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A PROGNOSIS AND COST-EFFECTIVENESS SYSTEMATIC REVIEW OF NON-INVASIVE TREATMENTS FOR ROOT CARIES

Revisão sistemática de prognóstico e custo-efetividade de tratamentos não invasivos para cárie radicular

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ABSTRACT

Aim: to evaluate the prognosis of root caries treatment with non-invasive methods, as well as to compare non-invasive therapies as viable alternatives for clinicians, indicating their cost-effectiveness. **Literature review**: Data collected were number of active lesions at baseline(BL) and in the last clinical assessment after follow-up(FL), and the follow-up period in months(P). The outcome was the monthly progression rate of the lesions that was calculated by (FL–BL)/P. A negative progression rate means the arrestment of the lesions. A cost-effectiveness rate was calculated. **Results:** From 596 titles retrieved in the search, 8 studies were included in a qualitative synthesis after assessed for eligibility. The monthly progression rate of lesions of home-based treatments (toothpastes, mouth rinses, supplemented milk intake) was an average of -0.79 (-3.68 to 2.3), while the office-based treatments (varnish, topic solutions) was 0.07 (-0.01 to 0.51), suggesting a better prognosis of the home-based treatments. The lowest monthly progression rate was -3.97 (toothpaste 5000ppm/F) while the highest was 2.31 (conventional toothpaste). The cost-effectiveness rate was better for treatments with toothpastes with 5000ppm/F (BRL21.78) when compared to mouthwashes (BRL579.47). **Discussion:** A better prognosis was found for toothpastes with a high fluoride concentration (5000ppm/F) compared to other therapies, as well as a better cost-effectiveness when compared to mouthwashes. **Conclusion:** Home-based therapies represented the highest rates of good prognosis for treating root caries lesions within the available scientific evidence. Although 5000ppm/F toothpastes have a very high cost for the Brazilian market, this treatment presented the highest cost-effectiveness when compared to mouthrinses (PROSPERO:CRD42019136035).

Keywords: Root caries. Fluorides, topical. Cost-benefit analysis.

RESUMO

Objetivo: avaliar o prognóstico do tratamento da cárie radicular com métodos não invasivos, bem como comparar as terapias não invasivas como alternativas viáveis para os clínicos, indicando seu custo-efetividade. **Revisão de literatura:** os dados coletados foram o número de lesões ativas no início do estudo(BL) e na última avaliação clínica após o acompanhamento(FL), e o período de acompanhamento em meses(P). O desfecho foi a taxa de progressão mensal das lesões calculada por (FL–BL)/P. Uma taxa de progressão negativa significou a inativação das lesões. Uma taxa de custo-efetividade foi calculada. **Resultados**: Dos 596 títulos recuperados na busca, 8 estudos foram incluídos em uma síntese qualitativa após avaliação de elegibilidade. A taxa de progressão mensal das lesões dos tratamentos caseiros (dentifrícios, enxaguatórios bucais, ingestão de leite complementado) foi em média -0,79 (-3,68 a 2,3), enquanto os tratamentos de consultório (verniz, soluções tópicas) foi de 0,07 (-0,01 a 0,51), sugerindo um melhor prognóstico dos tratamentos domiciliares. A menor taxa de progressão mensal foi de -3,97 (dentifrício 5000ppm/F), enquanto a maior foi de 2,31 (dentifrício convencional). A taxa de custo-efetividade foi melhor para tratamentos com dentifrícios com 5000ppm/F(R$21,78) quando comparados aos bochechos (R$579,47). **Discussão**: Foi encontrado melhor prognóstico para dentifrícios com alta concentração de flúor(5000ppm/F) em comparação com outras terapias, bem como melhor custo-efetividade quando comparados aos bochechos. **Conclusão**: As terapias domiciliares representaram as maiores taxas de bom prognóstico para o tratamento de lesões de cárie radicular dentro das evidências científicas disponíveis. Embora dentifrícios de 5000ppm/F tenham um custo muito alto para o mercado brasileiro, este tratamento apresentou o maior custo-efetividade quando comparado aos enxaguatórios bucais(PROSPERO:CRD42019136035).

Palavras-chave: Cárie radicular. Fluoretos tópicos. Análise custo-benefício.

INTRODUCTION

Root caries is a prevalent oral disease worldwide, in which the incidence increases with age[1]. It has been observed an increment of root caries lesions (RCL) in aging populations between 0.8 and 1.2 new surfaces per year[2]. Multiple risk factors contribute to this increment of RCL in the elderly, such as impaired oral hygiene resulting from poor oral care behaviors, drug-induced salivary flow reduction, complex health status due to concomitant systemic diseases and frequent snacking at home[3]. Just as importantly, both increased life expectancy and a reduced edentulism have been playing a role in these estimates[4]. Consequently, root caries has become a significant issue in Dentistry and its high restorative treatments failure rate make this management challenging[5,6]. New preventive and efficient treatment strategies are required, and the analysis of the current ones might provide meaningful information for the development of future strategies.

When cavitated caries lesions can be cleaned, a non-invasive treatment is possible[7]. Treatments for RCL include several non-restoratives (or non-invasive) protocols, and the decision on which protocol will be used must take into account the activity of the lesion. So as for the coronal caries, the RCLs activity is determined by a visual-tactile examination, in which parameters such as change in texture and color, as well as the distance from gingival margin are evaluated. Inactive or arrested lesions should be considered as a “scar” and do not demand treatment, unless there is some other type of anatomical requirement for rebalancing by a filling[8]. It is a consensus that the implementation of educational programs in oral health and/or the application of chemical agents by the dentist or by the patients can significantly reduce the RCL activity.

