parents in the next two years (overdiagnosis). Similarly, radiographs precipitate operative treatment of dental surfaces that could cavitate in a subsequent time, with no harms for the patients (lead time bias).

Radiographs simultaneous associated would be beneficial in 2 teeth that the caries lesions were missed by visual inspection and they progressed to endodontic treatment. Moreover, 23 non-restored surfaces due to the decision obtained with the visual inspection failed, and these surfaces presented radiolucency in the bitewings. On the other hand, this simultaneous association provoked harms in 17 dental surfaces with false-positives and in 42 surfaces that were not restored and have not failed in two years (overdiagnosis). Besides that, other surfaces were damaged by lead time bias. Therefore, in addition to the negligible therapeutic impact, in the dental surfaces in which the radiographic method simultaneously associated would change the treatment decision made by visual inspection alone, more harms than benefits were observed.

However, sequential association of visual inspection and radiographic methods could be considered. With this strategy, radiographs could be used to chose the best treatment approach (i.e. non-operative vs. operative treatment) for some lesions detected by visual inspection. This association would be more in line with the minimum intervention dentistry approach. Considering this strategy, bitewings would have been certainly useful in 3 surfaces with false-positive results reached by visual inspection. Moreover, the method could be benefit in 8 surfaces that were restored

following the positive result obtained with visual inspection, but that there were no radiolucency in the bitewings. Therefore, even considering the sequential association, the therapeutic impact was very low. Moreover, the advantage of this diagnostic strategy should be tested through a further randomized clinical trial.

Other possible problems that were not took into account in the present study was related to the hazards of the ionizing radiation, the costs involved and the impact of the diagnostic strategies on children's quality of life. Considering the findings presented in this thesis, however, it is possible to conclude that simultaneous association of visual inspection and radiographic method for caries detection in children, as recommended by most authors and several clinical guidelines around the world, does not avoid new operative interventions when compared to the visual inspection performed alone. Actually, there are many evidences that use of radiographs brings more harms than benefits for the children.

Until now, the present study represents the strong evidence related to caries diagnosis in preschool children. Therefore, the clinical guidelines related to caries care should revise their recommendations regarding caries diagnosis in children.

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[1] According to Vancouver style

ATTACHMENT A - Approval of the Research Ethics Committee

Plataforma Brasil - Ministério da Saúde

Faculdade de Odontologia da Universidade de São Paulo

PROJETO DE PESQUISA

Título: Impacto do exame radiográfico no diagnóstico e decisão de tratamento de lesões de cárie em dentes decíduos

Área Temática:

Pesquisador: Fausto Medeiros Mendes **Versão:** 1

Instituição: Faculdade de Odontologia da Universidade de São Paulo **CAAE:** 02952612.4.0000.0075

PARECER CONSUBSTANCIADO DO CEP

Número do Parecer: 47814

Data da Relatoria: 25/05/2012

Apresentação do Projeto:

Apesar da maioria dos guias de protocolo clínico indicar a realização de duas tomadas radiográficas interproximais para detecção de cárie nos molares decíduos de crianças assintomáticas, a evidência é apenas baseada na sua maioria em estudos transversais in vitro ou realizados em populações de conveniência. Os benefícios e o impacto da realização da radiografia no diagnóstico e na decisão de tratamento de lesões de cárie
em dentes decíduos não têm sido avaliados, no entanto, considerando desfechos ligados ao paciente, tais como, necessidade futura de tratamentos operatórios, custo e qualidade de vida dos pacientes. Assim, o objetivo do presente estudo será avaliar o impacto do exame radiográfico para detecção de lesões de cárie em dentes decíduos comparando com a realização do exame visual isoladamente, considerando diferentes desfechos de validade e desfechos ligados à saúde e bem estar das crianças. Para isso, serão desenvolvidos três diferentes estudos com diferentes desenhos experimentais, que terão os seguintes objetivos específicos: (1) avaliar a validade do exame radiográfico complementar ao exame visual na detecção de lesões de cárie proximais em molares decíduos em crianças com baixa e alta experiência de cárie num estudo transversal; (2) avaliar o impacto do exame radiográfico complementar ao exame visual no diagnóstico e decisão de tratamento de lesões de cárie em dentes decíduos através de um estudo de antes e depois; (3) avaliar o impacto do exame radiográfico complementar ao exame visual para detecção de lesões de
cárie em dentes decíduos sobre necessidades futuras de tratamentos operatórios e qualidade de vida relacionada à saúde bucal da criança, utilizando um estudo clínico randomizado. Para isso, 250 crianças de 3 a 6 anos de idade que buscarem tratamento odontológico na nossa escola serão aleatoriamente alocadas em dois grupos de acordo com a estratégia diagnóstica utilizada para detecção de cárie: exame visual isolado para elaboração do plano de tratamento (grupo controle) ou exame visual associado ao radiográfico (grupo teste). Após elaboração do plano de tratamento por dois examinadores, as crianças serão tratadas e acompanhadas por 2 anos, realizando-se avaliações após 12 e 24 meses da entrada da criança no estudo. O desfecho primário será o número de superfícies com necessidade de tratamento operatório nas consultas de acompanhamento. Isso contemplará a proposição contida no objetivo (3). Após a elaboração do plano de tratamento, as crianças alocadas no grupo controle serão avaliadas com relação ao desempenho na detecção de lesões proximais usando o método visual isolado e associado à radiografia, e um novo plano de tratamento será realizado após a consulta às radiografias. A performance das duas estratégias para detecção de lesões proximais será validada por separação temporária com elástico ortodôntico, e os planos de tratamento com e sem a radiografia serão confrontados e comparados.

