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REVIEW ARTICLE

Nonrestorative treatment of initial caries lesion in primary teeth: a systematic review and network meta-analysis

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ABSTRACT

Objective: To identify the best available approach to avoid initial caries lesions progression in primary teeth.

Materials and Methods: Search was performed in MEDLINE/Pubmed, Web of Science, Embase and CENTRAL databases until March 2021. Studies compared treatment options to avoid the initial caries lesion progression with at least 12 months of follow-up were included. Network meta-analyses were conducted considering the non-progression of caries lesions as an outcome.

Results: Potentially eligible studies were screened ($n = 2820$) and eleven were included. Six studies evaluated the use of fluoride varnish, resin infiltration, sealing, and toothbrushing/flossing on proximal initial caries lesions. When considering occlusal surfaces, only two studies evaluating the ozone gas, fluoride varnish, resin infiltration, and sealants were included. For buccal/lingual surfaces, three studies evaluating toothbrushing, CPP-ACP paste, fluoride varnish, and resin infiltration were included. For all types of surfaces, the resin infiltration showed the best probability to avoid the progression of initial caries lesions.

Conclusion: The limited number of included studies, most with a high risk of bias and lack of hard outcomes, such as frank cavitation, makes it not feasible to recommend a specific management approach for initial caries lesion control in primary teeth with a high certainty of evidence. PROSPERO: #CRD42016037781

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Introduction

Data from Global Burden of Disease study have shown that untreated caries lesions in primary teeth are still within the ten most prevalent health problems, affecting about 621 million children worldwide [1]. Despite the several attempts to reduce sugar consumption and the increased availability of fluoride approaches for caries prevention, its control is still a challenge for both dental practitioners and governments, responsible for delivering oral health care to populations.

The first clinical sign of dental caries is a non-cavitated caries lesion and, although these lesions have shown not to affect negatively the oral health-related quality of life [2], they can progress to a cavitated stage mainly in children with previous caries experience [3]. Data from a cohort study shows that around 10% of initial caries lesion evolves to cavitation after 2 years of follow-up [3]. Therefore, numerous approaches to arresting initial stage decay have been developed. The main mechanism for progression control is based on lesion remineralization using fluoride application [4]. Controversially, a systematic review has pointed out that at least 35% of initial caries lesions does not arrest with this approach [4]. In this sense, the physical barrier between a caries lesion and the biofilm created by sealing or infiltrating caries lesions is an effective option to avoid their progression to more severe stages [5,6].

Numerous systematic reviews have been conducted focussing on the comparison of interventions using control groups and/or placebo for the management of initial caries lesions in children [5–7]. However, the best therapy for this purpose has not been identified yet. Conducting network meta-analysis (NMA) could be useful to summarize the effectiveness and the certainty of the available evidence in an attempt to support the decision-making process of dental professionals to manage initial caries lesion in the primary dentition.

Although a previous systematic review and network meta-analysis has been published about nonrestorative treatments,

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Supplementary data for this article can be accessed here.

it considers studies in both permanent and primary teeth combined in the analysis [8]. Since the deciduous dental tissues present less mineral content and both enamel and dentine are thinner than in permanent dentition, the progression of caries lesions in primary teeth is much faster [9]. Therefore, results obtained for permanent teeth should not be extrapolated for primary teeth. Thus, the aim of this systematic review with NMA was to identify the best available approach to avoid initial caries lesions progression in primary teeth.

Materials and methods

Protocol and registration

The protocol of this systematic review and network meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42016037781 and is available on http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016037781. Additionally, the manuscript was reported following the PRISMA-NMA extension Statement [10]. In order to ensure the transparency of the research, the dataset is available on Mendeley data repository http://dx.doi.org/10.17632/t8jb5fz72j.1

Eligibility criteria

Search strategy was developed following the PICO question: 'In primary teeth with initial caries lesion, i.e. the initial stage of the lesion, also referred to as non-cavitated one (P), which available treatment is more effective (I/C) to avoid caries lesion progression (O)?' There was no language restriction or date of publication in studies selection.