Some of these interventions were able to prevent new RCLs and/or inactivate active lesions into inactive ones, as showed in three recently published systematic reviews[9-11]. These reviews agreed that the regular use of toothpastes containing 5000 ppm/F and quarterly professionally applications of either chlorhexidine (CHX) or silver diamine fluoride (SDF) varnishes present good efficacy on decreasing progression and initiation of root caries. The same conclusion was achieved by a fourth review showing that the use of high fluoride concentration toothpastes, containing 5000 ppm/F, as well as professionally applied both CHX varnish and SDF seemed to be more efficient to arrest root caries than conventional fluoride

toothpaste or placebo[12]. However, the articles included in these reviews compared groups with placebo, and there is no comparison between therapies and prognosis for the treatments protocols to be established in the treatment of RCLs.

As it could be observed, the interest from scientific community is evident due to the numerous reviews on that issue. However, there is a focus on the efficacy of various agents rather than the prognosis of treatments. Furthermore, it is interesting to note that most treatments were compared to placebo, so is expected any better clinical performance and the impacts in meta-analysis. As an example, in a meta-analysis carried out in a review it concluded that any self-administered or professionally applied fluoride regimen prevents the development of RCL[13], but did not considered the prognosis for these therapies neither the conclusion of which one should be better in different clinical situations.

Research on prognosis has increased steadily over the past two decades[10]. Nowadays, frequently echoed terms are ‘personalized-medicine’, ‘precision medicine’, or ‘risk-based medicine’, often used as synonyms, have been adopted by the scientific community. Personalized or precision medicine does not just address effectiveness of treatments or preventive strategies, but rather addresses how to use an individual’s prognostic information to make personally tailored choices about the best suited treatment or preventive management. Likely, this worldwide tendency of focusing on personalized medicine led to the need of studies on prognostic and predictive factors (markers), and models have become abundant in the dental research. Information on the prognosis could be helpful to determine recalls periods for each treatment proposed in the literature. Furthermore, the cost-effectiveness analysis involves comparing the additional costs and health benefits of an intervention with those of the available alternatives allowing the cost estimate per unit (RCL). A health intervention is said to be cost-effective if it produces justifiable clinical benefit for its use. A German study on cost-effectiveness of root caries treatments showed that among four therapies studied, SDF is probably the most effective and least costly application[14], but, in addition to several limitations, this study compared only four therapies.

Thus, the present systematic review aims to evaluate if teeth with root caries treated with any non-invasive methods have a good prognosis. We also aimed to compare non-invasive therapies as viable alternatives for clinicians, indicating this cost-effectiveness in the management of root caries.

LITERATURE REVIEW

Protocol and registration

This systematic review was written according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist[15]. A previous study protocol was designed and registered at the International Prospective Register of Systematic Review (PROSPERO) database, under the identification number CRD42019136035.

Question formulation and eligibility criteria

The acronym PICOs was used to design the review question: Population: Adults over 35 years old with teeth diagnosed with root caries active; Intervention: any non-invasive treatment; Control: any kind of treatment, control or no treatment; Outcomes: long-term performance; longevity; long lasting; survivor; lesion arrestment; progression rate; and Studies: clinical studies, randomized clinical trials (RCT). The review question was then “do teeth with root caries treated with any non-invasive/non-restorative protocol have a good prognosis and cost-effectiveness?”.

Studies eligible to this review were clinical studies and randomized clinical trials, involving adults or elderly over 35 years-old with root caries, that report any non-invasive root caries treatment (for example fluoride, varnish, CHX, SDF, etc.), who described root caries lesion activity with no restriction of publication period. Exclusion criteria were: (1) reviews or technical articles lacking primary clinical data; (2) studies that did not report at least 12 months follow-up outcomes; (3) studies that did not differentiate root lesions etiology (root caries or non-carious cervical lesions); (4) studies which included either hypossalivation-related caries (Sjöegren syndrome or head and neck radiotherapy) or several periodontal disease (tooth mobility, probing depth more than 3mm); (5) studies written in non-Latin alphabet.

Data sources and search strategy

Supplementary Appendix 1 shows the search strategy, performed in May 2020. “Root Caries, Longitudinal Studies, Clinical Trial, Non-invasive treatment, Remineralization, Demineralization” were used as main search terms, that were adapted for each electronic database: MEDLINE *via* PubMed, LILACS, Web of Science, Scopus,

Cochrane and Livivo. Grey literature was also searched in Google Scholar, ProQuest and OpenGrey. Moreover, reference lists from included studies were assessed to identify other articles that could be selected. No language or time restrictions were applied during the search strategy. For studies in foreign language, translation was performed and transcribed in English before data extraction. However, it is important to note that an exclusion criterion was added specifically for studies written in non-Latin alphabets. This exclusion was made to ensure that papers which would be impossible to be correctly translated were not included in the review. Duplicates were identified through *EndNoteWeb* (Clarivate Analytics, Mumbai) and then automatically identified at *Rayyan QCRI*® (Qatar Computer Research Institute, Qatar)[16].

Study selection

Selection process was performed in two phases. Firstly, two independent and blinded reviewers screened titles and abstracts and applied the eligibility criteria (F.L.R.C. and D.L.N.P.). This phase was carried out in a web application tool designed to systematic reviews (Rayyan *QCRI*®, Qatar Computing Research Institute). Any disagreement was discussed with an expert and the main supervisor (C.M.S and N.D.T). In a second phase, reviewers (F.L.R.C. and D.L.N.P.) gathered all the included studies by reading full articles independently and applying the same eligibility criteria. Once a study was selected for the second phase and the full-text was not available in any way through online sources, it was performed a protocol in which an email requesting the full-text was sent to authors every 3 days for 15 days.

Data extraction, outcomes and data analysis

Data was extracted by F.L.R.C. and D.L.N.P, and any disagreement was discussed with an expert and the main supervisors (C.M.S and N.D.T). When study results were published more than once or results were detailed in multiple publications, the most complete and recent data set from all sources was identified, and the data was included only once.