Objetivo da Pesquisa:

Objetivos específicos: (1) avaliar a validade do exame radiográfico complementar ao exame visual na detecção de lesões de cárie proximais em molares decíduos em crianças com baixa e alta experiência de cárie num estudo transversal; (2) avaliar o impacto do exame radiográfico complementar ao exame visual no diagnóstico e decisão de tratamento de lesões de cárie em dentes decíduos através de um estudo de antes e depois; (3) avaliar o impacto do exame radiográfico complementar ao exame visual para detecção de lesões de
cárie em dentes decíduos sobre necessidades futuras de tratamentos operatórios e qualidade de vida relacionada à saúde bucal da criança.

Avaliação dos Riscos e Benefícios:

Todas as crianças serão examinadas com um espelho e uma sonda para avaliação das lesões de cárie e farão aseradiografias para essa finalidade. Estes procedimentos são rotineiramente realizados na Disciplina de Odontopediatria da FOUSP, como parte de protocolos de atendimento clínico no mundo todo, apresentandop apenas os riscos inerentes ao procedimento. A exposição aos raios X é pequena e será feita com a proteção adequada, oferecendo riscos mínimos à criança.aquelas mais iniciais, que muitas vezes podem até paralisar sozinhas ou tem evolução mais lenta, não oferecendo grandes riscos à criança.
A criança terá como benefício direto o diagnóstico e tratamento dos problemas bucais apresentados, assim como quando atendida na clínica de Odontopediatria. Além disso, os resultados dessa pesquisa poderão contribuir para que todas as crianças futuramente
recebam a melhor forma de diagnóstico das lesões de cárie e, consequentemente, melhor planejamento do seu tratamento odontológico. Todas as.crianças terão atendimento integral das necessidades de saúde bucal. As crianças cujos pais recusarem participar da pesquisa, serão atendidas e tratadas da mesma forma. Ao término do tratamento, as crianças serão reexaminadas após 12 e 24 meses. Entretanto, qualquer problema entre essas reavaliações podem e devem ser comunicados aos pesquisadores e havendo necessidade de tratamento durante esse período, a criança será atendida e tratada. Após esses 24 meses, as crianças continuarão assistidas pela Disciplina de Odontopediatria para qualquer intercorrência decorrente da pesquisa. Mesmo as crianças que não tiverem seus planos de tratamento feitos com o auxílio da radiografia, por estarem sob acompanhamento, terão suas intercorrências identificadas e sanadas. Como benefício indireto acresce a contribuição para a determinação da melhor forma de diagnóstico de lesões de cárie.

Comentários e Considerações sobre a Pesquisa:

A pesquisa apresenta-se bem estruturada, com objetivos claros e metodologia adequada. Atende aos requisitos éticos de uma pesquisa envolvendo seres humanos e trará benefícios diretos e indiretos aos integrantes voluntários nesta pesquisa.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados os seguintes Termos de Apresentação obrigatória: Termo de Consentimento Livre e Esclarecido (TCLE); Folha de Rosto; Projeto de Pesquisa (Relatório de Pesquisa); Autorização para uso da Clínica. Estes documentos satisfazem a normativa para a realização esta pesquisa. O TCLE atende as exigências sobre o sigilo e disponibiliza o contato com os pesquisadores e o Cep-FOUSP.

Recomendações:

Tendo em vista a legislação vigente, devem ser encaminhados ao CEP-FOUSP relatórios parciais anuais referentes ao andamento da pesquisa e relatório final ao término do trabalho. Qualquer modificação do projeto original deve ser apresentada a este CEP, de forma objetiva e com justificativas, para nova apreciação

Conclusões ou Pendências e Lista de Inadequações:

Tendo em vista que não foram evidenciadas pendências ou lista de inadequações, esta relatoria considera que o projeto de pesquisa deva ser aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 29 de Junho de 2012

Assinado por:
Marcia Turolla Wanderley