MARIA EDUARDA FRANCO VIGANÓ

Is Silver Diamine Fluoride an option for treating non-frankly cavitated caries lesions on occlusal surfaces in toddlers?: findings on its efficacy and parents' acceptance from a randomized controlled trial

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“Mas é preciso ter manha, é preciso ter graça

É preciso ter sonho sempre

Quem traz na pele essa marca possui

A estranha mania de ter fé na vida”

Milton Nascimento

ABSTRACT

Viganó MEF. Is Silver Diamine Fluoride an option for treating non-frankly cavitated caries lesions on occlusal surfaces in toddlers?: findings on its efficacy and parents' acceptance from a randomized controlled trial [dissertation]. São Paulo: Universidade de São Paulo, Faculdade de Odontologia; 2021. Original Version.

The use of silver diamine fluoride (SDF) in non-frankly cavitated lesions had been rarely investigated. This dissertation presents results from a randomized controlled clinical trial (RCT) designed to assess whether SDF would be an efficacious option for fluoride varnish in treating these lesions on the occlusal surfaces in primary molars (NCT02789202). Additionally, we brought findings of a systematic review with meta-analysis (CRD42020186245) on caregivers' perception about the use of SDF and from the trial on their acceptance of treating non-frankly cavitated caries lesions with SDF in toddlers. In the Chapter 1, 109 children aged 1 to 4 years with at least one active caries lesion (ICDAS 1 to 3) on the primary molars were randomized into SDF or fluoride varnish and followed up for 24 months. Intent-to-treat analyses adopting multilevel logistic regression and Cox regression with shared frailty were performed. 309 molars were included and 239 reassessed. SDF prevented more progression (91%) than varnish (81%). Lesions treated using SDF presented, on average, a 69% less chance of progression than this last one when the model was adjusted for severity (initial vs microcavities). The progression was also longer in the SDF group. For the Chapter 2, a search was carried out in the MEDLINE, Scopus, Web of Science, Embase and Open Grey databases until May 2020. RCT, non-randomized clinical trials and observational studies that evaluated the caregivers' perceptions of silver compounds in the treatment of carious lesions were included. The risk of bias was assessed using a specific tool for studies on attitudes and practices. For meta-analysis, the studies were separated considering whether the respondents received the SDF as a treatment for their children or not and whether they were obtained regarding general satisfaction or specifically regarding discoloration. Subgroup and meta-regression analyses were performed to assess the influence of variables associated with the instrument on perception and explore possible sources of heterogeneity. Nineteen studies were included in the systematic

review and 12 in the meta-analysis. The general acceptance of treatment is moderate to well-accepted (26.9% to 100%), varying according to the methodology used. In general, caregivers responded more positively when the child had received the treatment (90%) than when only a picture after the application was shown (59%). Finally, the caregivers' perception of health and aesthetics related to children with enamel lesions treated with SDF or not was assessed (Chapter 3). Children included in three RCT who had enamel lesions treated with SDF were considered. A standard questionnaire was used. Firstly, we evaluated the overall caregivers' perception and then focus on the treated teeth. Multilevel analyses were performed to compare caregiver´s perception of children treated vs non-treated with SDF. The levels were set as the tooth and the child/caregiver. Treatment with SDF did not affect the general perception of caregivers about the aesthetic and oral health conditions related to their children (85%). However, when the assessment was focused, the perception in those children who receive SDF treatment was worse than for those who did not. In conclusion, SDF is a more efficacious option for controlling non-frankly cavitated caries lesions. Besides, it seems to be generally adequately accepted for caregivers. However, a different pattern of acceptance is observed when extra attention is directed to the treated tooth; showing the caregivers' education/information is an important issue when indicating such treatment in children.

Keyword: Cariostatic Agents. Efficacy. Dental Caries. Pediatric Dentistry.

RESUMO

Viganó MEF. O Diamino Fluoreto de Prata é uma opção para o tratamento de lesões de cárie não francamente cavitadas em superfícies oclusais em crianças?: achados sobre sua eficácia e aceitação dos pais em um ensaio clínico randomizado [dissertação]. São Paulo: Universidade de São Paulo, Faculdade de Odontologia; 2021. Versão Original.

O uso do diamino fluoreto de prata (DFP) em lesões não fracamente cavitadas raramente é investigado. Esta dissertação apresenta resultados de um ensaio clínico controlado randomizado (ECR) delineado para avaliar se o DFP seria uma opção eficaz ao verniz fluoretado no tratamento dessas lesões na superfície oclusal de molares decíduos (NCT02789202). Além disso, trouxemos os resultados de uma revisão sistemática com meta-análise (CRD42020186245) sobre a percepção de responsáveis em relação ao uso do DFP e os resultado do ensaio sobre a aceitação deles ao tratamento de lesões de cárie não francamente cavitadas com DFP em crianças. No Capítulo 1, 109 crianças de 1 a 4 anos com pelo menos uma lesão de cárie ativa (ICDAS 1 a 3) em molares decíduos foram randomizadas em DFP e verniz fluoretado e acompanhadas por 24 meses. Análises por intenção de tratar adotando regressão logística multinível e regressão de Cox com fragilidade compartilhada foram realizadas. 309 molares foram incluídos e 239 reavaliados. DFP preveniu mais progressão (91%) do que o verniz (81%). As lesões tratadas com DFP apresentaram, em media, 69% menos chance de progressão quando o modelo foi ajustado pela severidade (lesões iniciais vs microcavitadas). A progressão demorou mais para ocorrer no grupo do DFP. Para o Capítulo 2, foi realizada uma busca nas bases de dados MEDLINE, Scopus, Web of Science, Embase e Open Grey até maio de 2020. Foram incluídos ECR, estudos clínicos não randomizados e estudos observacionais que avaliaram a percepção de responsáveis sobre compostos de prata no tratamento de lesões de cárie. O risco de viés foi avaliado utilizando uma ferramenta específica para estudos de atitutes e práticas. Para a meta-análise, os estudos foram separados considerando se os entrevistados receberam o DFP como tratamento de seus filhos ou não e se foram obtidos quanto a satisfação geral ou quanto, especificamente, a descoloração. Análises de

subgrupo e meta-regressão foram realizadas para avaliar a influência de variáveis associadas ao instrumento na percepção e explorar possíveis fontes de heterogeneidade. 19 estudos foram incluídos na revisão sistemática e 12 na meta-análise. A aceitação geral do tratamento foi de moderada a bem aceita (26.9% a 100%) e variou de acordo com a metodologia utilizada. Em geral, responsáveis responderam mais positivamente quando a criança recebeu o tratamento (90%) do que quando a aplicação foi mostrada com uma foto (59%). Por fim, avaliou-se a percepção dos responsáveis sobre a saúde e estética em crianças que tiveram lesões em esmalte tratadas com DFP (Capítulo 3). Crianças incluídas em três ECR que tiveram as lesões em esmalte tratadas com DFP ou não foram consideradas. Um questionário padrão foi utilizado. Primeiramente, avaliamos a percepção geral e, em seguida, focada nos dentes tratados. Análise multiníveis foram realizadas para comparar a percepção de responsáveis de crianças tratadas vs não tratadas com DFP. Os níveis foram definidos conforme o dente e a criança/responsável. O tratamento com DFP não afetou a percepção geral dos responsáveis sobre as condições estética e de saúde bucal relacionadas a criança (85%). No entanto, quando a avaliação foi focada no dente tratado, a percepção naquelas crianças que receberam tratamento com DFP foi pior do que naquelas que não receberam. Concluindo, o DFP é uma opção eficaz no controle de lesões de cárie não francamente cavitadas. Além disso, geralmente, parece ser aceito de maneira adequada pelos cuidadores. No entanto, um padrão diferente de aceitação é observada quando destacamos o dente tratado, mostrando que a educação/informação é uma questão importante na indicação desse tratamento em crianças.

Palavras-chave: Cariostático. Eficácia. Cárie Dentária. Odontopediatria.

LIST OF ABBREVITIONS AND ACRONYMS

CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Corona Virus Disease
dmft	Decayed missing, and filled teeth index
FRF	Fernanda Rosche Ferreira
HR	Hazard Ratio
ICDAS	International Caries Detection and Assessment System
ICF	Informed Consent Form
IF	Isabela Floriano
IM	Minimum Intervention
ITT	Intention to treat
KHN	Karina Haibara de Natal
MEFV	Maria Eduarda Franco Viganó
MID	Minimal Intervention Dentistry
MMB	Mariana Minatel Braga
NNT	Number need to treat
OD	Odds Ratio
RCT	Randomized controlled clinical studies
RMST	Restricted means survival time
RR	Relative risk
SD	Standart Desviation
SDF	Silver Diamine Fluoride
SE	Standart error

CONTENTS

1 INTRODUCTION

The decline in the prevalence of dental caries in permanent teeth has been observed in the 2000s among Brazilian children (1). The decrease in caries prevalence observed for permanent dentition was not; nevertheless, observed among preschoolers (5-6 years-old children) (1). One reason to collaborate to this panorama may be insufficient oral health care offered to this age group (2). Indeed, burden caries is still a problem in preschoolers throughout the world (3). This finding may be a probable result both from a low actual value given to toddlers' dental care and/or difficulties in managing dental caries for different reasons at this stage.

The untreated, frankly cavitated caries lesions in children have been associated with impairment on their oral health-related quality of life (4). Non frankly cavitated have not impacted on children's life as cavitated ones (4). Nevertheless, detecting and controlling these lesions may benefit younger children because there are more these lesions than the frankly cavitated ones in this age group (5). Similar to caries experience for older children, the presence of non-cavitated carious lesions can be an important predictor for the development of new carious lesions compared to children who do not have the disease (6). These aspects emphasize the importance of controlling dental caries in these young children, aiming to avoid caries progression and the critical situation for older children, discussed above. Besides, it is believed that at this earlier stage of intervention, the use of techniques is less invasive and resulting in the conservation of dental tissue (7). It may be an excellent option contributing to the child's behaviour management at this age.

Oral hygiene and dietary control are primarily responsible for managing non-frankly cavitated caries lesions. However, non-invasive treatment of these lesions based on mineralization control is the best choice when the patient does not respond to controlling the ethiological factors solely (8). Currently, fluoride varnish is considered the most common form of professional use of topical fluoride in preschool children (9). In such cases, its use makes controlling the progression of those non frankly cavitated caries lesions possible since the

varnish combines a high fluoride concentration and a safe manner of professional fluoride use, reducing chances of fluoride intake for young children (9). This type of professional fluoride application is uniquely recommended for children under six by some evidence-based guidelines (10). Nevertheless, the fluoride varnish may be inaccessible to some public health systems due to its cost compared to other available options (11, 12), which may impact health inequalities in use depending on socioeconomic factors (12) and probably enhancing such patterns.

Silver diamine fluoride (SDF) has been a fluoride product usually used as an option even for deprived populations. The efficacy of this product on frankly cavitated caries lesions has been extensively demonstrated in the literature (13, 14). So it can become an element for more comprehensive oral health programs, increasing access to care, improving oral health and decreasing the need for emergency care and treatment (15). Silver compounds have been used in health for a long time due to their antimicrobial properties (16). In the late 1960s, the SDF was developed to prevent and arrest caries lesions (17). This fluoride product has a dual-action to organic and inorganic dental components. It has a bactericidal action on cariogenic bacteria, acts on the dentinal collagen matrix, inhibits demineralization and promotes the remineralization of enamel and dentin (18). In recent years, this product has gained space both in research and dental practice due to its release for use as a dental desensitizer in the United States in late 2014. During the pandemic, the SDF has also been frequently advocated for caries lesion management to reduce the aerosol during dental appointments (19).

Previous studies by our research group pointed to the possibility of using this product in lesions that are not frankly cavitated in situations of greater difficulty in mechanically controlling the biofilm (20, 21). However, little is known about the comparability of this treatment option as an alternative to fluoride varnish. In Chapter 1, the pieces of evidence from a randomized controlled clinical study to assess whether SDF is an option in the treatment of non frankly cavitated caries lesions on the occlusal surface of primary molars in toddlers.

The discolouration caused by SDF application on the treated surface is considered one barrier for its use in clinical practice (19, 22). There is still a resistance to using the SDF in some groups of professionals due to this

aesthetic component. Some experts often point out this aspect as a possible disadvantage of using it. This resistance can be attributed to the lack of robust scientific evidence on this subject (23). Still, dentists attribute this non-acceptance to the caregivers of their patients who treat caries lesions frankly cavitated with the SDF (24). Otherwise, this response may also result from the lack of information about treatment effects using SDF (25). Then, in Chapter 2, we will present a systematic review with meta-analysis to evidence the caregivers and dentists acceptance of using SDF and possible influence of methodology used for measuring that on the results found. Finally, we will demonstrate in Chapter 3 how the caregivers perceive the use of SDF for treating non frankly cavitated caries lesions as proposed by our group, considering both the child's health and dental aesthetic (tooth colour).

2 PROPOSITION

This dissertation aims to answer three different research questions related to the efficacy and acceptance of SDF in Pediatric Dentistry, divided into three distinct chapters. Along with these chapters, we aimed to assess whether SDF is an effective option to fluoride varnish for treating non-frankly cavitated caries lesions (ICDAS scores 1 to 3) on the occlusal surface of toddlers' primary molars. Besides, we aimed to show how is the perception of some stakeholders (caregivers/dentists) regarding the general use of the SDF and whether its use on non-frankly cavitated lesions, as proposed in the randomized clinical trial, would be accepted by caregivers.

3 CHAPTER 1:

Silver diamine fluoride in the management of non frankly cavitated caries lesions in occlusal of primary molars – randomized clinical trial with 24 months of follow-up

3.1 BACKGROUND

Silver diamine fluoride (SDF) is a fluoride compound used in the prevention and detention of caries lesions (17) and which has been gaining ground, again, in dental clinic and research, mainly due to its recent regulation in the United States and, currently, by the pandemic context of COVID-19 (26, 27). Clinical studies using SDF in frankly cavitated lesions have shown it is more effective in arrestment caries than other active treatments (13, 14). Its action mechanism may explain the superior potential of arresting caries using SDF. This cariostatic acts on organic and inorganic dental components, combining the anti-cariogenic properties of sodium fluoride and antimicrobials of silver nitrate (28). Fluoride ions act on the dental surface, inhibiting demineralization and promoting remineralization (29, 30). Besides, the inhibitory effect of silver salts interferes with the enzymatic degradation of dentin collagen (18).

Our group has investigated the possibility of using the SDF to arrest caries lesions that are not frankly cavitated in situations where lesions management may be more challenger (20, 21). We consider non-frankly cavitated lesions those initial lesions or microcavities without evidence of clinical dentine involvement. These lesions are more often observed in toddlers than in older children (5). They are usually scheduled to be managed using non-invasive treatment, including mineralization control (8). The fluoride varnish has been preferred for toddlers under these situations (9, 10, 31). Its easy technique and safety regarding acute fluoride toxicity are the reasons that have

contributed to its recommendation to this age group, even when a modest and uncertain anticaries effect is observed (32).

On the other hand, the fluoride varnish may be inaccessible to some public health systems due to its cost compared to other available options (11, 12), impacting health inequalities by using socioeconomic factors for this use in the real world (12). Oral health inequalities may hamper, in longer-time analyses, burden caries among children, a real oral health problem throughout the world (3). In this sense, SDF seems to be an alternative since it is usually indicated in oral health programs, increasing access to care (15). Besides, it is a safe option for toddlers, sice in different studies involving different age groups, no adverse effect was reported (14). It is unkown if SDF may present a comparable effect to fluoride varnish to the best of our knowledge. Thus, this study aimed to assess whether SDF is an efficacious alternative to fluoride varnish for treating caries lesions non-frankly cavitated on the occlusal surface of primary molars in toddlers. We believe that SDF might be a promising alternative that could reduce oral health inequalities, potentially minimising the need for more complex dental interventions and reducing burden caries during childhood.

3.2 MATERIAL AND METHODS

This chapter was written according to guideline CONSORT (Consolidated Standards of Reporting Trials) (33) (Appendix A).

3.2.1 Trial design and ethical aspects

This study is a randomized controlled clinical trial with two parallel arms (1:1) conducted in a mobile dental unit in Barueri, São Paulo, Brazil. It was approved by the Local Ethics Committee of the Faculty of Dentistry, University of São Paulo, São Paulo, Brazil (protocol 944.742) (Attachment A) and is

registered on the ClinicalTrials.gov platform (NCT02789202). In addition, all participants' parents or legal guardians read and signed the Informed Consent Form (Attachment B). As participants were toddlers and had limited ability for comprehending the study and their participation, the consent was only applicable to parents/guardians. All possible parents'/guardians' doubts regarding protocol were solved before participants' inclusion.

3.2.2 Sample size calculation

For the sample estimation, a significance level of 5% and a power of 80% were taken into account. A progression rate of 36% was assumed for caries in primary molars (34). A clinically relevant difference between the studied groups of 20% was set. The minimum sample size was then increased by 20% to compensate for possible losses of follow-up. Finally, a margin of 20% was added due to the clustering effect since more than one tooth could be treated in the same child. A final sample of 206 teeth with non-frankly cavitated caries lesions was finally estimated. Assuming two molars per child would be, on average, eligible to be included, the minimum sample required was 103 children.

3.2.3 Population, selection and eligibility

Toddlers (1-to-3-year-old) enrolled in nurseries or living in the neighbourhood of the research unit were invited to participate in the study. To be selected, these toddlers should have at least one primary molar with an active non-frankly cavitated caries lesion (ICDAS scores 1 to 3) on the occlusal surface. For screening, a clinical examination was performed by a previously trained and calibrated examiner (IF) following the International Caries Detection and Assessment System – ICDAS (35) associated with criteria for assessing caries lesions activity status (36).