Data extracted were number of active lesions at baseline (BL) and in the period after follow-up (FL), and the follow-up period in months (P). In order to classify the outcome (progression of the lesions), all results were analyzed according to the color, texture and other parameters to determine caries activity used by the authors. The treatments were classified according to type of use (home or professional) and

protocol/product presentation. Subgroup 1 was divided into two categories: 1) home (self-applied product); or 2) office-based treatment; while the subgroup 2 comprised eight categories according to the protocol and product presentation: (1=fluoride; 2=CHX; CHX+other; 3= Conventional toothpaste; 4= 5000 ppm/F toothpaste; 5= SDF; 6= Milk probiotic; 7= Milk fluoride; 8= placebo/negative.

The main outcome was the “monthly progression rate” of the lesions that was calculated by (FL – BL/P). The negative monthly progression rate proposes the regression (or arrestment) of the lesions, or a good prognosis. A null monthly progression rate means no new lesions and was also considered a good prognosis. Consequently, a positive monthly progression rate was a bad prognosis. This outcome was qualitatively compared by subgroups, either home-based or office-based (subgroup 1); and by type of protocol (subgroup 2).

Proportions of individuals with bad prognosis (positive progression rate) and individuals with good prognosis (null or negative progression rate) were calculated for each study and qualitatively compared by type of intervention.

Another outcome was an estimative of the cost-effectiveness of those treatments for the Brazilian market. In order to calculate estimated gross costs of each treatment, an average of the dental appointment price to the Brazilian private dental service (two values extracted from the health insurance table for Brazilian public service employees available in 2020, January, and the most recent table of private services made available by Union of dentists of the state of São Paulo, 2016) were calculated by values of the procedures that are part of a conventional routine appointment: initial dental appointment, prophylaxis, biofilm control and guidance, plus the cost of the procedure according to the therapy, included the cost of the product. A monthly amount was reached according to the number of appointments indicated annually. It was summed by the cost of the product and a monthly gross cost of the treatment was reached.

The cost-effectiveness rate was performed by calculated by the following formula: monthly gross cost of the treatment/number of lesions inactivated per month in treatments with negative progression rate. Therefore, the cost-effectiveness rate was calculated only for treatments with negative progression rates.

Risk of bias and quality assessment

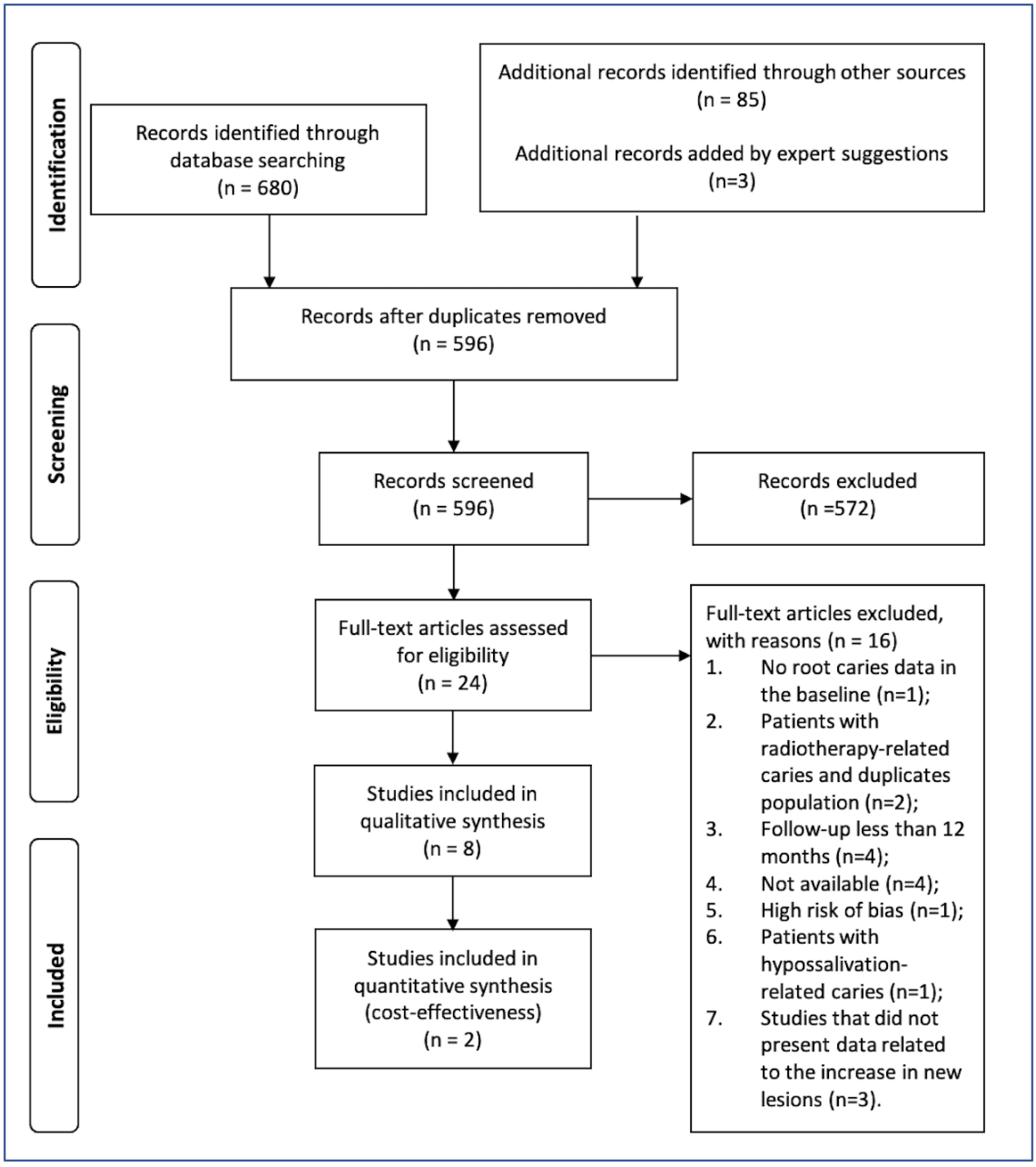
The risk of bias of the included studies was evaluated by two reviewers (F.L.R.C. and D.L.N.P.) independently, using the Joanna Briggs Institute Reviewers Manual[17] to randomized clinical trials. Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), since they were all randomized clinical trials, was used to perform the risk of bias figure. The risk of bias was defined according to the percentage of positive answers. A high risk of bias was considered ≤49% “yes” answers. Studies with a moderate risk of bias were 50% to 69% of “yes” answers, and low risk of bias studies were ≥70% “yes” answers.