Information sources

A systematic search of available studies was performed in the electronic databases MEDLINE/PubMed, Web of Science, Embase and CENTRAL. Grey literature was assessed using the OpenGrey database. References of potentially eligible studies were tracked to verify all relevant manuscripts that could not be identified from electronic databases. The last search was conducted on March 15th, 2021. The results from different databases were manually cross-checked to eliminate duplicates. The full electronic search strategy is displayed as Supplementary Table 1.

Study selection

Two reviewers independently (ALP and MPA) participated in all phases of studies' screening (Kappa = 0.79) and eligibility (Kappa = 0.90). All processes were performed in duplicate. A third reviewer (TKT) solved any discrepancies.

Titles and abstracts of potentially eligible studies were evaluated based on the inclusion criteria: (1) To evaluate approaches for managing initial caries lesions in primary teeth; (2) To be a prospective study with at least 12 months of follow-up.

Manuscripts fulfilling the inclusion criteria and listed without available abstracts were fully assessed. Manuscripts were excluded if presenting any of the exclusion criteria: (1) Absence of a comparison group; (2) Not comparing different types of interventions; (3) To evaluate outcomes not related to this review; and (4) Conducted in specific groups (e.g. disabled children with special needs or under medication).

When more than one study included the same sample, the one that presented more complete data was considered avoiding duplicated data.

The outcome of this systematic review was considered caries lesion progression, which could be both the changes of score or the presence of dentine cavitation, assessed by clinical or radiographic examination, depending on the study endpoint.

Data collection process and items

Relevant information from eligible studies was collected by two independent reviewers (ALP and NML) in duplicate. A third reviewer cross checked all collected data (TKT). The following data were extracted: publication details, sample characteristics, study methodology, and outcome information. Authors were contacted via email to provide missing data.

Risk of bias within individual studies

Two independent reviewers (AFBC and SS) performed the risk of bias assessment of included studies in duplicate. Disagreements between reviewers were solved by consensus. A RoB tool for intervention analysis was used to evaluate included randomized clinical trials (RCT) – Cochrane Handbook for Systematic Reviews of Interventions 5.0.1 [11]. The reviewers ranked the parameters as 'low risk of bias', 'unclear' (unable to identify or uncertainty about the potential risk of bias) or 'high risk of bias' for each study included.

Certainty of the evidence

The same reviewers evaluated the certainty of the evidence using the GRADE tool (Grading of Recommendations, Assessment, Development and Evaluation) in duplicate. It was judged as high, moderate, low or very low; while the reason for downgrading was based on five domains: study limitations, indirectness, inconsistency, imprecision and publication bias [12].

Summary measures, data synthesis and statistical methods for the network Meta-analysis

Initially, Cochran Q and I2 tests were conducted to evaluate the heterogeneity of the data included in the meta-analyses. We assumed the heterogeneity for all network of studies included in a network meta-analysis. Data synthesis were conducted in according to the surfaces involved. Meta-analyses were conducted considering the no progression of caries

lesions as an outcome. The random model was used to account for possible heterogeneity of studies.

NMA synthesized direct and indirect comparisons when three or more different treatments were available for a same surface of tooth. In order to consider both direct and indirect evidences simultaneously, a Bayesian analysis of mixed treatment comparisons (MTC) was conducted. Since all studies were conducted in groups of patients with similar characteristics that could impact the outcome (age range and caries experience), as well as performing the same protocols of the interventions assessed, this network meets the assumption of transitivity. MTC analyses were initially conducted using both fixed and random-effects models. The goodness of fit of the models was measured using the residual deviation and the Deviance Information Criterion (DIC). Because DIC value of the random-effect model was lower, it was used with homogeneous variability between studies. A node split analysis for inconsistency was not performed due to insufficiency of data.