Children who did not have their voluntary participation accepted by their caregivers were also not included. In addition, children who had a medical and/or behavioral condition that required special management/ treatment considerations and who were involved in other research that could impact this study were also excluded.

Those eligible participants who had occlusal surfaces with restorations, sealants, evident cavities of caries or other types of formation defects were generally included in the sample. However, these specific surfaces were not included in the assessments and analyses. The same was done for sound surfaces.

3.2.4 Randomization

The randomization list was generated by the research coordinator of the study (MMB) through the software *Sealed Envelope Ltda* (www.sealedenvelope.com), with blocks of different sizes (varying between 4, 6 and 8). The randomization was stratified considering the child's caries experience for the composition of the strata: low experience (dmft≤2) or high experience (dmft> 2). In the last Brazilian National Epidemiological Survey, a mean dmft of 2.4 was shown for 5-year-old children (37). In addition, the allocation sequence was distributed in opaque envelopes, sealed and sequentially numbered by a team member who was not part of the later phases of the study.

3.2.5 Interventions

All participants received standardized hygiene and dietary orientations by a researcher not involved in the implementation of interventions. The envelope containing the corresponding group was only opened immediately before the start of treatment to guarantee allocation concealment. This same examiner (IF)

was, afterwards, the one who performed the treatment in which the participant had been allocated. Previous to the interventions, occlusal surfaces were cleaning with prophylactic paste and Robinson's brush mounted on a low-speed motor piece. Cotton rollers and saliva ejector were used for moisture control.

Each group intervention was performed as described below. Only included occlusal surfaces received the intervention.

- SDF Group (test group): The petroleum jelly was used to protect from silver impregnation of the perioral region and intraoral soft tissues. The SDF solution (30% Cariestop, Biodinâmica®, Paraná, Brazil) was applied using a disposable microbrush. The solution was left on the surfaces for up to 3 minutes (whenever possible) and then washed. All procedures followed the manufacturer's recommendations.
- Fluoride Varnish Group (control group): the 22600ppm sodium fluoride varnish (Colgate Duraphat®, United States) was applied with a disposable microbrush. No additional procedure was done. Following the manufacturer's instructions, the patient was recommended not to eat hard food or brush his/her teeth for at least four hours after application (38).

During the follow-up, included occlusal surfaces were reassessed regarding their activity status (36) by an external examiner (FRF), unaware of participant's allocation. This assessment was made after tooth cleaning, with good lighting, air-drying for 5 seconds and the aid of a ballpoint probe and dental mirror. If they did not progress but remained active, an external operator (MEFV or KHN) repeated the assigned intervention. All clinical procedures followed the protocol above.

3.2.6 Follow-up

After the intervention on non-frankly cavitated caries lesions, the children were followed for 24 months. Assessments were performed at 6, 12, 18 and 24 months by an examiner (FRF) who was blinded to the assigned treatment and did not participate in any previous study stage.

In these assessments, surfaces were cleaned and then visually evaluated using the ICDAS (35).

3.2.7 Outcomes

The progression of non-frankly cavitated caries lesions treated to frankly dentin cavities (ICDAS scores 5 and 6) was considered the primary outcome.

The survival time of treatments was regarded as a secondary outcome. The time from the intervention to the progression (or to the last follow-up) was calculated based on registered dates on the participant's file. Although the economic and patient-centred have also reported as secondary outcomes in the protocol, they will be explored in further publications given their specificities.

3.2.8 Statistical methods

Interexaminer reproducibilities regarding caries detection and activity status assessment were calculated between examiners involved in the trial using, respectively, the weighted and Cohen's Kappa test (MedCalc® statistical software).

The analyses were performed in Stata® 13.1 statistical software. The statistical unit considered was the tooth. Chi-square test was used to assess the distribution of baseline characteristics between the groups. Furthermore, to facilitate the analyses, age was categorized as 1-2 and 3 years and caries experience as no caries (children with dmft=0) and with caries (children with dmft>0).

The analyses were carried out using an intention-to-treat approach. Conditional multiple imputations imputed Missig data related to both outcomes.

For the primary outcome, multilevel logistic regression was performed using the variables at two levels: patient (distal) and tooth (proximal). Then, the relative effect of using SDF could be estimated using the Odds Ratio (OR) with 95% of confidence interval (95% CI). The analyses were adjusted according to lesions severity, categorized as initial (ICDAS scores 1 and 2) and microcavities (ICDAS score 3). Then, possible different lesions pattern of progression due to their histological and clinical characteristics were considered in the analyses. Subgroup analyses were also conducted considering this categorization. We used logistic regression for imputations of missing data. The received intervention and baseline characteristics as sex, caries experience, and lesion severity were considered for imputing.

Finally, we calculated the absolute risk reduction and also the number needed to treat (NNT - number of patients who need to be treated for one patient to benefit), as a less subjective accounting of the likely benefits of tested intervention) (39).

For the secondary outcome, we performed survival analyses. Cox regression model with shared frailty was used to compare studied groups. Restricted means survival time (RMST) were used to illustrate the differences in time-related treatments effect (40). Only the cases in which participant did not comply with any follow-up were considered as missing data. Conditional imputation was used to impute, firstly, missing data related to the event (caries progression) and, further, the time to progression. The event was imputed using a logistic regression model. For imputing the time to event, a Poisson regression model was used. In both imputation models, we included the same independent variables considered for imputing primary outcome. For the time to event, we also used the occurrence of the event as a predictor.

The significance level for all the tests was set a 5%.

3.3 RESULTS

The inter-examiner reproducibility was 0.91 for the caries detection and 0.71 for activity assessment of caries lesions.

A total of 109 children were included in the study between September 2014 and September 2016. The logistics of scheduling inclusion consultations explains some extra participants as compared with the sample estimation.

At the baseline, Table 3.1 evidences the equivalence of groups before participants receiving the interventions. Three hundred five non-frankly cavitated lesions on occlusal surfaces were treated: 152 (49.8%) with fluoride varnish and 153 (50.2%) with SDF.

Table 3.1 - Baseline characteristics of both treatments groups

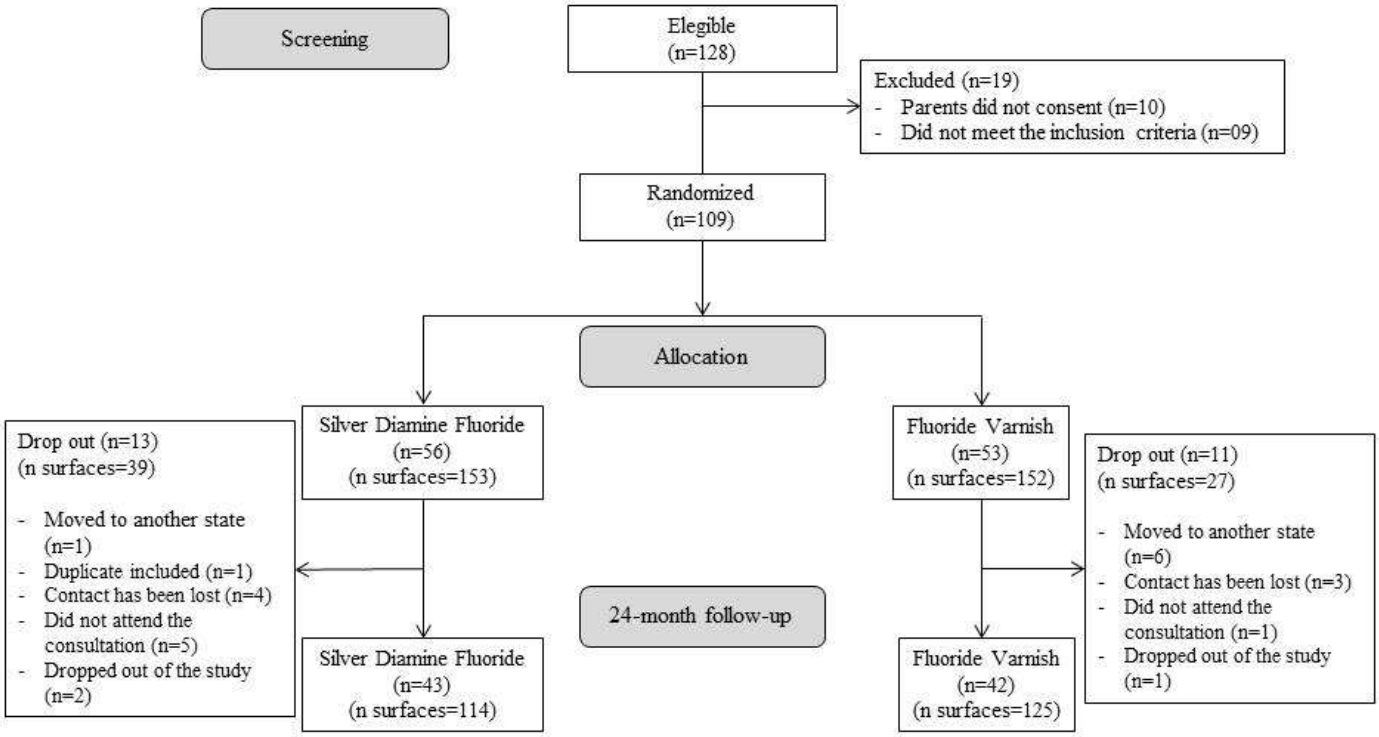
Variables	N†*	Varnish Fluoride	SDF	p value
Linked to the child				
Sex - n(%)‡ Female Male	109	27 (50.9) 26 (49.1)	30 (53.6) 26 (46.4)	0.93
Age (years) – n(%)‡ 1-2 3-4 *Missing data* §	109	31(28.4) 21(19.3) 1(0.9)	26(23.9) 29(26.6) 1(0.9)	0.27
Caries experience – n(%)‡ no caries with caries	109	33(62.3) 20(37.7)	42(75.0) 14(25.0)	0.22
Income (BR$) – Mean (SD) ¶		R$1960.26 (1471.92)	R$2298.13 (1471.92)	0.09
Linked to the tooth				
ICDAS – n(%)‡ Initials Microcavitated	305	130(85.5) 22(14.5)	127(83.0) 26(17.0)	0.65
Biofilm – Mean (SD) ¶		1.11(0.67)	1.14(0.67)	0.5

† N: Absolute number of patients/surfaces included in the study
‡ n(%): Number and percentage of patients/surfaces in relation to the variable
§ *Missing data:* Caregivers who did not complete the socioeconomic questionnaire completely
¶ BR: Brazilian Real; SD: Standard deviation
Source: By the author

The participants' flow since enrollment and the losses during 24-month of follow-up is shown in Figure 3.1. The 24-month evaluations were conducted from October 2016 to September 2018. 239 surfaces were reassessed after this time (78.4%). The rate of loss of follow-up in the SDF group was 25.5%, while in

the fluoride varnish was 17.8%. Those rates are statistically similar between the two groups (p=0.13). The mean time to final reassessment was 30 (±9.5) months. All children who were evaluated at least once during the follow-up were included in the survival analysis, only 8 (drop out rate 7.3%) children were never reassessed.

Figure 3.1 - Flowchart of patients included and followed up in the study



Source: By the author

In 24 months, there was an average increase of one decayed teeth (1.3±1.9) among treated patients, but this increase was found to be similar in both groups (p=0.36). Patients who had lesions that progressed had a higher mean dfmt index (2.4±1.6) than those who did not have that outcome (0.9±1.82). Indeed, caries experience was associated with caries progression (p<001).

In the intention-to-treat analyses, 305 treated surfaces were analysed for both outcomes. In univariate analyses, treatments did not show a statistically significant difference between them. When the model was adjusted for caries lesion severity, the SDF was shown to prevent the progression of non-frankly cavitated lesions compared to fluoride varnish (OR=0.29; 95%CI=0.10 to 0.91, p=0.03) (Table 3.2). While SDF avoided the progression in 92% of treated cases, the fluoride varnish prevented the event in 81% of cases. On average, 10 caries lesions would be treated with receive SDF (instead of fluoride varnish) for one additional lesion not to present caries progression (NNT=10). The difference between groups tended to be even more pronounced among the microcavities (SDF: 70% and fluoride varnish: 41%) (Table 3.3). For such subgroup, NNT decreased to 3.5.

The survival analysis showed similar patterns as above. On average, the lesions treated with SDF had a 53% lower probability of progressin at any time compared to fluoride varnish (HR=0.47; 95%CI=0.22 to 0.99). For both interventions, the initial lesions demonstrated the same time to the event occur (RMST=40.5; 95%CI:39 to 42). However, microcavitated lesions treated with SDF progressed later (RMST= 32 months; 95%CI: 26 to 32 months) than those treated with fluoride varnish (RMST=22 months; 95% CI: 18 to 28 months (Figure 3.2).

Table 3.2 - Univariate and multivariate logistic regression models for testing association between caries progression (primary outcome) and explanatory variables

Explanatory variables	N†	n(%)‡	Univariate OR§ (CI 95%)¶	p value	Multivariate OR§ (CI 95%)¶	p value
Treatment						
(Ref. Fluoride Varnish)	152	29(19.1)				
SDF a 30%	153	14 (9.1)	0.39 (0.14–1.10)	0.07	0.29 (0.10 - 0.91)	0.03
Sex						
(Ref. Female)	153	14(9.1)				
Male	152	29(19.1)	2.67 (0.94–7.58)	0.06	*	*
Age						
(Ref. 1-2 years)	142	22(15.4)				
3-4 years	153	21(13.7)	0.77 (0.27–2.16)	0.62	*	*
Carie experience						
(Ref. no caries)	188	4(2.1)				
With caries	117	39(33.3)	26.7 (8.10–88.07)	0.00	*	*
Severity						
(Ref. initials)	257	22(9.6)				
Microcavitated	48	21(43.75)	18.54 (5.41–63.50)	0.00	18.22 (5.57–59.60)	0.00

† N: Absolute number of surfaces included in the study
‡ n(%): Number and percentage of surfaces in relation to the variable
§ OR: Odds ratio
¶ 95%CI: 95% confidence interval
* Variables not included in the multivariate model

Source: By the author

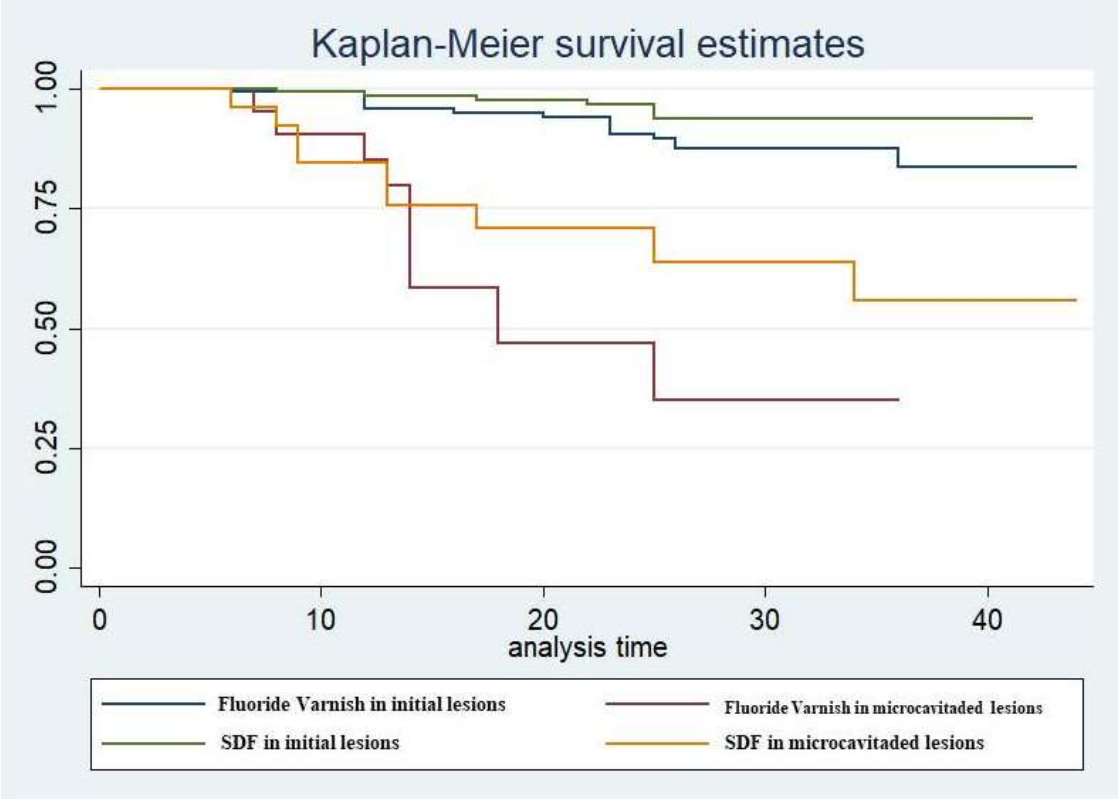
Table 3.3 - Subgroup analyzes for initial and microcavitated caries lesions

		No Progression		Progression	
		n(%)†	95%CI	n(%)†	95%CI‡
Initial	*Varnish*	87.7	(0.78-0.93)	12.3	(0.06-0.22)
	SDF	95.3	(0.90-0.98)	4.7	(0.02-0.10)
Moderate	*Varnish*	41.0	(0.22-0.62)	59.1	(0.38-0.78)
	SDF	70.0	(0.45-0.86)	30.8	(0.14-0.55)

†n(%): Number and percentage of surfaces in relation to the variable
‡95%CI: 95% confidence interval considering the cluster

Source: By the author

Figure 3.2 - Kaplan-Meier curves comparing the SDF and fluoride varnish regarding time to caries progression in surfaces presenting: initial and microcavitated caries lesions



Source: By the author

3.4 DISCUSSION

This randomized clinical trial showed that SDF is an efficacious option as an alternative to the fluoride varnish in treating non-frankly cavitated caries lesions. Although a slight absolute reduction (10%) has been evidenced on the effect of the tested interventions, we could observe 30% relative reduction in the chance of these lesions progression compared to the standard treatment for toddlers (10). Besides this clinical superiority in controlling the progression of such lesions, we could observe a relevant clinical effect of, on average, preventing caries progression of one non-frankly cavitated caries lesion for each ten treated using SDF. The NNT has been pointed out as one of the most clinically useful measures of the effectiveness of interventions established by research (39, 41). There is not an official rule for classifying the intervention regarding NNT.