RESULTS

Studies selection and risk of bias

Searches retrieved 680 titles through databases and 85 titles through grey literature. After removing duplicates, n=596 titles remained for screening. Figure 1 shows the PRISMA flowchart describing the identified, included, and excluded studies with reasons (see also Supplementary appendix 2). N=24 studies remained for a full-text review, being n=8 studies included in a qualitative synthesis, and n=2 for the cost-effectiveness comparison. All included studies were randomized clinical trials (RCT).

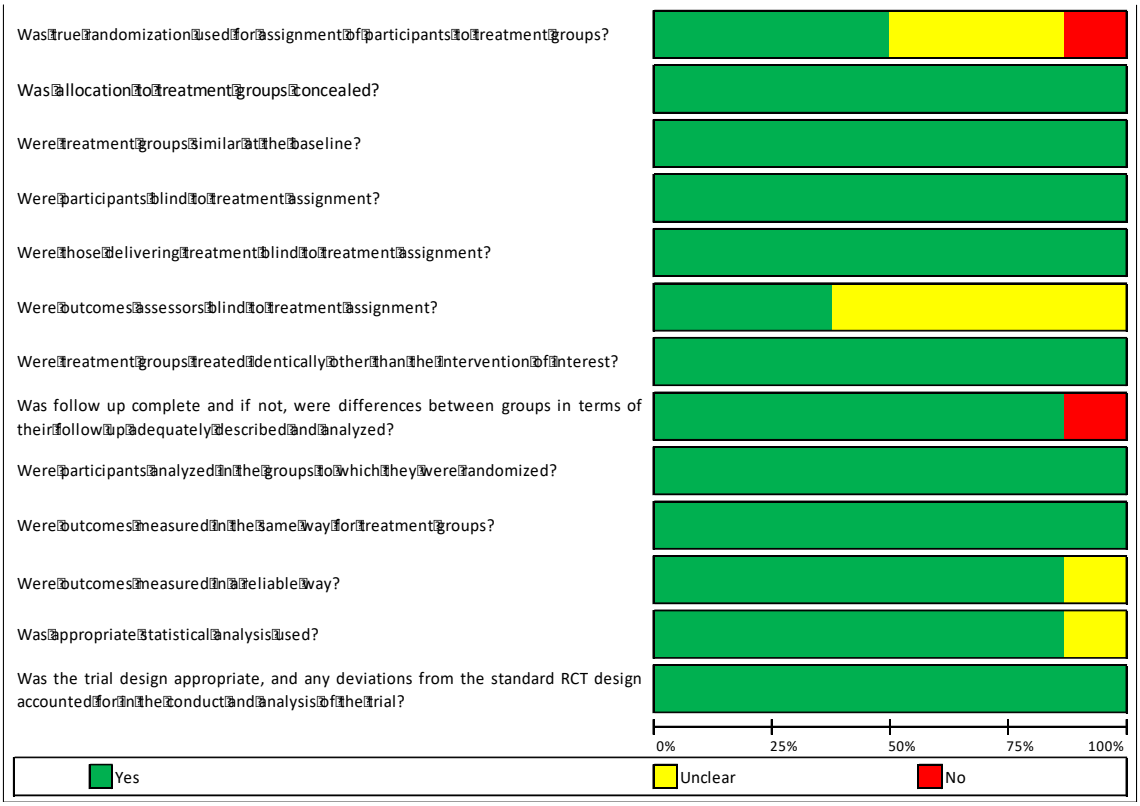
Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing identified, included, and excluded studies with reasons.



The quality assessment of the selected studies was determined by the review authors' judgments about each risk of bias item presented as percentages across all included (summarized at Figure 2; and complete information at Supplementary Appendix 3). The overall risk of bias demonstrated low and moderate in most studies. The highest risks of bias observed was for the definition of inclusion criteria and the appropriate description of the study objects such as the calibration of study

examiners, while the lowest risk of bias was observed by true randomization and blinding of the evaluators in studies and for the statistical analysis, which shows that overall studies had good qualitative analysis (Figure 2). Although overall studies were well designed, only two used the CONSORT checklist in their designs[18,19].

Figure 2 - Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Studies characteristics and location

The 8 included papers were published from 1987[20] to 2019[18]. Studies were conducted in seven different countries, amongst them two were conducted in United States[20,21], one in China[22], Sweden[23], Chile[18], Netherlands[24], Australia[25], and Spain[19] contributed to the literature with one study each. A total number of 2411 of patients were treated, and the age of the participants ranged from 45 to 89 years old.