All analysis was performed in the R statistical software, version 2.15.3 (R Core Team, 2012, Vienna, AUT). Meta-analyses were conducted using meta package, whilst network meta-analyses were conducted using the GeMTC package and the rJAGS package to estimate the models. The ranking probability of efficacy for all treatments was estimated. Odds ratio and 95% confidence intervals for pairwise comparisons, Odds ratio for mixed comparison and 95% credible intervals were calculated for comparisons.

Results

Study selection

A systematic search of the available studies identified 2820 potentially relevant publications from which 386 were considered as duplicates. After screening the titles and abstracts, 2349 studies were considered ineligible, as they did not evaluate interventions related to initial caries lesions in primary teeth. The remaining 85 studies were fully assessed for exclusion criteria. Eleven manuscripts fulfilled the eligibility criteria and were included in this systematic review. The flowchart shows the study selection process (Supplementary Figure 1).

Study characteristics

Supplementary Table 2 shows the main characteristics of the included studies. The majority of studies were designed as split-mouth randomized clinical trials (54.5%) [14–20]. Six studies evaluated treatment options for initial caries lesion on proximal surfaces (resin infiltration, sealing, fluoride varnish and toothbrushing/flossing) [13–18]. When occlusal surfaces were considered, two included studies evaluated four treatment options: ozone gas, resin infiltration, fluoride varnish and resin sealant [19,20]. For buccal/lingual surfaces, three studies presenting four different approaches for non-progression of initial caries lesions (toothbrushing with fluoride toothpaste, fluoride varnish, resin infiltration and 10% casein phosphopeptide– amorphous calcium phosphate paste (CPP-ACP) were included [21–23].

Among all included studies, seven used bitewing radiographs for outcome assessment (63.6%) [13–18,20], especially considering the change of the radiographic scores for caries lesion depth. Only three studies considered as an outcome the presence of a dentine cavitation [17,19,23]. Follow-up period ranged from 1 to 3 years and six studies (54.5%) were followed-up for 2 years [13,15–18,20].

Risk of bias within individual studies

Figure 1 shows the final risk of bias analysis of all RCT included. Among them, ten presents high risk of bias [13–21,23], and one study presents uncertainty about potential bias [22]. No studies have shown other sources of bias to be considered.

Certainty of the evidence

The certainty of evidence and reason for downgrading are presented in Table 1. For all comparisons, regarding the surfaces evaluated, the certainty of evidence is low, except for three pairwise. Resin infiltrations/fluoride varnish vs. fluoride varnish in buccal/lingual surfaces, resin infiltrations vs. fluoride varnish, resin infiltrations vs. toothbrushing/flossing were considered as moderate certainty of evidence. The reasons for downgrading were the study limitation due to high risk of bias of studies and imprecision.

Data synthesis

Initially, data from proximal surfaces were analyzed. Six studies evaluating four treatment options were included, and NMA was conducted [13–18]. Low heterogeneity and not statistically significant was observed among included studies ($p > .05$; I^2 test = 9%). In direct comparisons, fluoride varnish presented higher risk to caries lesion progression than resin infiltration (OR: 4.67; 95%CI:2.19–9.96) (Supplementary Figure 2). Toothbrushing/flossing also presented higher risk to caries lesion progression than resin infiltration (OR: 4.01; 95%CI:1.70–9.49) (Supplementary Figure 3). However, in MTC, no treatments showed higher odds to avoid caries lesion progression in the pair-wise comparisons, with one exception. Resin infiltration showed 6.9 (95%CrI:2.0–24.0) higher odds to avoid caries lesion progression compared with toothbrushing/flossing. The results of direct and mixed comparisons are displayed in Table 2. The rank probability showed that the resin infiltration had 79.3% of chance to present the best results when is used (1st), followed by sealing (2nd). At the same time, toothbrushing/flossing presented 80% of chance to result in the worst behaviour (Figure 2).

When occlusal surfaces were considered, two studies evaluated four approaches for initial caries lesion progression and NMA was conducted [19,20]. It also presented low heterogeneity and no statistical significance between the studies ($p > .05$; I^2 test = 21%). The results from MTC are shown in

Figure 1. Risk of bias summary: review authors' judgements for each included RCT.