Nevertheless, NNT may give an idea of the effort needed to avoid one undesirable effect when some intervention is implemented. In this case, avoiding caries progression, we consequently have prevention of pain, quality of life impairment and demand more complex and costly treatments. Finally, it is known that if when the progression rates are low, the NNT are prone to be large (42). Considering our progression rates, we believe a relevant clinical effect could be observed for this indication of SDF, still underexplored.

The magnitude of the SDF effect seems to be even more prominent for the microcavitated lesions (ICDAS score 3). Besides, the difference between groups in the time to caries progression tended to be higher for these lesions. However, this finding should be seen with caution since it is a subgroup analysis that usually lacks statistical power (37, 38) since the sample was not calculated to answer this specific question. This study was designed to investigate the effect of the intervention on lesions clinically restricted to the enamel. That is why lesions ICDAS scores from 1 to 3 were included, even considering the different prognosis that we could expect for initial (ICDAS scores 1 and 2) and moderate caries lesions (ICDAS score 3) (43, 44). Indeed, moderate caries lesions progressed, on average, 5-fold more than initial lesions. Expecting that, subgroup analyses considering the severity of the

lesions were planned. In this sense, possible distinct clinical behaviour between initial and moderate caries lesions caused by their different histopathologic patterns (45) could be explored. It can be considered as a limitation of the study since these analyses are exploratory.

On the other hand, the number of microcavitated lesions included in the study probably reflects their occurrence on occlusal surfaces in toddlers. In an epidemiological survey with Brazilian children, 5 to 10% of children presented at least one moderate caries lesion (considering all dental surfaces)(5). Fifteen per cent of lesions included in our sample showed this condition. Therefore, we believe this exploratory subgroup analyses with the 24-month follow-up data allowed evidence of some important differences between treatments, especially regarding the magnitude of treatment effect related to lesion severity.

The superiority of the SDF in the treatment of non-frankly cavitated lesions may reflect the combined effect of fluoride and silver. Different mechanisms of action of SDF has been tested over the years (18). Nevertheless, some of them would not be expected for enamel lesions, as changes caused by silver into demineralized dentine. Although our study design is not appropriate to address which mechanisms were responsible for the difference in treatments, we can suggest some hypotheses that should be investigated further.

One plausible possibility would be the higher fluoride concentration expected in 30% SDF (35,400 ppm F vs 22600 ppm F in the fluoride varnish). However, a recent study showed the commercial brand of SDF used in our study presented approximately one-third of the expected fluoride concentration (46), presenting, in this case, a lower fluoride concentration compared to fluoride varnish. Despite that, clinical superiority was observed. Certainly, fluoride bioavailability may be influenced by many other factors (47) than concentration by itself. SDF formulations, even presenting different fluoride concentrations, showed similar bioavailability in laboratory tests (46).

Another possible mechanical-physical effect could be related to silver (or silver-derived products, as the silver nitrate). We may speculate that it may change caries lesion surface, acting as a sealant or obliterate the enamel porosities, contributing to caries lesion arrest. Often microcavities may be histologically into the external half of the dentin dentine (48). Then, we could

also expect those modifications in the collagen structure of the dentine and the formation of microwires (49), which can have contributed to the more expressive control of moderate lesions using SDF. Although the silver properties in microbiological control have been extensively addressed, we do not believe such a mechanism may interfere with our findings. Other antimicrobial products, as chlorhexidine, have not been successful for caries control used when daily fluoride is available (49), as using fluoride toothpaste on a regular daily basis. Besides, we did not adopt a periodical protocol of use for SDF, which would not guarantee the antimicrobial effect for a long time.

In conclusion, the effect of the local intervention proposal using SDF can benefit non-frankly cavitated caries lesions management and may be an alternative to the fluoride varnish in toddlers. Besides its effect by itself, we should prospect the possible consequences it could devise. Reducing costs for the public health system and extending such type of dental care where the fluoride varnish is not available may probably contribute to lowering, in the future, the burden caries in toddlers and preschoolers. On the other hand, successful implementation in primary dental care and training adequately the professionals are further challenges to be considered (50).

4 CHAPTER 2:

Perception of the use of silver diamine fluoride for the treatment of caries lesions – how answers may vary depending on who and how it is assessed? A systematic review and meta-analysis.

4.1 BACKGROUND

Silver compounds have long been used in healthcare due to their antimicrobial properties(51). Initially, silver nitrate was used to manage caries lesions (51). Silver fluoride was also indicated in 1900´s due to antibacterial properties associated with caries arrestment (52), but interest in this product declined with the emergence of silver diamine fluoride (SDF). SDF is a fluoride compound developed in the late 1960s (17), and nowadays, it is the most used and studied silver compound for caries management. A significant body of scientific evidence corroborates its effectiveness for managing caries lesions.

Despite continuous clinical use and research on SDF in some areas, e.g. China and Japan (53), it was gradually substituted by other options in several countries. Some opinion-makers have adverted that, over time, the emergence of more sophisticated restorative techniques associated with the possible anti-aesthetic effect reported by patients made these compounds no longer used by dentists (16). Recently, the interest in using and researching SDF seemed to be increasing. The increase in demand for approaches that contemplate the concept of minimum intervention, aiming greater preservation of dental tissues and minor patient' discomfort (7) and approval for SDF use in some countries where dentists were not allowed to use it (26) may be in the background of these changes.

How users perceive the use of SDF (or even other silver compounds) to manage caries lesions is crucial in the professional's decision-making. It may be argued as a barrier raised by dentists when choosing options for this purpose (54). Besides, patient-centred outcomes have increasingly gained

space in dental research since the patient's preferences are one of the four cornerstones of evidence-based practice (22). Patients/caregivers' and professionals' point of views regarding aesthetical perception and acceptability/satisfaction with SDF use have already been explored in a previous systematic review (55). Although the dental discoloration has been reported as the main "side effect" of using SDF, no strict relationship was shown between participants' aesthetical perception and their acceptance of SDF (55).

Nevertheless, a large variety of methodologies for assessing perception patterns was used among the studies. Variations occurred in different fields, e.g. the instrument used to determine participants' perceptions, the population to whom the investigation is focused, and individual's personal experience with SDF. The patients' values may be influenced by method selection and instrument design and situations and/or type of decisions (56). Besides, treatment history influences patients' expectations (57, 58). Thus, we hypothesized methodologic aspects could have influenced such patient-centred outcomes during their assessment. This systematic review aimed to investigate how the patients/caregivers' and professionals perceive SDF usage in caries lesion management and how their perception of the aesthetics and the treatment by itself has been assessed in different studies. Then, using meta-analytic approaches, we investigated how the chosen methodology may have influenced the studied outcomes. Understanding these methodologic aspects may be useful both for digesting the actual contribution of scientific evidence and also collaborate for designing further research protocols.

4.2 METHODS

This paper is reported in according with PRISMA Statement guidelines (59) (Appendix B) and the protocol of this systematic review and meta-analysis was registered in PROSPERO, an international prospective register of systematic reviews (CRD42020186245).

4.2.1 Search strategy

A structured PICO question (P-caregivers/patients/dentists who had their perception evaluated regarding the use of silver compounds in the treatment of caries lesions; I- silver compounds; C- without comparator; O- how perception is assessed and whether the method used for that influences the findings) guided the development of a search strategy that was adapted to the electronic databases Pubmed (MEDLINE), Embase, Web of Science, Scopus and OpenGrey. Two blocks comprised the search strategy, the first with terms related to perception and acceptance and the second related to silver compounds. Boolean operators “OR” and “AND” were applied to combine terms and blocks, respectively. In Appendix C, a detailed description of the search strategies is presented. In addition, the search was carried out in May 2020, without language restriction or the date of publication of the records.

4.2.2 Eligibility criteria and study selection

All titles and authors of the found records were exported to an Excel spreadsheet. Duplications were excluded. Initially, all study titles and abstracts were examined according to the following inclusion criteria: (1) mention of silver compounds, (2) in vivo studies and (3) use in the dental setting. The included records were screened using two exclusion criteria. They must: (1) evaluate the perception of dentists and caregivers regarding the use of silver compounds and (2) use these silver compounds for managing carious lesions. Systematic or narrative reviews were also excluded. For studies with the same data set, only the most complete study was included. Thus, Randomized clinical trials (RCT), Non-randomized Clinical Trials and Observational studies that evaluated the perception of caregivers and dentists in the use of silver compounds in the treatment of caries lesions were finally retrieved. In addition, each author independently checked the references and identified possible studies that could be included.

Both steps were carried out by two independent reviewers (MEFV and KHN). Discussion followed by a consensus resolved the disagreements. When necessary, a third examiner on the subject (MMB) made the final decision. The Cohen Kappa value was calculated to assess the interexaminer reliability. Kappa values of 1.0 and 0.936 were respectively found for the inclusion criteria and exclusion criteria assessments, indicating an almost perfect agreement between the evaluators.

4.2.3 Data extraction

Data extraction was performed independently by two reviewers. Disagreements were resolved through discussion or with the involvement of a third expert examiner on the subject. The following items were collected: authors, year of publication, purpose of the study, study design, country and institution where the research was conducted, sample size, gender distribution of the participants, primary study outcome, the studied silver compound and its specifications (concentration and trademark), the instrument used to assess the perception, when and who applied the instrument, how the product's pigmentation was presented to the participant (clinically or pictures), percentage of acceptance and indifference to the color of the material.

4.2.4 Risk of bias

The risk of bias in each included study was assessed using the McMaster tool for cross-sectional surveys of attitudes and practices (60, 61). This tool consists of five domains: the representativeness of the sample, the adequacy of the response rate, the missing data in the completed questionnaires, the conduct of a pilot test and the established validity of the research instrument. And each of them provides 4 answer options: “definitely yes” classified as low risk of bias, “probably yes” and “probably not” classified

as higher risk of bias and “definitely not” classified as high risk of bias. The studies classified as higher risk of bias were classified as an intermediate category, presented using yellow color in the risk of bias diagram.

4.2.5 Summary of results

The collected data were firstly evaluated qualitatively. Considering users’ perception, for the quantitative analysis, the articles included were divided into four groups according to the outcomes and users’ (caregivers/patients) previous history with the SDF: (1) studies that evaluated the satisfaction of those users’ who had caries lesions treated with silver compounds (outcome: real satisfaction-treated group), (2) studies that assessed the users’ satisfaction but no previous experience with SDF treatment (outcome: hypothetical satisfaction), (3) studies that assessed the users’ acceptance concerning the staining caused on the child's tooth after treatment with SDF (outcome: real staining acceptance – treated group) and, finally, (4) studies that evaluated the users’ acceptance of caregivers regarding staining without a previous experience or a history of undergone treatment (outcome: hypothetical staining acceptance). Studies that showed findings on satisfaction and acceptance were included in both groups, with their respective results.

Whenever available, data were collected considering possible a priori defined subgroups: the location of the evaluated teeth (anterior vs posterior), country where the study was carried out (developed vs emergent), the way the staining was presented to the user (clinically vs picture), type of instrument used (structured vs unstructured) and manner of instrument application (self-applicable vs interviewer). Subgroup analyses were performed for each category to assess whether the subgroups influenced the satisfaction/perception of those caregivers and heterogeneity among the studies.

The satisfaction and staining acceptance rates regarding the SDF use were converted to the absolute number of events for the meta-analysis. The proportion of presenting the outcomes was used as the measure of effect with a

95% confidence interval (95% CI). The data were combined using random-effects models. Heterogeneity was assessed using the heterogeneity test, I^2 (level of inconsistency) and Tau^2/R^2 (estimate of variance between studies).

Meta-regression was performed for group satisfaction-treated to identify possible sources of heterogeneity. The number of included studies did not allow using meta-regression for exploring heterogeneity under other outcomes.

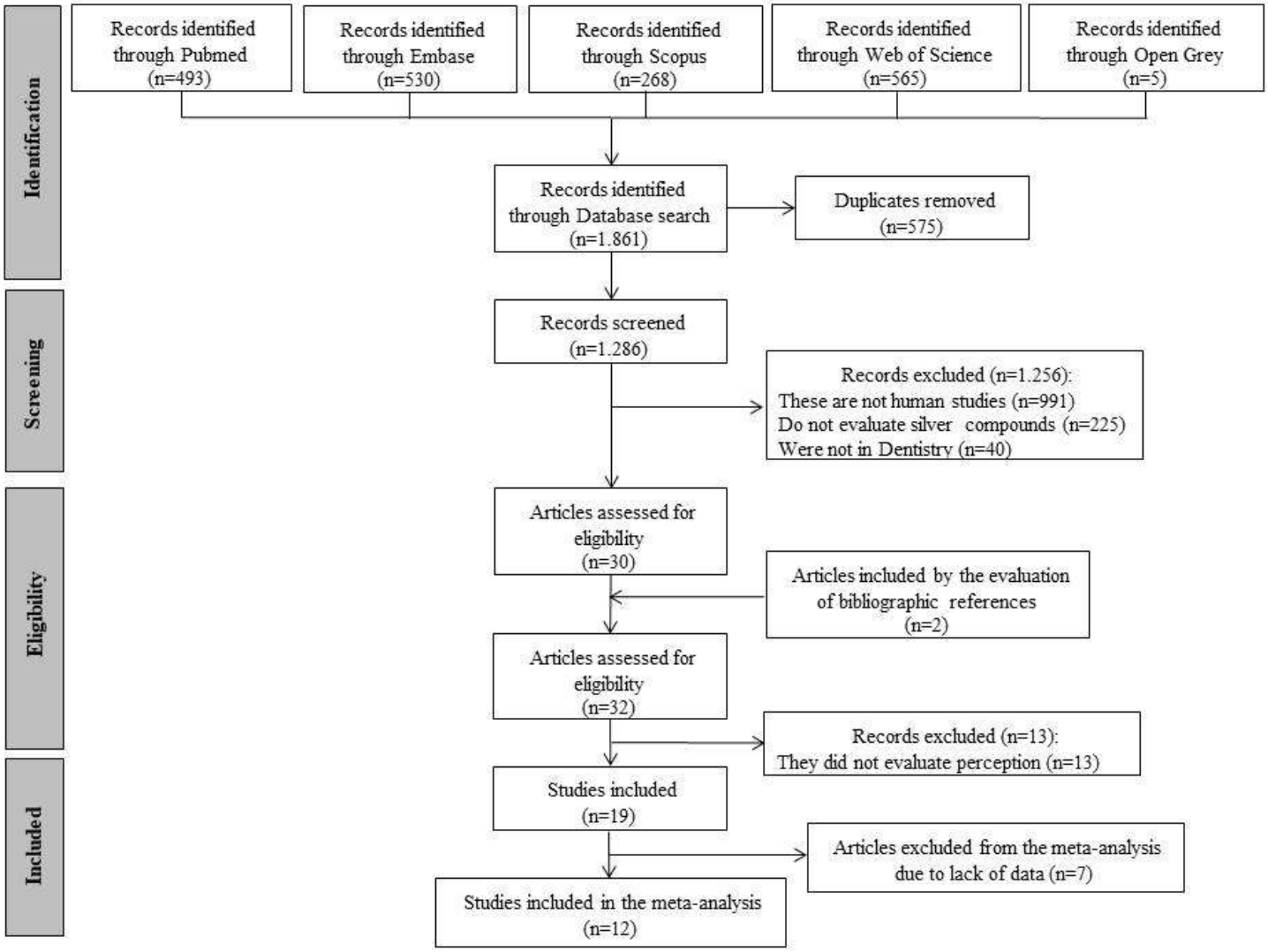
The software RStudio Meta version 4.9.6 (Massachusetts, United States) - 'meta' package - was used for all analyses.

4.3 RESULTS

4.3.1 Study selection

The flowchart of the studies included in the Systematic Review and Meta-analysis is shown in Figure 4.1. Of the 1.861 records identified in the electronic search, 575 were removed because they were duplicated. After reading the title and abstract, 991 articles were excluded. The main reason for non-inclusion was they were not in vivo studies (Figure 4.1). The remaining 30 articles were read in full and evaluated using exclusion criteria. From that, 13 studies were excluded for not assessing the users' or professional perception. Besides, two articles were included due to the evaluation of bibliographic references. Thus, 19 studies were included in the systematic review. Finally, 12 studies that reported any numerical data about one of the described outcomes were included in the meta-analysis.

Figure 4.1 - Flowchart for inclusion of studies in the systematic review and meta-analysis



Source: Author

4.3.2 Synthesis of results

The main characteristics of datasets from included studies are displayed in Table 4.1. Except for two studies in the Portuguese language, all studies were published in English. Thirteen articles were cross-sectional studies, four randomized controlled clinical trials, one non-randomized clinical study and one

retrospective study. Except for one (62), all cross-sectional studies found had the perception regarding the use of silver compounds as the primary outcome. The other studies presented perception as a secondary outcome.