The treatments identified in these studies included several types of comparison that are listed in Table 1:

In the subgroup 1, four studies[18,20,23,26] evaluated the success of home-based treatments, while five studies[19,21,22,24,25] evaluated the success of office-based treatments. The identified home-based treatments comprised the ones with

toothpastes[18], fluoride mouthrinses[20,26] and fluoridated/probiotic milks[23]. The office-based treatments were then fluoride gels[26]; fluoride varnishes[24,25]; CHX varnishes[19,24,25]; SDF[22,25].

For the eight categories comprising the subgroup 2, according to the active product, the following treatments were identified: 1=fluoride[20,24]; 2=CHX[19,24,25]; 3=conventional toothpaste[18]; 4=5000ppm/F toothpaste[18]; 5=SDF[22,25]; 6=Milk probiotic[23]; 7=milk fluoride[23]; 8= placebo or negative control treatments[19-21,23,24].

The Decayed Missing Filling Surfaces (DMFS) index was found to be the most frequently utilized measure for recording root caries, followed by the Root Caries Index (RCI), among others (as presented in Table 1). A relatively short follow-up period of the treatments was observed, ranging from 12 months to 36 months.

Qualitative synthesis

Table 1 shows studies characteristics including an estimative of the monthly progression rate for each non-invasive treatment for RCL.

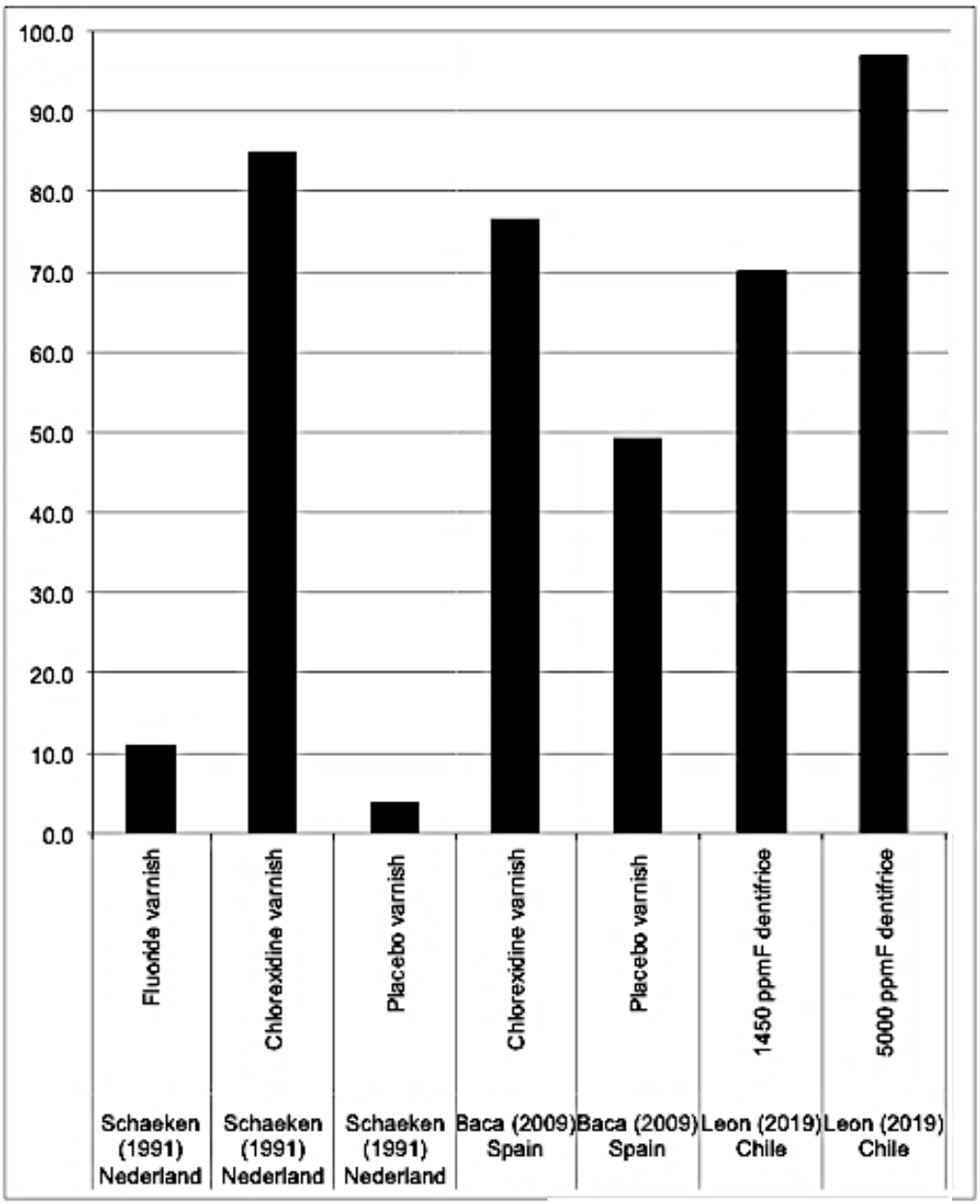
Placebos or negative controls groups had an average of the monthly progression rate of 0.89, meaning that one new lesion would be developed every two months in those who did not receive any non-invasive treatment. Based on this result, a monthly recall should be performed in studies including these groups.

The monthly progression rate of RCL of home-based treatments (toothpastes, mouthrinses, supplemented milk intake) was an average of -0.79 (ranging from -3.68 to 2.3), while the office-based treatments (varnish, topic solutions) was 0.07 (ranging from -0.01 to 0.51). The lowest monthly progression rate was -3.68 (5000 ppm/F toothpaste) while the highest was 2.31 (conventional toothpastes), both from Leon et al. (2019). What stands out from the results was that treatments either fluoride varnishes, APF gel 1.2%, or CHX varnish would have new lesions, according to their positive monthly progression rate. Also, treatments based only in the use of brushing with conventional toothpastes would have two new lesions monthly. This bad prognosis can define that these treatments should not be recommended to RCL or should be performed only with monthly recalls.