Table 3. In mixed comparison, no treatments showed higher odds to avoid caries lesion progression in all pair-wise comparisons. The rank probability showed that when resin infiltration is the treatment of choice, the odds for caries lesion control are higher (1st), followed by sealant/fluoride varnish (2nd) and fluoride varnish (3rd). Ozone gas, on the other hand, presented a 49% chance to result in the worst results (Figure 3).

For buccal/lingual surfaces, three studies evaluating four treatments to avoid the initial caries lesion progression were included. NMA was conducted and presented low heterogeneity with no statistical significance among included studies ($p > .05$; I^2 test = 18%) [21–23]. The results from MTC are displayed in Table 4. In mixed comparison, no treatments showed higher chances to avoid caries lesion progression in all pairwise comparisons. The rank probability indicated that resin infiltration combined with fluoride varnish offers an 82% chance to be the best approach to avoid caries lesions progression in buccal/lingual surfaces (1st), followed by fluoride varnish (2nd) (Figure 4).

Discussion

The absence of solid scientific evidence indicating the most effective approach for arresting initial caries lesions in primary teeth might hamper their control in a clinical scenario, which can favour the progression of lesions restricted to enamel to dentine cavitated stages. In light of this, the present study aimed to verify the best available clinical approach to avoid the progression of initial caries lesions in primary teeth by conducting a systematic review with NMA.

Analyzing the management options for proximal surfaces, six studies [13–18] included in the network meta-analysis showed that resin infiltration presents the highest probability to avoid the progression of initial caries lesions, probably because of the ability of a light-cured resin to penetrate into a subsurface enamel lesion and therefore, sealing enamel porosities and inter-crystalline spaces [24]. This is possible due to the use of 15% hydrochloric acid gel previously applied to the resin application that opens the pores for the diffusion of the resin presenting a high penetration coefficient [24].

Resin infiltration superiority might also be supported by the difficulty of biofilm control in proximal surfaces, especially for two evaluated interventions – fluoride varnish and toothbrushing/flossing, which have showed higher risk to caries progression in the direct comparisons. Although fluoride varnish might allow the remineralization of enamel lesions [4], the lack of biofilm control between applications could facilitate the progression of initial lesions. One previous study has demonstrated the non-compliance rate with daily flossing by children [25] reinforcing the higher probability for caries lesion development when fluoride varnish or toothbrushing/flossing are used singly. It is important to highlight that this finding is supported by six studies with high risk of bias, offering concerns specially because of selection bias – lack of description of random sequence generation and allocation concealment.

Another relevant point is the use of radiographic parameters as the primary outcome for the majority of studies. This surrogate outcome allows observing minor changes in the X ray images, and this can lead to hasty generalizations by overestimating the results. It would be better to use a hard outcome, such as frank dentine cavitation. However, the follow-up of studies sometimes is not enough to detect progression to the cavity, although previous research has shown that this outcome occurs after at least 12 months of follow up [26], being this the goal of our eligibility criterion for the screening phase.

Similarly, for occlusal surfaces, results from the network meta-analysis with two studies [19,20] showed better results when resin infiltration combined with fluoride varnish was used compared to three other options – sealants, fluoride varnish and ozone gas. This can also be explained by the resin infiltration mechanism of action previously mentioned. Furthermore, the application of fluoride varnish could provide a synergic effect participating in remineralization process. On the other hand, sealants associated with fluoride varnish showed to be the second better option to treat initial caries lesions on occlusal surfaces. The physical barrier

Table 1. Certainty of evidence and reason for downgrading for lesion arrestment in according with the surfaces involved.