Study	Country	Type of study	Silver Compound	Simple Size (n)	Perception of who	Perception is the primary outcome	Children received treatment with silver compound	Which instrument used to assess the perception	When the instrument used to assess perception was applied	Who applied the perception instrument	Presentation of Pigmentation	% acceptance	Indifference with coloring (%)
A - Hu et al. (2020)†	Singapure	Cross-sectional study	SDF	200	Caregivers	Yes	No	Likert Scale 5 points	Not specified	Self-applicable	Picture	62	35
B - Hu et al. (2020)†	Singapure	Cross-sectional study	SDF	200	Caregivers	Yes	No	Likert Scale 5 points	Not specified	Self-applicable	Picture	62	65
Huebner et al. (2020)	USA	Retrospective study	SDF	319	Caregivers	Yes	Yes	Interview	Not specified	Trained interviewer	Clinically	80.3	70
Cernigliaro et al. (2019)	USA	Cross-sectional study	SDF	48	Caregivers	Yes	Yes	Interview	When they arrived for an operative treatment schedule	Dentists	Clinically	81.3	87.5
Kumar et al. (2019)	USA	Cross-sectional study	SDF	546	Caregivers	Yes	Yes	Likert Scale 5 points	In dental visits	Trained interviewer	Clinically	79.5	29.1
Jiang et al. (2019)	China	Randomized controlled clinical study	SDF	194	Caregivers	No	Yes	Likert Scale 5 points	10 weeks after applying the SDF	Self-applicable	Clinically	38	Not specified
Vollú et al. (2019)	Brazil	Randomized controlled clinical study	SDF	67	Caregivers	No	Yes	Interview	2 days after applying the SDF	Dentists	Clinically	Not specified	97
Bagher et al. (2020)	Saudi Arabia	Cross-sectional study	SDF	104	Caregivers	Yes	No	Likert Scale 5 points	Not specified	Trained interviewer	Picture	56.6	17

*continue

*continuation

A - Alshammari et al. (2019)†	Saudi Arabia	Cross-sectional study	SDF	222	Caregivers	Yes	No	Likert Scale 5 points	Not specified	Self-applicable	Picture	Not specified	9.9
B - Alshammari et al. (2019)†	Saudi Arabia	Cross-sectional study	SDF	222	Caregivers	Yes	No	Likert Scale 5 points	Not specified	Self-applicable	Picture	Not specified	3.2
Crystal et al. (2019)	USA	Cross-sectional study	SDF	120	Caregivers	Yes	No	Questionnaire	Waiting room	Self-applicable	Picture	Not specified	Not specified
Clemens et al (2017)	USA	Randomized controlled clinical study	SDF	30	Caregivers	No	Yes	Likert Scale 5 points	2-3 weeks after applying the SDF	Self-applicable	Clinically	100	96.7
A - Duangthip et al. (2018)‡	China	Randomized controlled clinical study	SDF	222	Caregivers	No	Yes	Questionnaire	Baseline, follow-up 18 and 30 months	Self-applicable	Picture	67.6	60.3
B - Duangthip et al. (2018)‡	China	Randomized controlled clinical study	SDF	222	Caregivers	No	Yes	Questionnaire	Baseline, follow-up 18 and 30 months	Self-applicable	Picture	61.5	56.3
C - Duangthip et al. (2018)‡	China	Randomized controlled clinical study	SDF	222	Caregivers	No	Yes	Questionnaire	Baseline, follow-up 18 and 30 months	Self-applicable	Picture	70.8	64.4
D - Duangthip et al. (2018)‡	China	Randomized controlled clinical study	SDF	222	Caregivers	No	Yes	Questionnaire	Baseline, follow-up 18 and 30 months	Self-applicable	Picture	62.3	55
Chhokar et al. (2017)	USA	Cross-sectional study	SDF	222	Dental hygienists licensed	Yes	Not applicable	Likert Scale 5 points	Not specified	Self-applicable	Not specified	91	86
A - Crystal et al. (2017)†	USA	Cross-sectional study	SDF	120	Caregivers	Yes	No	Questionnaire	Waiting room	Self-applicable	Picture	53.6	67.5

*continue

*continuation

B - Crystal et al. (2017)†	USA	Cross-sectional study	SDF	120	Caregivers	Yes	No	Questionnaire	Waiting room	Self-applicable	Picture	26.9	29.7
Nelson et al. (2018)	USA	Cross-sectional study	SDF and Silver Nitrate	74	Pediatric dentistry residency program directors and associate program directors	Yes	Not applicable	Questionnaire	Not specified	Self-applicable	Not specified	Not specified	Not specified
Vollú et al. (2020)	Brazil	Cross-sectional study	SDF	409	Dentists	Yes	Not applicable	Questionnaire	Not specified	Self-applicable	Not specified	13.2	90.7
Triches et al. (2009)	Brazil	Cross-sectional study	SDF	50	Caregivers	Yes	No	Questionnaire	Not specified	Self-applicable	Picture	92	52
Patel et al. (2019)	India	Cross-sectional study	SDF	180	Paedodontic post-graduates and paediatric dentists	No	Not applicable	Questionnaire	Not specified	Self-applicable	Not specified	Not specified	Not specified
Belotti et al. (2015)	Brazil	Longitudinal clinical study	SDF	21	Caregivers	Yes	Yes	Questionnaire	After finishing the treatment	Self-applicable	Clinically	76.6	100
Antonioni et al. (2019)	USA	Cross-sectional study	SDF	582	Members of AAPD - paediatric dentists	Yes	Not applicable	Questionnaire	Not specified	Self-applicable	Not specified	Not specified	Not specified

†Studies whose sample was divided between anterior and posterior teeth; ‡Studies whose sample was divided between

Source: By the author

Mostly, studies focused on the users' perception related to SDF. In only one study, the perception of silver nitrate was evaluated (54). In six studies (24, 63-67) patients (children) had undergone treatment with SDF, and their caregiver's perception was assessed.

Few studies reported the presence of a trained interviewer to apply the assessment instrument (64, 68-71). All others were self-applicable instruments. Mainly, structured questionnaires, using a 5-point Likert scale, were used.

Caregiver/dentist satisfaction with the silver compound was less than 50% in three studies (66, 71, 72) and seven of the included articles did not report this data. Only in seven studies, the indifference concerning the staining caused by the use of silver products was less than 50% (63-66, 70). Only one study reported findings of comparisons between the perception of staining in posterior and anterior teeth (65).

Four studies that evaluated dentists' perception of silver compounds and everyone used a self-administered instrument (54, 62, 71, 73, 74). In addition, these studies were not included in the quantitative analysis because they did not report their results numerically or comparable to others to conduct a meta-analysis.

In Patel et. al (62) and Vollú et al. (71), SDF was the material of choice and factors related to this choince was explored. Factors such as the patient's age and behavior (62, 71). Other study explored possible barriers to the use of silver compuounds (54, 73), revealing dentists reported that the greatest barrier to the use of these products is parental acceptance (98% - Nelson et al. (54)), (56% - Chhokar et al.(73)). The latter would not accept treatment due to staining (54, 73).

Jiang et al. (72) and Crystal et al. (24) were not included in the meta-analysis because they did not report the number of events (either the percentage of the outcome occurrence) related to data on the perception of caregivers concerning the use of silver compounds for managing caries lesions.

Figure 4.2 shows the classification of the studies according to the established outcome (satisfaction vs staining acceptance) and previous experience using the silver compound (actually treated vs hypothetical).

Figure 4.2 - Classification of studies included in the meta-analysis

Satisfaction-treated	Satisfaction-hypothetical	Staining-treated	Staining-hypothetical
Huebner et al. 2020	A - Hu et al. 2020	Huebner et al. 2020	A - Hu et al. 2020
Cernigliaro et al. 2019	B - Hu et al. 2020	Cernigliaro et al. 2019	B - Hu et al. 2020
Kumar et al. 2019	Bagher et al. 2020	Kumar et al. 2019	Bagher et al. 2020
Clemens et al. 2017	A - Crystal et al. 2017	Vollü et al. 2019	A - Alshammari et al. 2019
A - Duangthip et al. 2018	B - Crystal et al. 2017	Clemens et al. 2017	B - Alshammari et al. 2019
B - Duangthip et al. 2018	Triches et al. 2009	A - Duangthip et al. 2018	A - Crystal et al. 2017
C - Duangthip et al. 2018		B - Duangthip et al. 2018	B - Crystal et al. 2017
D - Duangthip et al. 2018		C - Duangthip et al. 2018	Triches et al. 2009
Belotti et al. 2015		D - Duangthip et al. 2018	
		Belotti et al. 2015	

Source: By the author

4.3.3 Risk of bias

Figure 4.3 shows the risk of bias assessment using the McMaster tool for cross-sectional surveys of attitudes and practices. Only four studies (65, 68-70) were classified as “high risk of bias” (in red colour). The domain that was, in its entirety, classified in the studies as “higher risk of bias” was the missing data within completed questionnaires. While, the domain most classified as “low risk of bias” was the representativeness of the sample.

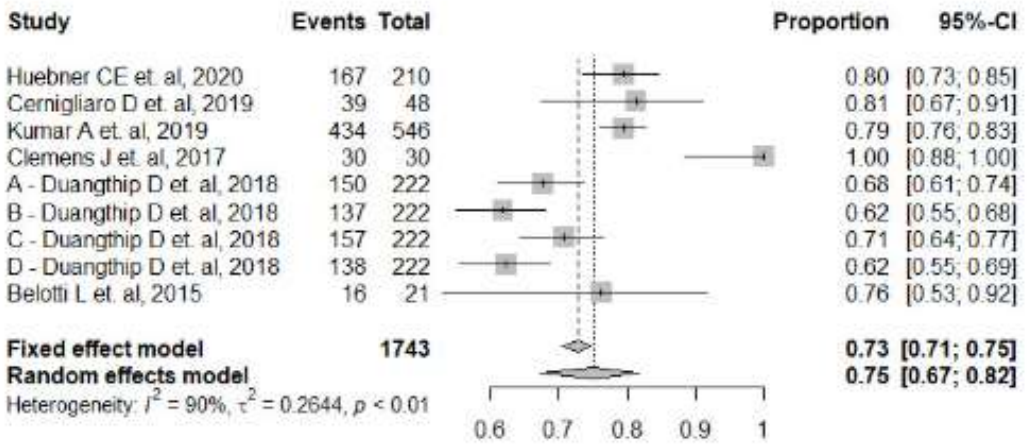
Figure 4.3 - Bias risk assessment using the McMaster tool for cross-sectional surveys of attitudes and practices

Source: By the author

4.3.4 Meta-analysis

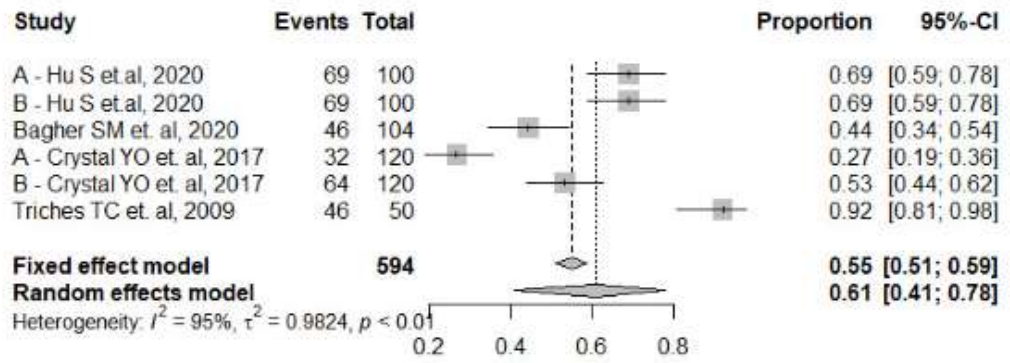
Figures 4.4, 4.5, 4.6 and 4.7 illustrate the results obtained in the meta-analysis of the four study outcomes (satisfaction-treated, satisfaction-hypothetical, staining-treated, staining-hypothetical). The satisfaction with the SDF use was moderate (50-70%) and tended to be higher when the previous experience of SDF treatment was present (Figures 4.4. and 4.5). On the other hand, acceptance regarding SDF-caused staining was also around 55% and similar between those who had had previous experience using SDF in their kids (Figures 4.6 and 4.7).

Figure 4.4 - Forest plot of the group that evaluated the caregivers' satisfaction about treatment with silver compounds in children who had received treatment (satisfaction-treated)



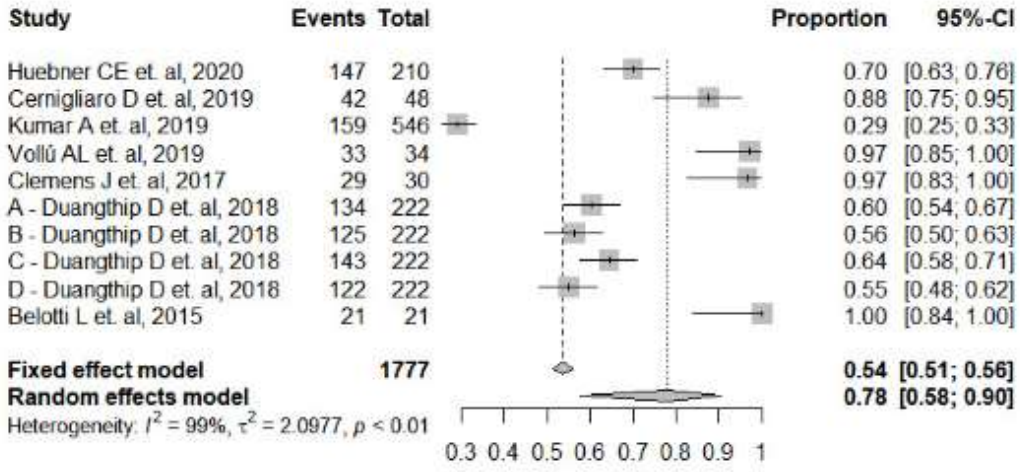
Source: By the author

Figure 4.5 - Forest plot of the study group that evaluated caregivers' satisfaction but children had not received any type of treatment with silver compounds (satisfaction-hypothetical)



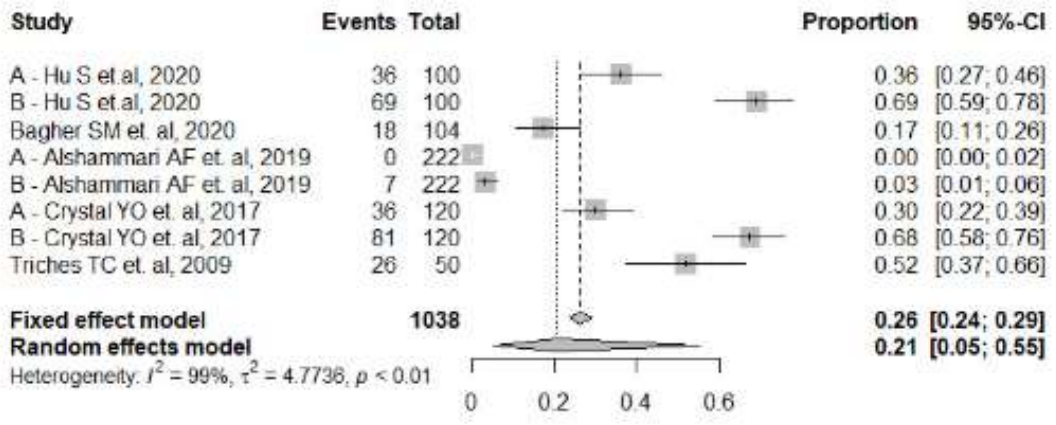
Source: By the author

Figure 4.6 - Forest plot for the study group that evaluated staining among caregivers whose children had received treatment with silver compound (staining-treated)



Source: By the author

Figure 4.7 - Forest plot of the group of caregivers who evaluated the staining after the treatment of caries lesions with silver compounds but their children patients had not received this treatment (staining-hypothetical)

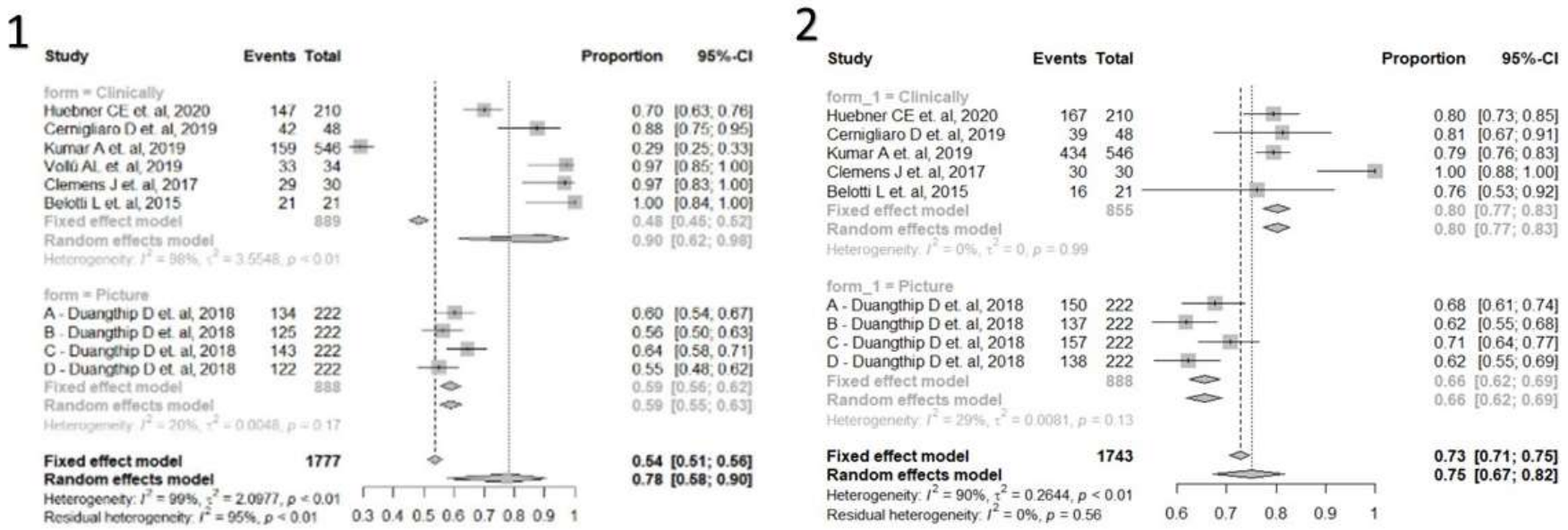


Source: By the author

4.3.4.1 Subgroup Picture vs. Clinically

In this subgroup analysis, only the groups in which the patients were treated were analyzed. For the staining-treated group, there was a statistically significant difference (p=0.038). The groups that evaluated pigmentation clinically after treatment with silver compounds had a better acceptance of staining in relation to patients who evaluated pigmentation by pictures (90% Clinically vs. 59% Picture). For the satisfaction-treated group, there was a statistically significant difference (p=0.0001). The subgroup of studies that evaluated treatment satisfaction showing the tooth clinically had better satisfaction than by photographs (80% Clinically vs. 66% Picture). The forest plots of this subgroup are illustrated in figure 4.8.