Figure 3 displays the proportion of lesions with a favorable prognosis, which was assessable across three studies (including fluoride, CHX, or placebo varnish, as well as conventional or high fluoride concentration toothpastes). From this chart, it could be observed a great difference between the placebo varnish from Baca (~50%)

and Schaeken (~10%). A reason to this difference was not identified in the studies, but we can infer it could be a result of differences in methodology or even in the environment in which patients were allocated, access to fluoride or sugar consumption. A higher proportion of lesions with good prognosis was higher than 70% in treatments with 5000ppm/F toothpaste and chlorhexidine varnish when compared to fluoride varnish, conventional toothpaste and placebo groups.

Figure 3 - Proportion of root caries lesions with good prognosis after non-invasive treatments (negative or null monthly progression rate).



Cost-effectiveness results

It was simulated a table for an annual cycle of treatment, considering costs of the Brazilian market (table 2). Gross costs for oral hygiene instruction, mouthrinse NaF 0.05%, conventional toothpaste, toothpaste with 5000 ppm/F, APF gel 1.2%, fluoride varnish, CHX varnish, and SDF were obtained and estimated.

The cost-effectiveness rate was calculated as the monthly good prognosis with the estimated costs. N=2 treatments were then evaluated and, surprisingly, the lowest cost-effectiveness was identified for the mouthrinse NaF 0.05% (BRL 579.00 for each month for a good prognosis). Toothpaste with 5000 ppm/F represented the highest cost-effectiveness (BRL 21.78 for each monthly for a good prognosis) when compared to mouthrinses. A cost-effectiveness rate was not calculated for treatments with bad prognosis. Also, as supplemented milks are not available in the Brazilian market with this purpose, it was not possible to calculate its cost-effectiveness rate, although it presented a good prognosis.

Table 1 - Characteristics of the included studies (n=8).

Author (Year) Country	Age in Years (mean±SD and/or range)	Gender	Subjects	Treatment (N) /subgroup 1/subgroup2	Subgroup 1/subgroup 2*	Root caries index used	Follow-up (P; in months)	Baseline (BL) active lesions (N; % or mean±SD)	Follow-up (FL) active lesions N; % or mean±SD)	Estimated monthly Progress rate (%)*
Ripa (1987) USA	20 - 65 years (39.9 mean age)	NR	1006 individuals	Fluoride 0.05% Neutral mouthrinse (F con = 0.02%; 225 ppm) (n=503)	1/1	DFT and DFS, visual (loss of surface continuity and colour) and tactil (texture and rougheness) criteria	36	0.86 (2.40)	N/A (Increment DFS=0.69)	0.02**
				Placebo rinse (n=503)	1/9			0.95 (2.39)	N/A (Increment DFS=0.84)	0.02**
Schaeken (1991) Nederland	44.4 mean age	NR	44 individuals	Control (n=13 individuals)	2/9	DMFS + color and texture	12	32	45	3.39
				Fluoride Varnish (Duraphat) (n=15)	2/1			66	70	0.51
				Chlorhexidine varnish 40% (w/w) (n=16)	2/2			93	95	0.18

Table 2 - Characteristics of the included studies (n=8).

Author (Year) Country	Age in Years (mean±SD and/or range)	Gender	Subjects	Treatment (N) /subgroup 1/subgroup2	Subgroup 1/subgroup 2*	Root caries index used	Follow-up (P; in months)	Baseline (BL) active lesions (N; % or mean±SD)	Follow-up (FL) active lesions N; % or mean±SD)	Estimated monthly Progress rate (%)*
Wallace (1993) USA	60 years and older	NR	603 (baseline); 532 (12 months); 497 (24 months); 481 (36 months); 466 (48 months)	Placebo mouthrinse s daily (n=171)	1/9	DMFS + color and texture	24	1.3	1.99	1.11
				APF gel 1.2% Fluoride (n=147)	2/1			1.3	1.36	0.10
				Fluoride rinse daily 0.05% NaF (n=148)	1/1			2.1	1.72	-0.38
Petersson (2011) Sweden	58-84 years; mean age of 67.6 (7.1)	35 males; 65 females	100 individuals (n=160)	Placebo (milk)	1/9	Root Caries Index (RCI) and Electric resistance measurements (ECM)	15	100	84	-0.01
				Milk supplemented with 5 ppm F and probiotic bacteria	1/7,8			100	41	-0.04
				Milk with only probiotic bacteria	1/7			100	63	-0.02
				Milk containing only fluoride	1/8			100	59	-0.03

Table 3 - Characteristics of the included studies (n=8).

Author (Year) Country	Age in Years (mean±SD and/or range)	Gender	Subjects	Treatment (N) /subgroup 1/subgroup2	Subgroup 1/subgroup 2*	Root caries index used	Follow-up (P; in months)	Baseline (BL) active lesions (N; % or mean±SD)	Follow-up (FL) active lesions N; % or mean±SD)	Estimated monthly Progress rate (%)*
Zhang (2013) China	60-89 years; mean age of 72.5 (5.7)	68 males; 168 females	266 subjects	OHI	2/-	Activity	24	1	0.91	0.00
				OHI + SDF	2/6			1.17	0.99	-0.01
				OHI + SDF + Oral health education	2/6			0.85	0.83	0.00
Leon (2019) Chile	61-88 years; mean age of 69.63 (6.25)	258 females; 87 males	345 individuals	Control toothpaste (1450 ppm)	1/3	Nyvad criteria for lesion activity per root	24	N=589 4.27 (3.35)	N=429 6.63 (4.2)	2.30
				Toothpaste (5000 ppm)	1/4			N=804 5.66 (3.52)	N=37 0.66 (2.36)	-3.68
Tan (2010) Australia	mean age of 78.8 ±6.2	73 males; 233 females	306 individuals (n=160)	OHI	2/-	Visible plaque index	36	1.3	1.3	0.00
				OHI + Chlorhexidine varnish	2/2			1.1	1.1	0.00
				OHI + sodium fluoride varnish	2/1			1.3	1.5	0.01
				OHI + SDF	2/6			1.3	1.5	0.01

Table 4 - Characteristics of the included studies (n=8).