Comparison	Nature of evidence	Certainty of evidence	Reason for downgrading
Proximal surfaces			
Fluoride varnish vs. Resin infiltration	Mixed, mainly direct	Moderate	Study limitation – High risk of bias
Fluoride varnish vs. toothbrushing/flossing	Mixed, mainly direct	Low	Study limitation – High risk of bias; Imprecision*
Fluoride varnish vs. Sealing	Indirect	Low	Study limitation – High risk of bias; Imprecision*
Resin infiltration vs. toothbrushing/flossing	Mixed, mainly direct	Moderate	Study limitation – High risk of bias
Resin infiltration vs. sealing	Indirect	Low	Study limitation – High risk of bias; Imprecision*
Toothbrushing/flossing vs. sealing	Mixed, mainly direct	Low	Study limitation – High risk of bias; Imprecision*
Occlusal surface			
Resin infiltration/fluoride varnish vs. fluoride varnish	Mixed, mainly direct	Low	Study limitation – High risk of bias; Imprecision*
Resin infiltration/fluoride varnish vs. sealant/fluoride varnish	Mixed, mainly direct	Low	Study limitation – High risk of bias; Imprecision*
Resin infiltration/fluoride varnish vs. ozone gas	Indirect	Low	Study limitation – High risk of bias; Imprecision**
Fluoride varnish vs. sealant/fluoride varnish	Mixed	Low	Study limitation – High risk of bias; Imprecision*
Fluoride varnish vs. ozone gas	Mixed, mainly direct	Low	Study limitation – High risk of bias; Imprecision*
Sealant/fluoride varnish vs. ozone gas	Indirect	Low	Study limitation – High risk of bias; Imprecision*
Buccal/Lingual Surface			
Resin infiltration/fluoride varnish vs. fluoride varnish	Mixed, mainly direct	Moderate	Imprecision*
Resin infiltration/fluoride varnish vs. toothbrushing	Indirect	Low	Study limitation – High risk of bias; Imprecision*
Resin infiltration/fluoride varnish vs. 10% CPP-ACP paste	Indirect	Low	Study limitation – High risk of bias; Imprecision*
Fluoride varnish vs. toothbrushing	Mixed, mainly direct	Low	Study limitation – High risk of bias; Imprecision*
Fluoride varnish vs. 10% CPP-ACP paste	Indirect	Low	Study limitation – High risk of bias; Imprecision*
Toothbrushing vs. 10% CPP-ACP paste	Mixed, mainly direct	Low	Study limitation – High risk of bias; Imprecision*

*Wide credible intervals.

Table 2. League table with all and mixed* comparisons of treatments for non-progression of caries lesion in proximal surfaces.

Resin infiltration			
3.2 (0.94–10.0)	Fluoride varnish		
6.9 (2.0–24.0)	2.1 (0.52–9.0)	Toothbrushing/flossing	
2.3 (0.26–21.0)	0.74 (0.07–7.5)	0.34 (0.05–2.1)	Sealing

Comparisons between treatments should be read from left to right. Results are OR (95CI%), where OR >1 favours the cell-defined treatment.
*Random effect model, Model fit: residual deviance; DIC = 22.84.