Figure 4.8 - Forest plot subgroup Picture vs. Clinically: 1. staining-treated group 2. satisfaction-treated group



Source: By the author

4.3.4.2 Subgroup Developed countries vs Emerging

In this subgroup, there was no difference regarding the acceptance staining on caregivers with previous history of using SDF in their kids (developed countries=0.77, 95%CI= 0.42-0.94; emergent countries=0.79, 95%CI: 0.51-0.93; p=0.93). However, still considering the previous experience with SDF, caregivers from developed countries showed a higher satisfaction rate in using the product (developed countries =0.80, 95%CI: 0.78-0.83; emergent country=0.66, 95%CI: 0.62-0.70; p=0.0001). The same trend of higher caregivers' acceptability in developed countries was observed for hypothetical outcomes (staining acceptance - developed countries=0.50; 95%CI: 0.33-0.68; emergent countries=0.05; 95%CI 0.003-0.45 / satisfaction - developed counties=0.80, 95%CI: 0.78-0.83; emergent countries= 0.66; 95%IC:0.62-0.70; p=0.0001).

4.3.4.3 Subgroup Interviewer vs Self-applicable

In this subgroup, there was no statistical difference between any of the groups (Staining-treated: Interviewer=0.78, 95%IC: 0.42-0.94; Self-applicable=0.78; 95%IC: 0.51-0.9; p=0.99 / Satisfaction-treated: Interviewer=0.80, 95%IC: 0.77–0.8; Self–applicable=0.74; 95%IC: 0.59-0.85; p=0.359 / Staining-hypothetical (Self-applicable proportion=0.21; 95%IC: 0.04-0.62; Interviewer=0.17; 95%IC: 0.11-0.25; p=0.82) / Satisfaction-hypothetical: (Self-applicable proportion=0.74, 95%IC: 0.77-0.82; Interviewer proportion=0.80, 95%IC: 0.59-0.85; p=0.36).

4.3.4.4 Subgroup Structured vs Unstructured questionnaire

The studies using non-structured questionnaires were associated with better caregivers' acceptance of silver compounds staining than those studies that used a structured questionnaire (Structured =0.71, 95%CI: 0.48-0.87/ Unstructured=0.92, 95%CI: 0.80-0.97, p=0.0335). The same was not observed for caregivers' satisfaction (Structured=0.75, 95%CI: 0.66-0.82; Unstructured=0.81; 95%CI: 0.68-0.90; p= 0.366). For those with no previous experience in having child treated with SDF, acceptance of staining seemed not to be interfered with the form of application of questionnaire (Structured=0.14, 95%CI: 0.02-0.55/Unstructured=0.49, 95%CI: 0.24-0.74; p=0.131), but hypothetical satisfaction was higher when used structured instruments (0.71, 95%CI: 0.50-0.86 than unstructured ones (0.39, 95%CI: 0.22-0.59; p=0.029).

Another subgroup was evaluated by analyzing whether there was a difference in acceptance of pigmentation and satisfaction between anterior and posterior teeth. Only two studies were included for this meta-analysis because only these studies had sufficient data to perform it. Then, we considered them as different samples in the same study. There was no statistically significant difference between the caregivers' satisfaction with SDF when anterior (0.48, 95%CI: 0.20-0.76) or posterior (0.61, 95%C: 0.50-0.71; p=0.415) had been treated. Regarding the acceptance of staining caused by silver compounds, 6 studies were included, also having no significant difference between areas in which the treatment had been used (anterior teeth=0.05, 95%CI: 0.001-0.7 /posterior teeth =0.35, 95%CI:0.05-0.84; p=0.33).

Metaregression was performed to understand and detect points that could influence the high heterogeneity of our study. For this analysis, only satisfaction-treated group studies were included (68-70, 75-77). All variables tested, except for the questionnaire structure, were associated with heterogeneity among studies (Table 4.2). Some variables as the manner of presenting the problem and country where research was conducted explained

mostly or completely this heterogeneity, resulting in a residual heterogeneity close to 0.

Table 4.2 - Results of the Metaregression carried out with the satisfaction-treated group

Independent variable	**Type of variable**	**Univariate p value**	**95%CI**	**I^2 (Residual Heterogeneity)**
Ref. Clinical Picture	CATEGORICAL	-0.7581	-3.24 to -0,16	0%
Ref. Interview Self-applicable	CATEGORICAL	-0.60	-1.02 to -0.17	50.32%
Ref. Structured Unstructured	CATEGORICAL	0.43	0.67 to – 1.45	98.07%
Ref. Developed Emergent	CATEGORICAL	-0.7564	-0.99 to -0.51	2.9%

Source: By the author

4.4 DISCUSSION

Silver compounds have been studied and used for a long time and are an effective option to control caries lesions (51). On the other hand, the staining resulting from their application to manage caries lesions has been reported as a possible barrier to their use. Indeed, the present study showed that there had been a significant increase in articles published on this subject during the past few years, especially related to the use of SDF, making evident the growing interest in this product in recent years. An increased interest in more conservative approaches to the management lesions caries (78), its recommendation in guidelines (79) and, even by its approval for clinical use in some countries (26) may be a justification for these findings.

In emerging countries, such as China and Brazil, these compounds are widely used because they have areas, where financial resources are limited,

lacking access to basic oral health care. In these case, conventional therapeutic methods of treating caries lesions are not always available, making silver compounds an affordable approach that can solve this situation. On the other hand, our findings show greater satisfaction and acceptance of silver compounds in developed countries, mainly in the United States, which represented the majority of our sample. This fact can be explained by the population seeking alternatives to treatment under general anaesthesia, a common approach in dental treatment in some countries like the US (24).

Corroborating the previous scoping review (55) on this topic, our meta-analyses confirmed the pooled rates for caregivers' satisfaction with SDF treatment tended to be higher than those obtained with their acceptance of staining. Thus, we suppose the professionals' perception may be resultant their own beliefs that the caregivers or patients would not accept the SDF treatment of caries lesions due to staining caused by its use. Consequently, they tend not to offer it. One possible reason is that they may not be convinced about the actual SDF effect or may not be aware of the evidence showing their potential benefits (23). Some published studies have presented application protocols associated with potassium iodide to soften this staining and make these products more aesthetic (80, 81). However, these formulae have not been systematically studied regarding their effect on caries progression or users' perception.

These findings, however, are based on studies that present, on average, a moderate risk of bias. The main concern is related to the manner of assessment. Besides, a high level of heterogeneity is observed among the studies. Although randomized controlled clinical studies and nonrandomized studies had been included in this systematic review, mostly the assessment of perception within these studies behaved as a cross-sectional study of attitude and practice, not involving the study of the intervention, but the collection of data at a certain point in the monitoring. That is why we chose a specific tool for assessing such type of outcomes in cross-sectional studies. Finally, meta-analytic approaches were used in the present study to explore the heterogeneity and the influence of methods using in the studies on the exposed results.

We investigated whether the factors associated with the instruments used to assess the perception of caregivers and dentists regarding the use of silver compounds could influence the results of this outcome. We observed that the mode of presentation to caregivers (using pictures vs considering the own child' clinical case) of the situation expected or observed after SDF use influenced their acceptance of staining and their satisfaction with the treatment. Images can present a more exacerbate staining result after SDF. Pictures are usually taken to evidence the "bad aspect", and they are shared to evaluate a condition that not always is observed precisely in the same way. Besides, previous experiences in needing dental care and previous dental care received may also influence studied outcomes (57, 58). This differential perception may have been evidenced on different results reported for those caregivers´ whose children have been treated (or not) using the SDF. Finally, according to studies by our group, presented in the next chapter, especially for lesions clinically into enamel (ICDAS scores 1, 2 and 3), this staining may not be as evident as when applied to dentin cavitated lesions and, this fact may increase caregivers' acceptance of treatment.

Another issue addressed in studies of the perception of the use of silver compounds is the tendency of greater acceptance when they are applied to posterior teeth compared to anterior teeth (24, 64, 70). However, we did not find statistically significant differences between SDF use on anterior or posterior teeth in this study. This finding can be explained by the fact that few studies are included in the quantitative analysis. Besides, they had a small sample, leading to large confidence intervals and less precision. Then, it is still necessary to carry out further studies addressing this research question.

Other factors related to the assessment instruments were analyzed quantitatively, showing a statistical non-significance for self-administered questionnaires or applied by trained interviewers. Regarding the structuring of the questionnaires, the findings were controversial. While some outcomes seem to be higher values when structured questionnaires were used, others showed the opposite. Even working on similar outcomes related to caregivers' perception about a dental treatment, there is an absence of standardization for what implies difficulties for data synthesis. In systematic review, heterogeneity was considered

and explored in different ways. Studies of this nature may include different types of heterogeneity, including statistical heterogeneity and methodological and problem-related heterogeneities. We have tried to reduce the heterogeneity using subgroup analysis. However, due to the wide variation in protocols, a difficulty in grouping these studies was inherent. As we can see, one of the subgroups consisted of only one study (75), characterizing another limitation regarding generalizations. The structure and manner of applying instruments to assess the studied outcomes were responsible for greater responsibles for explaining the heterogeneity observed in models. Then, some standardization in these aspects could help construct more robust and combinable results to base further clinical decision making.

4.5 CONCLUSION

We conclude that how the SDF results are presented to caregivers can influence their satisfaction and acceptance of the treatment. However, more studies are needed to create a standardized instrument that allows assessing the perception of caregivers/dentists concerning the use of silver compounds in caries lesions management. Then, a more accurate understanding of these patient-centred outcomes and actual implementation of such type of treatment in clinical practice may be achieved.

5 CHAPTER 3:

Silver diamine fluoride to treat caries lesions: is it actually a hamper under caregivers' point of view?

5.1 BACKGROUND

Untreated dental caries is still one of the health problems that most affect children in the world (82). In Brazil and other Latin American countries, even with a tendency to reduce caries on permanent dentition, there is an absence of a decline in the prevalence of caries over the years in younger children with primary dentition (1). Thus, strategies to control the disease and its consequences (caries lesions) are essential to reverse this epidemiological situation.

Developed in the late 1960s in Japan and widely used in Brazil since the late 1980s, silver diamine fluoride has been a cariostatic agent used to control caries lesions, associating fluoride and silver properties arrestment of caries lesions (18). Its clinical efficacy for prevention and stopping frankly cavitated caries lesions in children has already been extensively demonstrated (83). It involves a quick to perform and easy technique, being indicated to pediatric patients, irrespective of their behaviours. Besides, it has been pointed out in different dental care protocols in the trans and post-pandemic periods of COVID-19 (84-87). However, the use of SDF in the management of caries lesions not frankly cavitated has not been explored, which has been done in a series of studies by our group and also addressed in Chapter 1 of this dissertation.

Even with the growing use of the product internationally (26), there is still resistance from Brazilian professionals to adhere to its use in the clinic, claiming that caregivers would not accept a treatment that would cause pigmentation, despite arresting caries lesion. This resistance to using is justified by parents' or caregivers' attitude on SDF staining. It can; however, prevent such professionals from applying it for the control of caries using the SDF.

As addressed in a recent review of the literature, a reinforced in Chapter 2, although dentists may have an unfavourable judgment about the use of SDF, caregivers, in general, accept the use of the product well (55). This finding is found despite the intense staining it can cause when used in frankly cavitated lesions (usually presented in the reviewed studies). Our research group studied the possibility of using SDF in early caries lesions, especially in areas with greater difficulty in controlling caries lesions, aiming at its arrestment even before it becomes a large cavity (20, 21).

For these cases, as explored in Chapter 1, we expect an aesthetic impact even smaller. The staining caused by such lesions tends to be similar to that caused by naturally-arrested caries lesions. Besides, SDF has been used in areas with difficult visual access can contribute to a greater acceptance of those responsible (24). The caregivers' reported perception when the chosen treatment is SDF is an important outcome to be evaluated in parallel with its effectiveness. This essential aspect may guarantee the technique is promoted in clinical practice. However, most studies on the perception of treatment with SDF use clinical photos of teeth previously treated with the product and/or do not have a control group for comparison (35).

As part of the efficacy studies testing the use of SDF in non-frankly cavitated caries lesions in children, we evaluated, as a secondary outcome, the caregivers' perception of the treatment received. Then, we could understand the acceptability of treating these lesions with SDF. This study is the first one focused on assessing the acceptance of this treatment using other non-invasive approaches as possible comparators.

5.2 MATERIAL AND METHODS

5.2.1 Trial design and ethical aspects

This study is a secondary analysis of outcomes related to the caregivers' perception of the treatment received by their children from three randomized

controlled clinical studies (RCT) (Figure 5.1), designed to evaluate, as a primary outcome, the efficacy of SDF in controlling caries lesions not frankly cavitated (scores 1 to 3 of the International Caries Detection and Assessment System - ICDAS) (35). All of them had one group treated with SDF and another with at least one control treatment, a treatment option available for the studied clinical condition. As a control, other non-invasive or micro-invasive options were used. However, these treatments were not directly associated with the staining of the treated surface (Figure 1). Every study adopted the following characteristics to include children:

- RCT 1 (ClinicalTrials.gov NCT01508611/CEP-FOUSP 944.742) (20): 192 children between 4 (four) and 7 (seven) years old, who had at least one lesion, as defined, on the occlusal surface of the first permanent molars.

- RCT 2 (ClinicalTrials.gov NCT01477385/CEP-FOUSP 140/11): 141 children, between 3 (three) and 10 (ten) years, who had at least one lesion with the characteristics defined above, on proximal surfaces of the primary molars. Only part of the sample was considered since the secondary outcome was included after the start of the RCT, totalling 62 children potentially evaluable for the present proposal.

- RCT 3 (ClinicalTrials.gov NCT02789202/CEP-FOUSP 944.742): 100 patients between 1 (one) and 4 (four) years old, with at least one non-frankly cavitated lesion on the occlusal surface of the primary molars. In this RCT, all children could be evaluated for this proposal.

All children were included in the RCTs after their parents' written consent and the child's verbal consent (studies approved before the need for an informed consent term for literate children). The secondary outcome collection was already planned in the initial protocols. However, they had been planned to be assessed by the end of the study. Still, they are contemplated in the terms presented to those responsible.

Participants and their caregivers had not been formally aware of which group they had been randomized and which active treatment their children had received (despite possible differential staining and sequence of clinical procedures among groups). Besides, attempts were made, whenever possible, to perform the sequence of clinical steps more closely between them, including clinical simulations (placebo) to resemble sections between patients from different groups.

5.2.2 Examiner training

For data collection, an external examiner not involved in treatment sessions in the RCTs was previously trained and calibrated to apply the questionnaire to caregivers in a standardized way. An interview format was used, and the questions were asked in the same way and with the same voice intonation.

5.2.3 Outcome assessment

Six months after the treatment, at the follow-up appointment, the trained and external examiner applied a validated questionnaire aimed at how guardians perceived their child's dental appearance and health (88) (Appendix D). Although the questionnaire is broader, for this study, it was partially considered. We are going to explore two specific domains, one related to the general health of their child's teeth and the other focusing on child's teeth colour (specifically, seeking to analyze the question of the possible staining caused by SDF).

The questionnaire was applied in two moments. In the first moment, the caregiver's overall perception was assessed, considering the entire oral cavity (general perception - Appendix D – Part I). Secondly, the same questions were used to determine the localized perception of some teeth. Then, four specific teeth were assessed. We randomly chose two teeth that have not been treated, and two others have received SDF or control treatment (localized perception - Appendix D – Part II). These teeth are shown to caregivers with the aid of a hand and a dental mirror. The participants were not aware of which tooth had been treated or not. This second moment was only performed for the caregivers of RCT 1 and 3 studies, since treated surfaces were more visible surfaces.