Author (Year) Country	Age in Years (mean±SD and/or range)	Gender	Subjects	Treatment (N) /subgroup 1/subgroup2	Subgroup 1/subgroup 2*	Root caries index used	Follow-up (P; in months)	Baseline (BL) active lesions (N; % or mean±SD)	Follow-up (FL) active lesions N; % or mean±SD)	Estimated monthly Progress rate (%)*
Baca (2009) Spain	78.24±6.59	30 females; 16 males	21 patients	Varnish 1% chlorhexidine/ 1% thymol with antimicrobial (Cervitec, Ivoclar)	2/2	Width, Height, Distance from gingival margin, change in texture and change in color	12	2.86	0.67	-0.05
	75.64±7.11		25 patients	Varnish Placebo	2/9			2.6	1.32	-0.03

* Subgroup 1 – 1=home (self-applied product); or 2=office-based. Subgroup 2 - 1=fluoride; 2=CHX; CHX+other; 3=conventional toothpaste; 4=5000ppm/F toothpaste; 5=SnF2; 6=SDF; 7=milk probiotic; 8=milk fluoride; 9=placebo/negative. NR = Not reported. Monthly progress rate was not calculated to the studies that followed the same injuries from the beginning to the end. There was no increase in injuries;
** Based on the failure rate, presented by the authors;
N/A = Not Available;
--- Not calculated.

Table 5 - Estimated cost-effectiveness of non-invasive treatments for root caries of the included studies.

Treatment	Group	Commercial price (BRL)	Number of applications	Protocol	Material cost per application (BRL)	Number of suggested dental visits/year	Annual dental visits cost (BRL)	Total annual cost to avoid new lesions (BRL)	Average monthly progression rate **	Maximum patient recall time according to the results of the studies	Cost-effectiveness rate* (BRL)
Oral Hygiene instruction	2	N/A	N/A	N/A	N/A	1	248.95	248.95	0.0	N/A	---
Mouthrinse NaF 0.05%	1	16.90	25	1x/day	0.68	2	1,004.91	1,251.65	-0.18	N/A	579.47
Conventional Toothpaste	1	3.65	60	2x/day	0.06	2	497.91	506.67	2.30	N/A	---
SnF2/sodium Toothpaste	1	14.99	100	2x/day	0.15	2	497.91	557.87	N/A	N/A	---
Toothpaste 5000 ppmF	1	77.00	360	2x/day	0.21	2	805.91	962.05	-3.97	N/A	21.78
APF Gel Fluoride	2	15.56	40	2x/year	0.39	2	580.09	580.86	0.1	1x/6-10 months	---
Fluoride Varnish	2	199.00	60	4x/year	3.32	4	1,182.28	1,195.55	0.01	1x/2-4 months	---
Chlorexidine Varnish	2	592.62	20	4x/year	29.63	4	1,300.80	1,419.32	0.04	1x/5-6 months	---
Silver Diamine Fluoride	2	40.07	40	1x/year	1.00	1	291.40	292.40	0.0	1x/year	---

Group (1= home-based; 2= office-based); the annual of each gross cost was calculated by an average of the cost from two different Brazilian health insurances and from the private service in 2020, and multiplied by the number of suggested visits (number of appointments in the dental office) per year; all costs were calculated in Brazilian Real (BRL);
NA=Not available;
--- Not calculated;
* Only treatments with negative monthly progression rate were included;
** The average monthly progression rate was calculated only with studies presenting the BL and FL in averages, not number of lesions

DISCUSSION

The high failure rates of conventional treatments have brought attention to the increasing challenge of managing RCL for dentists. The evidence regarding the cost-effectiveness of prevention or arrestment methods for RCLs remains unclear[18]. In order to address this gap, a systematic review was conducted to assess the prognosis of non-invasive treatments for RCL. The review involved an extensive literature search, which identified 8 studies that evaluated the prognosis of teeth treated with various non-invasive methods for root caries. Our findings indicate that, with the exception of topical application methods such as fluoride gel, fluoride varnish, and CHX varnish, all other therapies showed positive outcomes. Surprisingly, home-based treatments exhibited a better prognosis, mainly towed by the very encouraging results of the 5000 ppm/F toothpastes[18]. However, it is important to note that only one study evaluated the use of gel, with two annual applications. The lack of a recommended treatment protocol for active lesions further complicates the consensus on the topical application of fluoride gel for prevention.

The American Dental Association (ADA) expert panel suggests using 5000 ppm/F toothpastes, fluoride varnishes, SDF and CHX varnish as non-invasive therapies indicated for the prevention and management of these lesions[27]. In the present study, in addition to these therapies, conventional toothpastes, fluoride mouthrinses and concentrated fluoride gel, commonly used in the Brazilian practice, were also analyzed.

Previous reviews have shown that the use of fluoridated agents in synergy with oral hygiene instruction (OHI) is probably the most effective way to deal with RCL[28-30]. Clinical studies in this review confirm this information[22,25], but these studies mostly involved groups associating OHI with some other method that includes fluoride as an active agent, not clearly isolating each therapy efficacy. We found a null monthly progression rate for both studies when the therapy was partially isolated (we considered that a conventional fluoride toothpaste was used), and an annual cost of BRL 248.00 to this therapy when isolated.