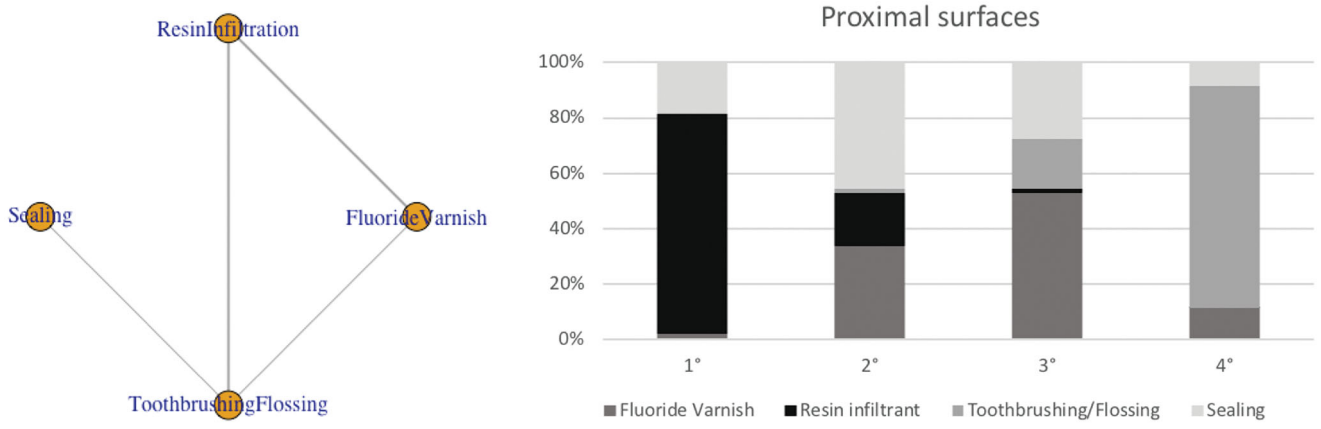

Figure 2. Network comparisons and rank probability of treatments for non-progression of carious lesion in proximal surfaces. The width of lines connecting each pair of treatments is proportional to the number of studies. A: fluoride varnish B: resin infiltration; C: toothbrushing/flossing; D: sealing.

Table 3. League table with all mixed* comparisons of treatments for non-progression of caries lesion in occlusal surfaces.

Resin infiltration/fluoride varnish			
3.4 (0.64–19.0)	Fluoride varnish		
1.4 (0.25–7.9)	0.41 (0.076–21.0)	Sealant/fluoride varnish	
3.5 (0.33–40.0)	1.1 (0.19–6.0)	2.6 (0.24–29.0)	Ozone gas

Comparisons between treatments should be read from left to right. Results are OR (95CI%), where OR >1 favours the cell-defined treatment.
*Random effect model, Model fit: residual deviance; DIC = 10.18.

between the enamel lesion and the cariogenic biofilm formation after materials' application in the above-mentioned techniques, in addition to avoiding the biofilm accumulation on the dental surface, and also interrupts the nutritional supply so that the microorganisms in such ecosystem can metabolize sugars into acids, controlling the lesion progression and arresting the demineralization process [20].

Ozone gas showed to be the worst effective alternative to manage occlusal initial caries lesions. It has been theorized that ozone gas is a potent oxidant and antimicrobial agent,