5.2.4 Statistical methods

The percentages of responses for each of the domains evaluated (health and colour-aesthetics) were calculated for both groups. Their intervals were calculated with 95% of confidence and adjusted by the cluster (RCT). Spearman's correlation test was used to verify the dependence between the responses attributed in each of the domains for the entire sample and for each of the RCTs. In the latter case, Bonferroni's adjustment for the level of significance was used.

For data analysis, the responses regarding the perception of those responsible for health were dichotomized into: positive (responses: very healthy, slightly healthy, neither healthy nor ill) vs negative (slightly ill, very ill). Regarding aesthetics, the outcome was dichotomized similarly: positive perception (very white, slightly white, neither white nor stained) vs negative perception (slightly stained or very stained).

To test whether the guardians' negative perception regarding the health and aesthetics of their child's teeth was associated with the type of treatment received (SDF or control), Poisson multilevel regression models were used, considering the child and the child's RCT in which it was included as levels. Other variables, such as caries experience (children with dmft = 0 vs with dmft> 0 - dmft: index of primary tooth surfaces classified as decayed, with indicated extraction, lost due to caries or filled) and RCT of origin, were also tested as independent variables. For each condition, the relative risk (RR) of the person responsible for presenting a negative perception was calculated (89) with a 95% confidence interval.

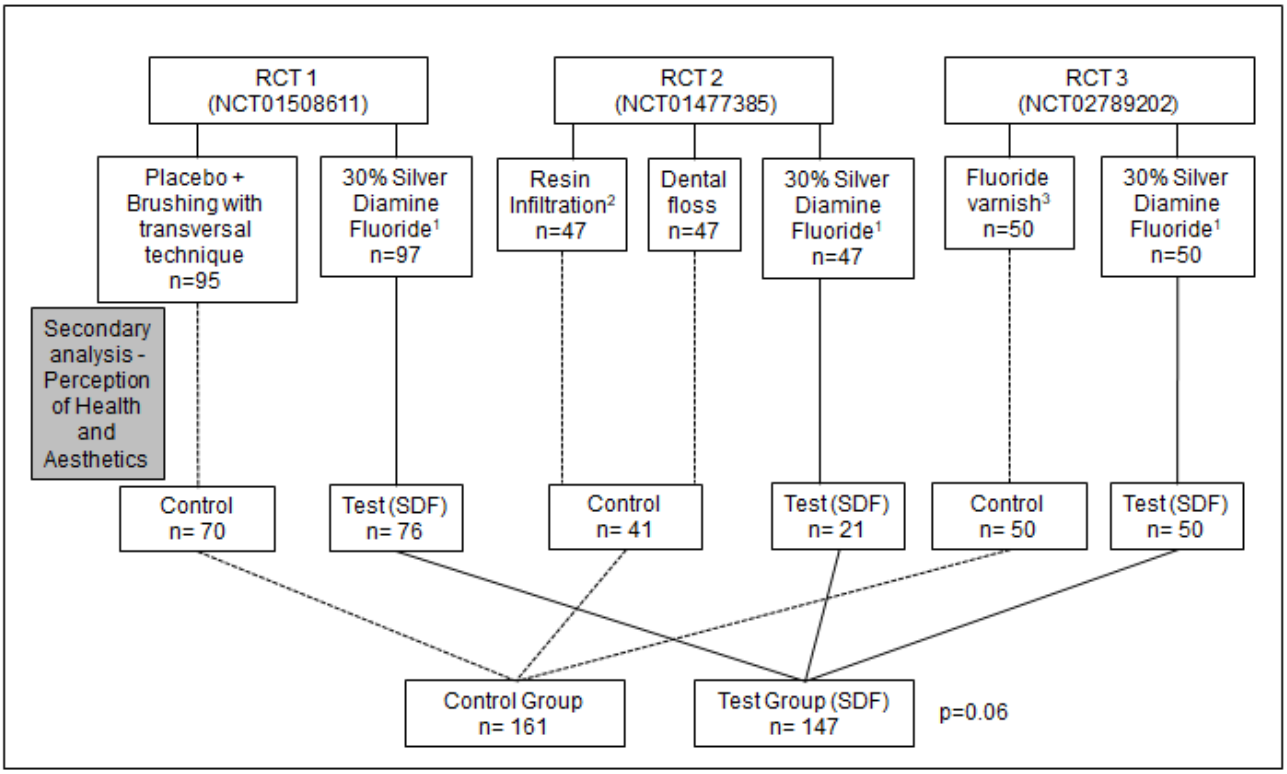
5.3 RESULTS

5.3.1 General perception

Three hundred and eight guardians answered the questionnaire after their children had received the treatments proposed in each of the RCTs, representing a response rate of approximately 90% in both groups (Figure 5.1). Among the children

whose parents were included, 51.8% were female and 48.2% male. The average dmft index (±standard deviation) was 2.2 (±2.7) and there was no difference between the different RCTs (p=0.87).

Figure 5.1 - Flowchart of the RCTs of origin of the children whose parents were included in the present study, showing the composition of the groups that received treatment with SDF or not

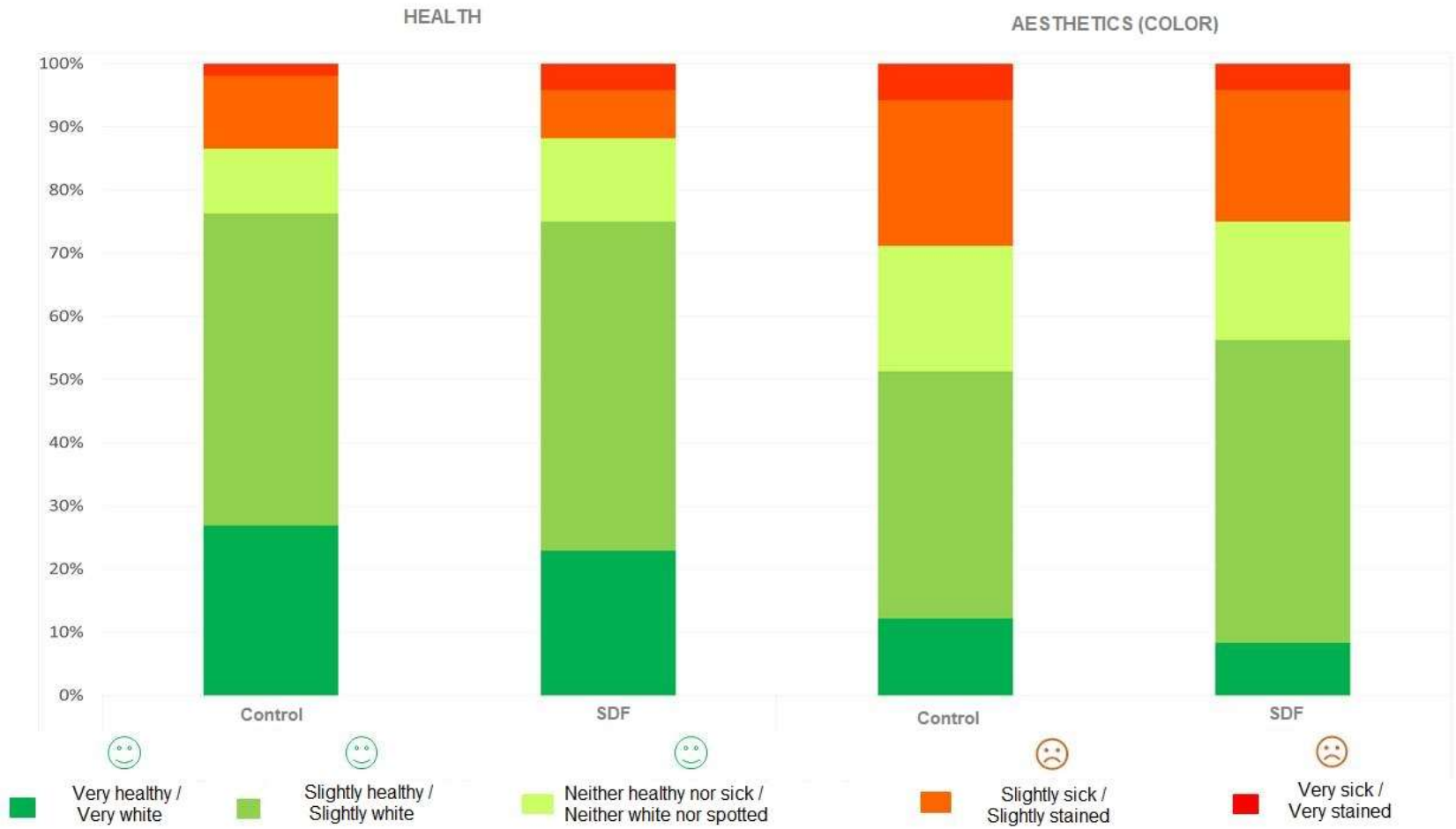


[1]30% Silver Diamine Fluoride: Cariestop® Distributed by BIODINÂMICA QUÍMICA E FARMACÊUTICA LTDA, Brasil.
[2]Resin Infiltration: Icon®, DMG, Alemanha.
[3]Fluoride Varnish: Colgate Duraphat®.

Source: By the author

Most of the guardians (more than 85%) showed a positive perception regarding the health of their children's teeth (Figure 5.2, Table 5.1). Approximately 50% of them classified the child's teeth as slightly healthy, regardless of whether they were treated with DFP (Figure 2). Regarding the perception of teeth staining, about 70% of the parents indicated a positive impression, classifying them as very white (10%, 95% CI: 7% to 16%), slightly white (43%, 95% CI: 27% to 61%) or neither white nor spotted (19%, 95% CI: 7% to 43%) (Figure 5.2).

Figure 5.2 - Distribution of the responses of those responsible for the perception of health and aesthetics (colour/staining) of their children's teeth



Source: By the author

A weak correlation was observed between the responses of those responsible in both domains (Spearman's correlation coefficient ranging from 0.3 to 0.46, depending on the RCT, $p<0.01$). There was no association between the chosen treatment and the perception of those responsible for the aesthetics and health of the children's teeth (Table 5.1).

For colour perception (staining), the effect of the RCT was identified (variance: 0.05 - Table 5.1). Although in one of the RCTs (RCT2), the negative perception about the colour of the children's teeth was greater, the treatment did not influence this outcome (Table 5.1). In this RCT, a greater proportion of guardians (44%; 95% CI: 32% to 56%) classified the teeth as slightly or very stained, regardless of the treatment received (Table 5.1). On the other hand, for the perception of health, the effect of the RCT was not evidenced, being able to be considered equivalent to a model of fixed effect.

The caries experience was not associated with the parents' perception of tooth staining but rather about their health. Those responsible for children who had already had caries experience (dmft> 0) showed, on average, four times more negative responses regarding the health of their children's teeth. This finding was also independent of the treatment received (Table 5.1).

Table 5.1 - Multilevel Poisson regression models considering the outcomes of the guardians' perception regarding the health and aesthetics (colour/staining) of their children's teeth (Data collected in São Paulo, SP - 2014-2016)

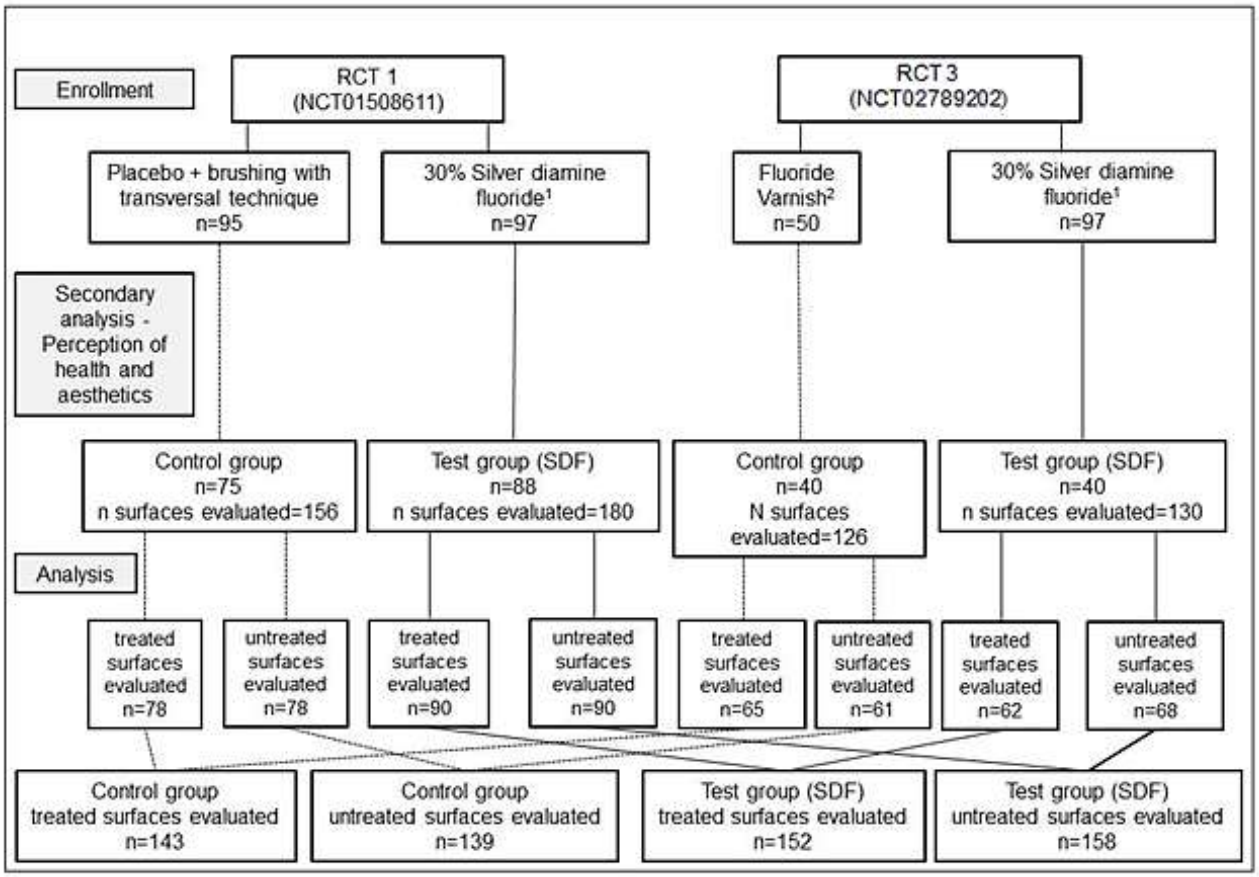
	HEALTH		**AESTHETICS (COLOR)**	
	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude RR (95%CI)	Adjusted RR (95%CI)
Treatment				
Control (Ref.)				
SDF	0.88 (0.46 a 1.66)	0.86 (0.45 a 1.62)	0.91 (0.58 a 1.42)	0.91 (0.59 a 1.44)
Caries experience				
dmft=0 (Ref.)				
dmft>0	3.91 (1.85 a 8.27)	3.92 (1.86 a 8.29)	1.34 (0.86 a 2.08)	1.34 (0.86 a 2.09)
Random effect (Level>RCT)		--	*Null Model:* σ2 =0.05, SE=0.07 *Final Model:* σ2 =0.04, SE=0.07	
RR= Risk relative; 95% CI: 95% Confidence Intervalo; σ2 = variance; SE=Standart error				

Source: By the author

5.3.2 Localized perception

A total of 243 caregivers were included for this stage. 592 surfaces were evaluated considering the localized perception of received treatments. The flow of participants from each randomized clinical study included in this clinical study is shown in Figure 5.3.

Figure 5.3 - Flowchart of patients included in part II (localized perception) of the clinical study



[1]30% Silver Diamine Fluoride: Cariestop® Distributed by BIODINÂMICA QUÍMICA E FARMACÊUTICA LTDA, Brasil.
[2]Fluoride Varnish: Colgate Duraphat®.

Source: By the author

The randomized clinical trial in which the patient was allocated did not influence the caregivers' perception. For both outcomes, differently for the overall perception, SDF use, showed more closely, impacted caregiver's answers (Table 6.2). We observed a negative impact on caregivers' perception about aesthetics, on average, 30% higher when the SDF was used. The same occurrence was observed in approximately 65% of cases for health perception after localized assessment. The variable identifying if the evaluated tooth had been treated or not, irrespective of studied groups, seemed to lose its statistical significance in the multiple models. Then, we performed a subgroup analysis to explore this issue. We actually observed the difference in caregivers' aesthetical perception for those teeth treated with SDF (RR=1.43; 95%CI: 1.02 – 2.09), while teeth non treated even in the SDF group did not present the same trend (RR= 1.22; 0.82 – 1.83). The same was observed for the

health when the localized assessment was proposed (treated teeth: RR= 1.34; 95%CI: 1.08 – 1.68) and non treated teeth: RR= 1.20; 95%CI: 0.93 – 1.55).