Regarding fluoride mouthrinses, our results shows that there is scientific evidence available to justify their use for the management of RCLs, as the monthly progression rate was negative. However, in two included studies[20,26], groups testing fluoride mouthrinses had access to fluoride toothpastes in oral hygiene, which can be

considered a confounding factor to highlight their isolated effect. It does not exclude the treatment as part of an adjunct preventive regimen for patients at risk. However, a low cost-effectiveness was identified, being BRL 579.47 for the effect of an inactivated lesion.

The best prognosis within all non-invasive therapies among all of the results was from 5000 ppm/F toothpastes[18]. Although the available products for this treatment were apparently expensive, our results showed that a better cost-effectiveness could be achieved when compared to other home-based treatments, as fluoride mouthrinses. When office-based treatments were analyzed, the estimated gross cost was only lower in relation to CHX varnish and fluoride varnish. As an advantage, toothpastes do not require dental visits; instead, the patient is responsible for self-care. Home-based methods seems to be effectives, but it is important to note that age affects the physical and cognitive aspects of impairment as well as reduced access to oral health care[31]. Participants in the included studies were between 45 and 89 years-old, which cause some concerns about the use of these methods for everyone. Albeit efficient for a patient in perfect health, the effect may not be the same in 80-year-old patients, which probably already have some health issues. Furthermore, a single study fitted in the eligibility criteria of this review evaluating the 5000 ppm/F toothpastes. This was a well-designed study, based on the CONSORT checklist and with a low risk of bias[18].

Fluoride varnishes are historically effective in managing enamel caries lesions[32]. One unforeseen finding was that these treatments, among those available in Brazil, had the worst prognosis for RCL and the highest gross cost. There is a requirement of a greater number of dental appointments to ensure their action and an average of the monthly progression rate was positive. As for topical applications of fluoride gels, the result of this review shows an average of the positive monthly progression rate in the included studies, but with lower gross cost than the fluoride varnishes. A RCT trial shows that the combination of the use of a fluoride toothpaste and the application of fluoride gel can provide additional protection against root caries when compared only to isolated toothpaste[33]. A study demonstrated that the combined use of fluoride varnish monthly associated with regular use of conventional 1450 ppm/F toothpastes was not as effective as using only 5000 ppm/F toothpaste without associating with any other therapy[34], and was excluded from our analysis for having a follow-up of less than 12 months. In contrast, in dentin, the difference

between the use of a 5000 ppm/F toothpaste did not show a significant difference to the synergistic use of a conventional fluoride toothpaste, 1100 ppm/F with the topical application of fluoride gel[35].

Among these therapies with fluoride, the SDF stands out as viable one because it is simple, does not require expensive equipment or support infrastructure, which makes it useful in the dentistry arsenal to meet the WHO's millennium goals. In cultures where aesthetics is not a primary concern, it can be used routinely[36], and when there is no possibility of a regular monitoring of the patient, it should be considered. However, in the meta-synthesis of all results of studies evaluating SDF for RCL, there was a null monthly progression rate, and a cost-effectiveness was then not calculated. The synergistic antimicrobial action of silver combined with the remineralizing effect of fluoride seems to favor the SDF as a good alternative among the therapies performed in the office (office-based).

Among the three published systematic reviews of effectiveness on this field[9,11,12], the most recent one brought comparisons between methods of application of fluoride, but only in prevention of new lesions[11]. All reviews agreed that 5000 ppm/F toothpastes, chlorhexidine varnishes and SDF are the most effective methods, but also state that their conclusions are based on a few well-conducted studies. The present review, when addressing the prognosis of these therapies, despite the limited number of studies, offers a counterpoint to demonstrate a superior prognosis of 5000 ppm/F toothpastes when compared to chlorhexidine varnish and SDF. In addition, it presents a better cost-effectiveness when compared to mouthwashes.

The only non-fluoride office-based method tested in included studies was the CHX varnish. A review showed its beneficial effects to patients in need of special care[37]. Recent systematic reviews showed evidence of its effectiveness in controlling RCL[9,12], however, there is also a recommendation of use with caution, due to possible risk of antimicrobial resistance[38]. This varnish is not available for use in the Brazilian market and has the highest estimated annual dental visits cost when compared to other therapies. In the present study, in terms of prognosis, it showed better results than fluoride gel and fluoride varnish only[19,24,39].

Only five out of the eleven studies included in this study showed comparisons between therapies, of which only one[25] had a follow-up period of 36 months. All other studies, in addition to using placebo or negative controls, had follow-up periods between 12 and 30 months. The available data were collected from studies carried

out in different countries, in different populations, and without a pre-established age criteria, which demonstrates a study limitation. In addition, there are no studies in the literature that compare home-based to office-based therapies (SDF and 5000 ppm/F toothpaste, for example). The placebo or negative control groups had a positive average monthly progression rate. This means that new clinical studies should not use this type of treatment as a comparator, unless the patient is followed up on monthly recalls.

The strengths of this study include the methodology adopted, extensive literature search, cost-effectiveness analysis. However, our results should be evaluated with caution, since studies with irradiated patients or those with more general health problems are excluded. In this sense, we do not know if the result of this review applies to them. It is also necessary to take into account that the cost analysis was performed for the Brazilian private dental practice and it was not possible to calculate the costs for the public service. In addition, further studies are needed to confirm the superiority of treatments with 5000 ppm/F toothpaste in terms of cost-effectiveness before further generalization of results to the whole population at risk for root caries.

CONCLUSION

Home-based therapies, particularly the one with 5000 ppm/F toothpastes represented the highest rates of good prognosis for treating root caries lesions within the available scientific evidence. Although this product has a very high cost for the Brazilian market, this treatment presented the highest cost-effectiveness when compared to mouthrinses. Non-invasive treatment with fluoride varnishes, APF gel 1.2%, or CHX varnish can be performed only with monthly recalls.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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