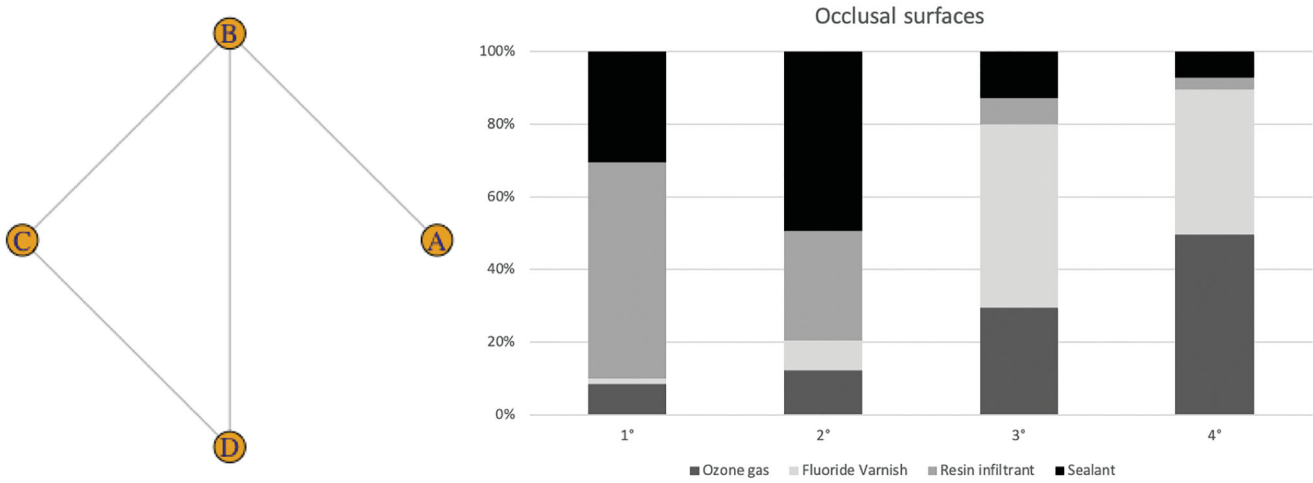

Figure 3. Network comparisons and rank probability of treatments for non-progression of carious lesion in occlusal surfaces. The width of lines connecting each pair of treatments is proportional to the number of studies. A: ozone gas; B: fluoride varnish, C: resin infiltration; D: sealant.

Table 4. League table with all mixed* comparisons of treatments for non-progression of caries lesion in buccal/lingual surfaces.

Resin infiltration/Fluoride varnish			
6.8 (0.59–77.0)	Fluoride varnish		
6.7 (0.25–18$e+02$)	0.99 (0.10–10.0)	Toothbrushing	
6.6 (0.10–4.1$e+02$)	0.97 (0.034–27.0)	0.97 (0.084–12.0)	10% CPP-ACP paste

Comparisons between treatments should be read from left to right. Results are OR (95CI%), where OR >1 favours the cell-defined treatment.
*Random effect model, Model fit: residual deviance; DIC = 12.22.

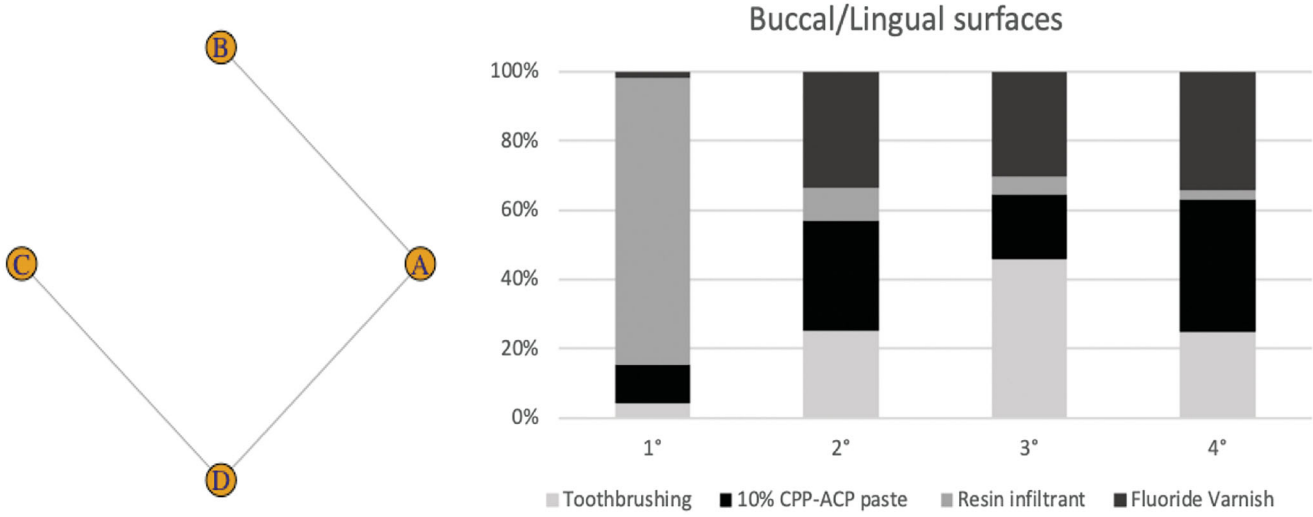

Figure 4. Network comparisons and rank probability of treatments for non-progression of carious lesion in buccal/lingual surfaces. The width of lines connecting each pair of treatments is proportional to the number of studies. A: toothbrushing; B: 10% CPP-ACP paste; C: resin infiltration; D: fluoride varnish.

which would lead to the reduction of cariogenic bacteria in lesions *in vitro* [27]. Thus, authors had hypothesized that ozone application could also reduce biofilm-formation clinically and, as consequence, arrest initial lesions. However, since dental caries is a sugar-dependent bacterial dysbiosis [28], the reduction of microorganisms alone does not seem to result in a positive impact on caries lesion arrestment [19]. Results from rank probability must be considered with caution, since the certainty of evidence for treatment comparisons in occlusal surface is low, especially due to the wide credible intervals, which results in an uncertainty about the estimative, besides the high risk of bias of included studies.