Table 6.2 - Univariate and multivariate analyses between the main outcome and explanatory variables

	AESTHETICS		**HEALTH**	
	Crude RR (95%CI) p value	**Adjusted RR (95%CI) p value**	**Crude RR (95%CI) p value**	**Adjusted RR (95%CI) p value**
Treatment				
Other non-invasive (ref.)				
SDF	1.35(1.03-1.76) p=0.03	1.34(1.01-1.77) p=0.04	1.67 (1.16-2.43) p=0.006	1.64 (1.14-2.37) p=0.008
Treated surface				
No (ref.)				
Yes	1.30(1.00-1.70) p=0.048	1.29(0.99-1.69) p=0.05	1.38 (1.00-1.91) p=0.006	1.36 (1.00-1.91) p=0.06
Carie experience				
Low (ref.)				
High	1.04(1.00-1.07) p=0.026	1.04 (1.00-1.07) p=0.04	1.05(1.00-1.10) p=0.03	1.05(1.00-1.10) p=0.05

RR: Relative risk; 95%CI: Confidence Interval; p<0.05;**Variable not included in the analysis

Source: By the author

5.4 DISCUSSION

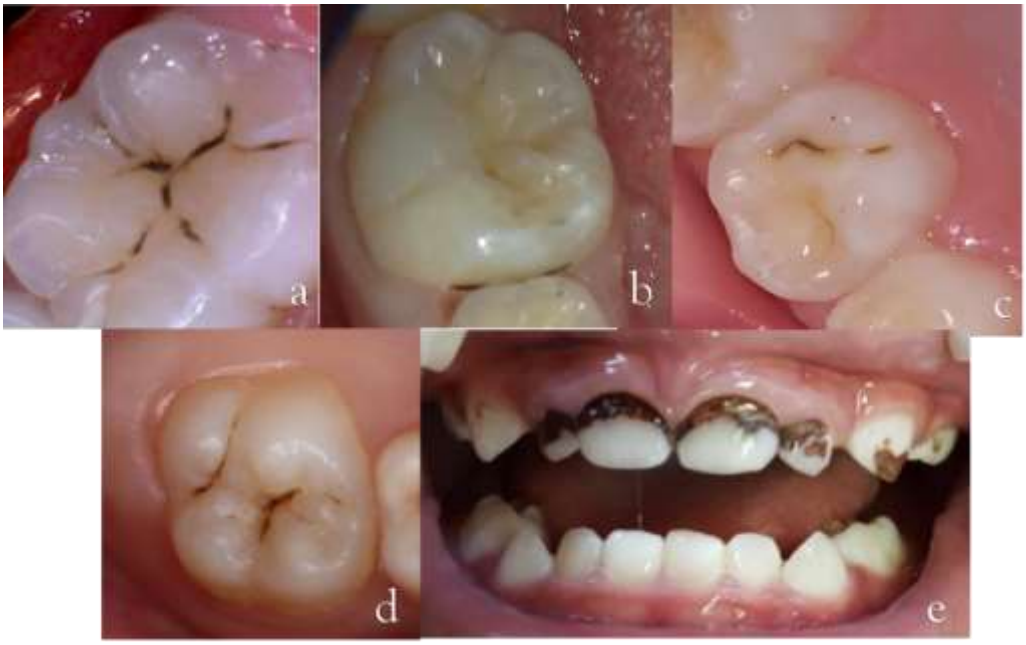
The appearance of the teeth greatly impacts the perception and judgment of other people, directly affecting the patient's quality of life (90, 91). In addition, noticeable discolouration of teeth can negatively impact a person's self-image and self-confidence (92). Nowadays, the perception of clear patterns of facial and general appearance has been established at an earlier age, mainly due to social media and often influenced by the caregivers' judgment (93).

The caregivers’ perception of the SDF used in the management of caries lesions is crucial in the professional's decision making. Dentists raise that as a barrier to the choice of these products for the management of dental caries (54). Currently, the scientific literature reports the caregiver’ perception of the treatment of frankly cavitated caries lesions in children using the SDF (54). However, most of the respondents (caregivers) have been introduced to the staining caused by this product through images. This choice can influence the acceptance of the staining and the satisfaction of the treatment used (Chapter 2).

This study shows that the use of SDF, compared to other available treatment options for caries lesions using fluorides or resin materials, did not influence the caregivers’ perception of the aesthetics and health of their children's teeth. In many cases, there was staining of the dental surface treated with SDF, as shown in Figure 5.4. Nevertheless, the SDF does not seem to have had a different impact on caregivers' health and aesthetic assessment.

On the other hand, when the focus was given to the treated area, caregivers altered their perception about SDF use. We believe this change may be due to the extra attention directed to them during such type of assessment. We hypothesized that, until the time of this evaluation, caregivers might not be noted any change in their children’s teeth, but, since they were evidenced in the process, they might have been seeing differently. This raised hypothesis emphasizes the need to educate caregivers and parents about conditions related to tooth staining, including the use of SDF and its effectiveness and the possibility of staining due to caries arrestment by itself. Possibly, we may have contributed to a concern they never imagined about treated teeth, as evidenced by the first overall assessment.

Figure 5.4 - Illustrative images of teeth submitted to the treatment of non-frankly cavitated lesions with SDF in the different RCTs (a: RCT 1 - permanent molars, b: RCT 2 - proximal surfaces of primary molars, c: RCT 3 - occlusal surfaces of primary molars). It is possible to compare an inactivated lesion without the use of SDF (d) with the others inactivated after its use (a-c) and also a more advanced lesion in the anterior region, also inactivated after using the product (e). Image (e) kindly provided by Prof. Cassia Cilene Dezan Garbelini, Children's Specialty Clinic, Baby Clinic, State University of Londrina



Source: By the author

Another finding of this clinical study was the negative impact of the high experience of caries on the caregivers' perception of both children's health and aesthetics, corroborating with studies that show that the severity of dental caries has a negative impact on both the quality of life of the patient and family members (91, 94).

We believe that many professionals can claim the non-use of this product due to the parents' non-acceptance (55), reflecting their judgment of the post-treatment condition, compatible with a natural aesthetic sense of the dental professionals (95). On the other hand, it may also be related to the lack of available scientific evidence on the impact of this staining on the guardians' and patients' perception (23). Thus, the results obtained in this study can assist professionals in making clinical decisions regarding the use of silver diamine fluoride in the treatment of caries lesions and guiding programs to update these professionals, especially to encourage and demystify the use of minimally invasive techniques, like this, in the daily clinic. In addition, the conclusion of this study may help managers to permanently include SDF

as an effective option in the management of caries lesions in the public health system, especially in contexts of populations with difficult control and monitoring of caries disease.

The appearance resulting from SDF application on the initial caries lesions, such as those considered for this study, is different from that observed after its application in dentine lesions. It tends to be very similar to what would occur "naturally", in most cases, when the caries lesion is arrested even without the use of SDF (Figure 5.4). As it is similar to what would happen without using the product, this cannot be seen as a real disadvantage of the technique. Although SDF may have a more anti-aesthetic effect for more advanced lesions, it may represent, in some countries, an alternative to more radical treatments or even that they are associated with the child's sedation (24, 64, 96), which can interfere in the perception of those responsible. Even in the face of more advanced cases treated with SDF, those responsible tend to accept the use of the product reasonably well (55).

In addition, as we treat posterior teeth, the perception of any alteration could be more limited (24, 64) compared to anterior teeth. When asked about children's dental health and aesthetic, that is one reason why caregivers may not have complained when used SDF in a first attempt but changes their answers after a localized assessment. On the other hand, this was not the proposal intended here since the idea was to explore the use of SDF for lesions that are not yet frankly cavitated in areas of difficult control, such as proximal and occlusal surfaces.

On the other hand, we know that a limitation of the study is that RCTs included children who were linked to public primary care services to receive dental care, whether it be preventive or curative, but free of charge. Such a question can cause those responsible, out of gratitude, to accept the problem as an inherent and inevitable consequence, or even, inhibition to complain, to refer to a different perception than other responsible people found in other services. However, thinking about the public health service offered, for example, in basic health units, one would find very similar a pattern to this. Although the evaluation was made after the treatment, we tried to focus the questions on the child's teeth regardless of the treatment received. As the assessment was made few months after the treatment, we also believe that this effect has been minimized.

Another limitation is that this study comprises a secondary analysis of data prospectively collected in three different RCTs. Although they were designed with

similar purposes and developed by the same team, certain peculiarities can be inherent to each one of them. For this reason, the approach for data collection was considered as a possible source of linking between the RCTs. On the other hand, we should reiterate that RCTs were not initially designed to measure this outcome. In one of the RCTs, this outcome was included during the study, making it impossible that all participants could be included in the present analysis. Even so, samples proportional to those included in all RCTs were finally considered for the present study, with no imbalances between the groups and not harming the global inferences. Further studies should be planned considering the patients' or guardians' perception as the primary outcome, which deserves to be outlined including other possible scenarios, contexts not linked to free treatment and may bring even more robust contributions to clinical practice.

Other variables not explored in our study, such as income and general health perception, can also influence the perception of those responsible for aspects related to children's health (97). The perception of aesthetics can also be influenced by socioeconomic and cultural factors (24, 70). Thus, considering the characteristics of our sample, other contexts deserve to be explored to assess this same outcome, seeking different conditions and profiles of people looking for dental treatment. However, this does not invalidate the findings presented here regarding the perception of health conditions and tooth colour after using SDF.

The idea of exploring the domain related to the health of teeth arose precisely to observe whether those responsible, even observing the staining, would better assess the child's teeth because these teeth have been treated or are really healthy. In fact, although we observe an association between the domains evaluated, satisfaction with the health of the teeth was, on average, greater than with the color of the teeth, but this was also not associated with the type of treatment received (using SDF or not). On the other hand, caregivers whose children has caries experience (presence of untreated caries or restorations), a characteristic that is known to influence the caregivers' perception of oral health (97), managed to point out some type of problem regarding the health of their children's teeth, classifying them as slightly ill or very ill. Thus, the validity of the questionnaire for the proposal in question is reiterated and the idea of not changing the perception of those responsible due to the staining caused by the SDF is reinforced.

Even in this study, until the moment of the evaluation, it had not been revealed to those responsible about the use of SDF (or other equivalent treatment for the condition), it is believed that the correct indication of the therapeutic approach using the product, associated with the clarification of possible doubts or even prejudgments, by the reserachers, may have contributed that the SDF have been well accepted by caregivers. This acceptance is certainly an important factor for its implementation in the dental clinic and favours the concept of evidence-based practice, which combines the available scientific evidence with the users' preferences of the patient (in this case, caregivers) and professionals. Thus, we minimize the problem of duality between the use of a treatment that is effective in managing caries lesions and that would be extremely advantageous from the point of view of public health, but that could be underutilized in the dental clinic due to users' non-acceptance.

In the current pandemic moment, the use of minimally invasive techniques such as SDF has been encouraged and pointed out by many protocols proposed by different associations and entities as an interesting measure in controlling caries during the COVID-19 pandemic (83-86). This fact may be explained since SDF implies a technique that allows it to be performed without generating aerosols and being quick and practical to be implemented, even in younger children or with more challenging behaviours. Besides, it complies with the philosophy of "Minimal Intervention Dentistry" based on the early detection and prevention of dental caries, leading to less invasive treatments that allow greater preservation of the dental tissue and offer greater comfort to the patient (7).

Professionals can then disconnect from the idea that there is resistance from parents in using this product. Otherwise, they have not emphasized these advantages or did not clarify about reasons for that and similarity to arrested lesions. Then, they may start to use its benefits in favour of the management of caries lesions, especially at this moment, when they are looking for minimally invasive alternatives with the characteristics that this treatment option can offer. We believe such treatment may be more widely indicated and disseminated within public health, after reporting these results associated with what is already known about the effectiveness of the treatment. Then, a contribution to reducing the number of children with untreated caries may be achieved in Brazil and the world since it is still a concern when considering all different health conditions (98).

On the other hand, even knowing that minimally invasive techniques like this could contribute to solving the problem of untreated caries disease, it is known that other barriers are imminent with regard to their implementation, emphasizing, in this regard, the importance of implementation in primary care and training a new generation of dentists to use this knowledge in clinical practice (50). Thus, the importance of outlining public policies that favor these priority actions in oral health is emphasized once again. In this way, the scientific knowledge produced can effectively assist in informing the process of formulating and implementing public health policies, making them more effective, reducing costs, and improving the population's quality of life.

Thus, we conclude that, differently from what many professionals claim, the silver diamine fluoride is not related to the negative perception of the caregivers of children who received this treatment in clinically active enamel caries lesions. However, when the treated (probably stained) area is under focus, their perception can be altered, probably due to extra attention directed at it during such type of assessment.

6 FINAL CONSIDERATIONS

The prevalence of dental caries is still high in several countries and it is still a concern in Brazil, especially considering untreated caries in young children (1). In addition, the detection of the initial signs (non-frankly cavitated lesions) of the disease is a predictor of the development of cavitated caries lesions in children of preschool age (6). The control of the etiological factors of the disease associated with the non-invasive treatment of these lesions may be the best option for patients at this age. Toddlers may offer great difficulty in mechanical removal of the biofilm and implementing these actions may result, in the future, in reducing the development of frankly cavitated lesions, and, consequently, the prevalence of dental caries.

As shown in Chapter 1, SDF was efficacious in arresting non-frankly cavitated lesions in toddlers compared to fluoride varnish, and this trend was more prominent in microcavitated enamel lesions. It may be the ideal choice for treating these patients, especially in the current pandemic context in which we need to treat the patient in a smaller number of sessions and with procedures that do not generate aerosols, avoiding contamination. In addition, toddlers tend to be less collaborative in dental care. The easy application related to SDF can encourage professionals to use it, especially those who are not specialists or work in public health units, or even those who do not have access to the fluoride varnish for any reason.

In Chapter 2, we observed that the manner that the staining caused by the treatment of caries lesions with silver compounds is evaluated can impact caregivers' perception. The lack of further explanations about the benefits and harms of the use of SDF can also interfere in the adherence to the choice of treatment by caregivers. The lack of robust evidence concerning this subject, especially in non-frankly cavitated lesions, may be the main barrier to using this product in clinical practice by dentists (23). This scientific gap motivated us to outline the studies presented in the subsequent chapter.

When asked about their children's general oral health, caregivers did not perceive the health and aesthetics affected by the treatment the child received. When we turned their attention to the teeth treated, the aesthetic perception, and consequently the health perception about the teeth, may have been negatively

affected in those treated with SDF. This finding may show that caregivers began to untie staining from the presence of caries disease, which may result from the professional explaining the benefits of the procedure and explaining what they may have experienced throughout the treatment.

Thus, at the end of this dissertation, it is evident that SDF is a viable option for the local management of non-frankly cavitated caries lesions in toddlers' primary molars. It may be a better and alternative compared to fluoride varnish in these cases, and we speculate it could be more relevant in microcavitated lesions. In addition, SDF is a treatment that does not affect caregivers' perception of health and aesthetics since well communicated to caregivers and patients about its benefits and effects.

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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	31
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	N/A
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	31
	2b	Specific objectives or hypotheses	32
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	32
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	33/34
	4b	Settings and locations where the data were collected	32
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	34/35
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	36
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	33
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	34
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	34

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	34
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	34
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	35
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	36/37
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	37
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	40
	13b	For each group, losses and exclusions after randomisation, together with reasons	40
Recruitment	14a	Dates defining the periods of recruitment and follow-up	38
	14b	Why the trial ended or was stopped	38
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	39
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	42
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)	42
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	43
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	44/45
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	44-46

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	44-46
Other information			
Registration	23	Registration number and name of trial registry	32
Protocol	24	Where the full trial protocol can be accessed, if available	32
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	N/A

*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 – PRISMA Statement guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	47
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	47
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	47/48
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	48
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	49/50
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	49
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	49
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	49/50

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	50
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	50
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	50/51
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	51
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	51
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	51
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	52
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	55-57
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	60
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	59/60
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	63
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	63-71
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	71/72
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	72/73
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	73
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

APPENDIX C - Search strategy in each electronic database until 2020

Pubmed (MEDLINE) – 493 Articles	((((((((((("silver compounds") OR "silver diamine fluoride") OR "silver ammonia fluoride") OR "silver nitrate") OR "silver fluoride") OR "cariostatic agent*") OR "ammoniacal silver fluoride") OR "silver-fluoride") OR "silver diamine fluoride solution") OR "silver diammine fluoride") OR "diamine silver fluoride") OR SDF) OR "alcoholic silver nitrate")) AND (((((((((perception[MeSH Terms]) OR perception*) OR esthetics[MeSH Terms]) OR esthetic*) OR aesthetic*) OR "patient acceptance of health care"[MeSH Terms]) OR accept*) OR appearance) OR satisf*)
Embase – 530 Articles	'silver derivative' OR 'silver diamine fluoride' OR 'silver ammonia fluoride' OR 'silver nitrate' OR 'silver fluoride' OR 'cariostatic agent' OR 'ammoniacal silver fluoride' OR 'silver-fluoride' OR 'silver diamine fluoride solution' OR 'silver diammine fluoride' OR 'diamine silver fluoride' OR sdf OR 'alcoholic silver nitrate' AND perception OR perception* OR esthetics OR esthetic* OR aesthetic* OR 'patient acceptance of health care' OR accept* OR appearence OR satisf*
Scopus – 268 articles	((TITLE-ABS-KEY ("silver compounds") OR TITLE-ABS-KEY ("silver diamine fluoride") OR TITLE-ABS-KEY ("silver ammonia fluoride") OR TITLE-ABS-KEY ("silver nitrate") OR TITLE-ABS-KEY ("silver fluoride") OR TITLE-ABS-KEY ("cariostatic agent") OR TITLE-ABS-KEY ("ammoniacal silver fluoride") OR TITLE-ABS-KEY ("silver-fluoride") OR TITLE-ABS-KEY ("silver diamine fluoride solution") OR TITLE-ABS-KEY ("silver diammine fluoride") OR TITLE-ABS-KEY ("diamine silver fluoride") OR TITLE-ABS-KEY (sdf) OR TITLE-ABS-KEY ("alcoholic silver nitrate"))) AND ((TITLE-ABS-KEY (perception) OR TITLE-ABS-KEY (perception*) OR TITLE-ABS-KEY (esthetics) OR

	TITLE-ABS-KEY (esthetic*) OR TITLE-ABS-KEY (aesthetic*) OR TITLE-ABS-KEY ("patient acceptance of health care") OR TITLE-ABS-KEY (accept*) OR TITLE-ABS-KEY (appearence) OR TITLE-ABS-KEY (satisf*)))
Web of Science – 565 Articles	TS= ("silver compounds" OR "silver diamine fluoride" OR "silver ammonia fluoride" OR "silver nitrate" OR "silver fluoride" OR "cariostatic agent*" OR "ammoniacal silver fluoride" OR "silver-fluoride" OR "silver diamine fluoride solution" OR "silver diammine fluoride" OR "diamine silver fluoride" OR SDF OR "alcoholic silver nitrate") AND TS= (perception OR perception* OR esthetics OR esthetic* OR aesthetic* OR "patient acceptance of health care" OR accept* OR appearance OR satisf*)
Open Grey – 5 Articles	("silver compounds“ OR "silver diamine fluoride" OR "silver ammonia fluoride“ OR "silver nitrate“ OR "silver fluoride“ OR "cariostatic agent*“ OR "ammoniacal silver fluoride“ OR "silver-fluoride“ OR "silver diamine fluoride solution“ OR "silver diammine fluoride“ OR "diamine silver fluoride“ OR SDF OR "alcoholic silver nitrate") AND (perception OR perception* OR estheticsOR esthetic* OR aesthetic* OR "patient acceptance of health care“ OR accept* OR appearance OR satisf*)

APPENDIX D - Questionnaire used to assess caregivers' perception of the treatment received by the child

Nº _____

Nome: _____

Parte I - Questionário dos pais sobre a aparência dos dentes de seu/sua filho(a)

1. Durante os últimos meses, o quanto a aparência dos dentes de seu/sua filho(a) incomodou você?
☐ Muito ☐ Um pouco ☐ Muito pouco ☐ Nada ☐ Não sei

2. Durante os últimos dois meses, o quanto a aparência dos dentes de seu/sua filho(a) deixou você preocupado(a)?
☐ Muito ☐ Um pouco ☐ Muito pouco ☐ Nada ☐ Não sei

3. Durante os últimos dois meses, o quanto a aparência dos dentes de seu/sua filho(a) impediu que ele sorrisse espontaneamente?
☐ Muito ☐ Um pouco ☐ Muito pouco ☐ Nada ☐ Não sei

4. Por favor, classifique os dentes de seu/sua filho(a) de acordo com a descrição abaixo e indique se a situação preocupa você:

A. Os dentes do(a) meu/minha filho(a) estão:
☐ Muito bons
☐ Levemente bons
☐ Nem bons nem desagradáveis
☐ Levemente desagradáveis
☐ Muito desagradáveis

Estou preocupado(a) por causa disso:
☐ Sim ☐ Não

B. Os dentes do(a) meu/minha filho(a) estão:
☐ Muito alinhados
☐ Levemente alinhados
☐ Nem alinhados nem tortos
☐ Levemente tortos
☐ Muito tortos

Estou preocupado(a) por causa disso:
☐ Sim ☐ Não

C. Os dentes do(a) meu/minha filho(a) estão:
☐ Muito brancos
☐ Levemente brancos
☐ Nem brancos nem manchados
☐ Levemente manchados
☐ Muito manchados

Estou preocupado(a) por causa disso:
☐ Sim ☐ Não

D. Os dentes do(a) meu/minha filho(a) estão:
☐ Muito saudáveis
☐ Levemente saudáveis
☐ Nem saudáveis nem doentes
☐ Levemente doentes
☐ Muito doentes

Estou preocupado(a) por causa disso:
☐ Sim ☐ Não

5. Por favor, diga o quanto você concorda com a frase: "a cor dos dentes do(a) _____ é agradável e bonita".

☐ Concordo totalmente ☐ Concordo
☐ Nem concordo nem discordo ☐ Discordo
☐ Discordo totalmete

Parte II

A. Os dentes de seu filho estão:

a) Muito bons
b) Levemente bons 1. _____
c) Nem bons nem desagradáveis 2. _____
d) Levemente desagradáveis 3. _____
e) Muito desagradáveis 4. _____

B. Os dentes de seu filho estão:

a) Muito brancos
b) Levemente brancos 1. _____
c) Nem brancos nem manchados 2. _____
d) Levemente manchados 3. _____
e) Muito manchados 4. _____

C. Os dentes de seu filho estão:

a) Muito saudáveis
b) Levemente saudáveis 1. _____
c) Nem saudáveis nem doentes 2. _____
d) Levemente doentes 3. _____
e) Muito doentes 4. _____

ATTACHMENT A – Approval of the Research Ethics Committe

FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE DE SÃO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Titulo da Pesquisa: Custo-eficácia e aceitabilidade do diamino fluoreto de prata a 30% na paralisação de lesões de cárie em esmalte em molares em erupção: Estudo Clínico controlado e Randomizado

Pesquisador: Mariana Minatel Braga

Área Temática:

Versão: 2

CAAE: 39687714.0.0000.0075

Instituição Proponente: Universidade de Sao Paulo

Patrocinador Principal: Financiamento Próprio
FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO
Universidade de Sao Paulo

DADOS DO PARECER

Número do Parecer: 944.742

Data da Relatoria: 03/02/2015

Apresentação do Projeto:

Este projeto apresenta a proposta de um estudo randomizado, com grupos paralelos. Os participantes serão divididos em grupo teste e grupo controle sendo que a alocação para tratamento será aleatória. Serão selecionadas 100 crianças de 1 a 3 anos de idade e 283 crianças de 4 a 7 anos de idade que apresentem primeiros molares permanentes em erupção. Um dos grupos receberá o tratamento ativo (cariostático) enquanto o outro receberá um tratamento consagrado e corriqueiramente utilizado para paralisar este tipo de lesão. O objetivo principal é avaliar a relação custo-eficácia da aplicação do diamino fluoreto de prata a 30% em superficies oclusais de molares decíduos e permanentes no controle de lesões de cárie comparada a um grupo controle que receberá a técnica mais corriqueira. Os autores levantam a hipótese de que o diamino fluoreto de prata seja uma técnica mais custo-eficaz no tratamento de lesões iniciais de cárie e mesmo causando a pigmentação dos dentes pode ser bem tolerada pelos responsáveis, especialmente se compreendido o efeito benéfico do mesmo. Ressalta-se que o protocolo

apresentado solicita a aprovação do comitê referente a dois estudos (estudo 2 e 5) que compõem um estudo maior vinculado ao Auxílio Pesquisa 2012/50716-0 composto, ao todo, por 5 estudos, sendo os demais 3 estudos (1,3 e 4) já aprovados pelo CEP

Objetivo da Pesquisa:

Apresenta como objetivo primário: avaliar a relação custo-benefício da aplicação do diamino fluoreto de prata a 30% em superfícies oclusais de molares decíduos e permanentes no controle de lesões de cárie comparada a um grupo controle que receba uma técnica para a mesma finalidade, que seja consagrada na prática clínica (para os bebês: uso de verniz fluoretado; e para as crianças com molares em erupção: técnica transversal direcionada aos dentes em infra-oclusão). Apresenta como objetivo secundário: avaliar a aceitabilidade e satisfação dos pais/responsáveis e pacientes em relação à aplicação da solução cariostática.

Avaliação dos Riscos e Benefícios:

Os riscos e benefícios ao participante da pesquisa estão bem mensurados.Os riscos são mínimos à saúde e incluem: a possibilidade de das lesões de cárie incipientes presentes na superfície do esmalte devido ao cariostático (o que pode também ocorrer com a simples paralisação da lesão), ressaltando o fato de que se isso ocorrer ocorrerá em dentes posteriores, não sendo isto caracterizado um risco para o sujeito da pesquisa. Quanto aos benefícios, os autores ressaltam o fato de que as crianças incluídas na pesquisa receberão atenção às lesões iniciais o que evita, em muitos casos, a necessidade de tratamentos posteriores mais complexos. Os pesquisadores ressaltam que em caso de uma técnica ser superior à outra, ao final do estudo, será oferecido a todos os participantes que apresentam a condição testada. Além disso apontam o benefício indireto de se verificar qual é a técnica mais custo-e também aceita para este tipo de tratamento

Comentários e Considerações sobre a Pesquisa:

A pesquisa é relevante uma vez que irá contribuir para o tratamento referente a paralisação de lesões de cárie verificando qual a técnica mais custo-eficaz e de maior aceitabilidade e satisfação.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados os seguintes Termos: Folha de Rosto; projeto detalhado; carta de parceria entre a disciplina de Odontopediatria da Faculdade de Odontologia da Universidade de São Paulo

com o Coordenador de Ações Básicas em Saúde da Prefeitura Municipal de Barueri e Termo de Consentimento Livre e Esclarecido.

Recomendações:

Tendo em vista a legislação vigente, devem ser encaminhados ao CEP-FOUSP relatórios parciais semestrais 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:

Todas as solicitações presentes no parecer anterior (versão 1) foram atendidas pelo autor responsável pela pesquisa. Dessa forma, não há pendências neste projeto.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

SAO PAULO, 04 de Fevereiro de 2015

Assinado por:
Maria Gabriela Haye Biazevic
(Coordenador)

ATTACHMENT B - Informed Consent Form (ICF)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
CRIANÇAS DE 0 A 3 ANOS

Por esse documento, o Sr(a) está sendo convidado para que seu (sua) filho(a) participe voluntariamente da pesquisa intitulada "*Custo-eficácia e aceitabilidade do diamino fluoreto de prata a 30%, na paralisação de lesões de cárie em esmalte de molares decíduos: um estudo clínico randomizado"*, coordenada pela Profa. Dra. Mariana Minatel Braga, na Faculdade de Odontologia da Universidade de São Paulo e realizada pela Faculdade de Odontologia da Universidade de São Paulo em parceria com a Prefeitura Municipal de Barueri, SP. Este documento também dará maiores informações sobre os procedimentos a serem realizados, que serão detalhados a seguir. Sua participação não é obrigatória e não haverá prejuízo algum, caso se recuse a participar.

Nesta pesquisa seu filho receberá o tratamento das lesões de cárie iniciais presentes nas faces oclusais (parte que mastiga) dos dentes posteriores (do fundo). Estas superfícies apresentam sulcos que dificultam a remoção das bactérias e, por isso, é mais fácil se encontrar lesões de cárie nesses locais. Essas lesões, muitas vezes, são mais difíceis de serem controladas. O objetivo da pesquisa é observar qual forma de tratamento é melhor para essas lesões localizadas nesses sulcos. Por isso, para algumas crianças, será aplicada uma substância chamada verniz de flúor e para as outras, será feita a aplicação de uma substância chamada cariostático. As duas substâncias contém flúor e ajudam a paralisar as lesões de cárie. Apenas o dentista saberá o grupo em que a criança está. A criança e o responsável não saberão em qual grupo a criança estará participando (só o profissional), pois uma simulação do outro tratamento será feita junto com o tratamento real. As lesões avançadas (com cavidade), que são as que oferecem maior risco de causar dor e aumentarem, serão sempre tratadas.

Algumas pesquisas anteriores já mostraram que as lesões de cárie iniciais (manchas) podem, muitas vezes, paralisar sozinhas apenas com o uso de da pasta de dente com flúor. Além disso, elas demoram mais para progredir e caso isso ocorra com seu filho, que estará em acompanhamento no estudo, isso será prontamente identificado e tratado. Portanto, a criança não estará sendo prejudicada

por participar do estudo. Se qualquer coisa diferente for notada ao longo do estudo, o(a) Sr(a) podem e devem procurar os membros da equipe para esclarecimento e/ou atendimento odontológico de seu filho (a), se necessário for.

Todas as crianças selecionadas serão convidadas, juntamente com seus responsáveis, para uma palestra/atividade sobre higiene bucal e serão também orientadas para escovação com pasta com flúor. No primeiro atendimento odontológico, elas realizarão uma limpeza profissional dos dentes e serão examinadas com um espelho e uma sonda para avaliação das lesões de cárie. Em seguida, elas receberão o tratamento correspondente ao seu grupo. A aplicação dura cerca de três minutos. Esses procedimentos oferecem desconforto e risco mínimos para a criança. Poderá ocorrer escurecimento da lesão de cárie quando houver a aplicação do cariostático e/ou a paralisação da mesma, porém isso não prejudicará a estética, por se tratar de lesões de cárie nos dentes do fundo. Após essa parte, as crianças também receberão atendimento odontológico básico, com remoção dos focos de infecção e fechamento das cavidades que estiverem abertas. Assim, as demais sessões necessárias para o tratamento podem variar entre as crianças e correspondem ao tratamento que cada uma precisar (etapas não vinculadas à pesquisa, mas que serão executadas para devolver saúde à criança, quando necessário). As consultas serão agendadas para não atrapalhar o rendimento escolar.

Para participarem do estudo as crianças deverão aceitar participar do estudo. Se chorarem ou não aceitarem mesmo após o dentista conversar e explicar sobre o atendimento, elas não serão incluídas na pesquisa. Se necessário, será solicitado que um dos responsáveis autorize e auxilie na contenção da criança durante o atendimento, pois são crianças pequenas que podem não permanecer sozinhas na cadeira odontológica.

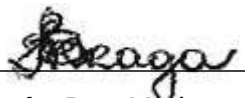
Todos os procedimentos serão realizados em um trailer que possui um consultório odontológico montado em seu interior, que ficará no terreno do Complexo Educacional Prodessor Carlos Osmarinho de Lima. Eles seguirão as normas de biossegurança e alto rigor técnico. Terminada a primeira consulta, a criança será reexaminada após 6, 12, 18 e 24 meses. Os atendimentos serão realizados por membros da equipe da pesquisa e por alguns profissionais do município de Barueri, SP. Após 24 meses do fim do tratamento, com o término da pesquisa, a criança continuará assistida pelos dentistas da rede pública de Barueri-SP e casos mais complexos, podem ser encaminhados para atendimento na Faculdade de Odontologia da Universidade de São Paulo, na Disciplina de Odontopediatria.

Esta pesquisa pretende contribuir para a melhora da qualidade da saúde bucal das crianças, inclusive dos participantes deste estudo, evitando que a lesão inicial identificada progrida, reduzindo assim o número de lesões de cárie maiores (com cavidade) e evitando a necessidade de tratamento mais complexo, como a restauração, e até mesmo episódios de dor decorrentes da doença, tratamentos de canal e extrações precoces. Como benefício direto da pesquisa, as crianças participarão de atividades de educação em saúde bucal e prevenção de cárie, além de receber tratamento odontológico necessário. Caso um dos tratamentos apresente melhor efeito em relação ao outro, as crianças não tratadas por está técnica terão a oportunidade de receber também a técnica de melhor desempenho. Se identificado qualquer problema ou inferioridade significativa de um dos grupos, a pesquisa poderá ser suspensa e o melhor tratamento garantido à criança. Para os que não participarem da pesquisa, o atendimento odontológico pelo município continuará sendo garantido.

O responsável pelo participante terá escolha em não participar da pesquisa, tendo a possibilidade de retirar seu consentimento posteriormente, caso mude de opinião por qualquer motivo. A criança será acompanhada por dois anos e se necessário, o responsável poderá entrar em contato com os pesquisadores para tirar dúvidas e relatar qualquer ocorrência.

Não será revelada, sob nenhuma hipótese, a identidade do participante bem como de seu responsável, mesmo na divulgação dos resultados. Os resultados obtidos serão publicados, independentemente de serem favoráveis ou não. Os pesquisadores garantem o caráter confidencial das informações.

Havendo qualquer problema ou dúvida durante a realização da pesquisa, a professora Mariana Minatel Braga, responsável pela pesquisa, pode ser encontrado pelo telefone 11-992014818 ou no Departamento de Odontopediatria, pelo telefone 11- 39017835. Eventuais dúvidas poderão ser esclarecidas pelas pesquisadoras responsáveis, na própria sede da Faculdade de Odontologia da Universidade de São Paulo – FOUSP – sito à Av. Lineu Prestes 2227, 05508-000 São Paulo. Dúvidas sobre a ética da pesquisa entre em contato com o Comitê de Ética em Pesquisa da FOUSP, (Av. Lineu Prestes 2227 | 05508-000 | São Paulo/SP | (11) 30917960 | e-mail cepfo@usp.br).



Profa. Dra. Mariana
Minatel Braga CRO SP
81102

CONSENTIMENTO PÓS-INFORMAÇÃO

Eu, _____, de RG _____, certifico que fui esclarecido pelas pesquisadoras sobre todos os itens descritos do estudo “Custo-eficácia e aceitabilidade do diamino fluoreto de prata a 30%, na paralisação de lesões de cárie em esmalte de molares decíduos: um estudo clínico randomizado” e dúvidas que apresentei e concordo com a participação do meu filho/minha filha, o(a) menor _____, por qual sou responsável legal, participe de forma voluntária desta pesquisa. Informo também ter recebido uma cópia desse documento.

Declaro que, em caso de necessidade de uso de dados decorrentes dessa pesquisa para outras pesquisas:
( ) NÃO autorizo a utilização de dados em outra pesquisa.
( ) SIM autorizo a utilização de dados ou em outra pesquisa

Se a resposta for SIM, para utilizar esses dados em outra pesquisa, declaro que:
( ) NÃO quero ser consultado da utilização dos dados de meu/minha filho(a) em outra pesquisa, desde que a nova pesquisa seja aprovado pelo Comitê de Ética em Pesquisa,
( ) SIM quero ser consultado da utilização dos dados de meu/minha filho(a) em outra pesquisa

Barueri, ___de_____de 2015.

Nome do responsável:
RG:
CPF:

_____

Assinatura do Responsável