Finally, in relation to the buccal/lingual surfaces, resin infiltration associated with fluoride varnish was also considered the best approach to avoid the progression of initial caries lesions in comparison to fluoride varnish, CPP-ACP paste and even toothbrushing with fluoride-containing toothpaste. Although biofilm control on buccal/lingual surfaces seems to be easier due to their morphology and free-surface nature, patient/caregiver's oral hygiene compliance is a key factor for the success of any caries control intervention. Evidence is widely clear about the indication of fluoridated toothpaste and toothbrushing not only for permanent teeth but also for children with primary and mixed dentition to

prevent and control caries. The association of CPP-ACP and fluoride has shown a synergistic effect for caries prevention [29]. However, such effect does not seem to be enough for controlling the progression of initial carious lesions, since CPP-ACP paste showed the highest probability for lesions progression. As previously mentioned, there is a moderate or low certainty of evidence to support these recommendations. Data came from comparisons with wide credible intervals, and studies with high risk of bias, with exception for resin infiltration/fluoride varnish vs fluoride varnish. The blinding of personnel and examiner had not been mentioned in one of the included studies, whilst another did not report if a random sequence generation was used.

Overall, our findings converge from previous systematic reviews, which showed that the use of micro-invasive approaches, as resin infiltration or sealing, are more effective than non-invasive professional treatment or oral hygiene to arrest proximal caries lesion [5,6]. On the other hand, while the results from our analysis have suggested the best probability to avoid the caries lesion progression when fluoride varnish is applied compared with toothbrushing, previous study has showed still a decrease in number of new caries lesion compared to toothbrushing [7]. However, both earlier published studies evaluated primary and permanent teeth together. As previously mentioned, the difference between both about morphology and composition hamper the evaluation of protocols without considered them separately [9].

Therefore, results from this systematic review suggest that resin infiltration as the most effective approach to avoid progression of initial caries lesions in primary teeth, especially in proximal surfaces. Patient-independent methods were most successful after long-term follow-up, what reinforces the importance in recognizing aspects related to lower effectiveness of oral health-related habits and possibly, subject's compliance. Nevertheless, other points need to be considered in decision-process making, as the patients' values and preferences, the clinical experience of dentists as well as the cost-effectiveness of treatments. This factor is relevant, especially in public health, when the treatment needs to be cost-saving for the budge of government. In this specific case, other strategies that were well ranked, as fluoride varnish in proximal surfaces and buccal/lingual surfaces, and sealant in occlusal surfaces, could be useful, especially because the results is based on low certainty of evidence.

We need to emphasize that the majority of conclusions from this systematic review is based on the rank probability, since even the evidence from direct comparison, in the most of the cases, shows a lack of superiority for one treatment over another, with exception of the proximal surface. Although the rank probability is a useful tool of NMA, which is performed when three or more different treatments are available for the same health condition, enabling to identify the preferential order of the treatments, the results take from this should be considered with caution. This is because the rank probability does not necessarily presuppose clinically relevant effect size.

On the other hand, the limited number of included studies, most with a high risk of bias and lack of hard outcomes, such as frank cavitation, makes it not feasible to recommend a specific management approach for initial caries lesion control in primary teeth with a high certainty of evidence at this point. The conduction of well-designed studies focussing in therapeutic management, combined to choosing hard outcomes, is highly encouraged to strengthen the scientific evidence that supports the clinical decision-making process of paediatric dentists when facing the control of initial caries lesions.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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