UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

BRUNA MACHADO DA SILVA

Effect of fluoride solution and dentifrice on dental erosion associated or not with abrasion in human enamel: systematic review and metanalysis

[Efeito das soluções e dentifrícios fluoretados na erosão dentária associada ou não a abrasão em esmalte humano: revisão sistemática e metanálise]

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Orientador: Prof. Dr. Heitor Marques Honório

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FOLHA DE APROVAÇÃO

DEDICATÓRIA

Dedico este trabalho primeiramente a Deus, ao meu pai Braz, minha mãe Cristina, minha irmã Betânia, ao meu irmão Thiago e ao meu amor Silvio. Quero dedicar também às pessoas com quem convivi nesses espaços ao longo desses dois anos, aos meus colegas de profissão e aos professores que compartilharam com amor e muita dedicação suas experiências, em especial ao meu querido orientador Heitor, que me adotou como filha assim que cheguei na FOB-USP. Espero que este trabalho seja compartilhado e explorado da melhor forma possível pelos colegas de profissão do mundo todo.

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"O maior valor da vida não é o que você obtém. O maior valor da vida é o que você se torna."

Jim Rohn

RESUMO

As evidências do efeito preventivo do fluoreto sobre a erosão dental provêm de estudos in vitro e in situ, mas essa premissa tem sido questionada em relação a sua aplicação na clínica, uma vez que ainda não se tem conhecimento de um ensaio clínico. Assim, considerando que os estudos in situ/ex vivo que se aproximam dos ensaios clínicos, esta dissertação compôs de duas revisões sistemáticas com metanalises, com o objetivo de avaliar a eficácia das soluções fluoretadas (SF) e dentifrícios fluoretados (DF) monovalentes e polivalentes em comparação ao grupo controle negativo (ausência de flúor) na prevenção e controle da erosão do esmalte associado ou não à abrasão. O objetivo secundário foi comparar a eficácia entre as SF e DF fluoretados monovalente vs. SF e DF polivalentes. A variável de resposta utilizada neste estudo foi o desgaste do esmalte, medido por perfilometria. Esta revisão sistemática foi registrada no banco de dados do PROSPERO (CRD42017071118) e seguiu as diretrizes do PRISMA. Foi realizada uma busca sistemática e abrangente utilizando PUBMED, WEB OF SCIENCE, SCOPUS, EMBASE, BBO, LILACS, SCIELO e literatura cinzenta IBICT-BDTD. Um total de 625 estudos foram obtidos e após a exclusão de artigos duplicados, apenas 264 foram incluídos neste estudo. Em ambas revisões, a fase de seleção foi seguida sistematicamente (kappa = 0,98), conduzida por dois autores independentes e encerrada com dez estudos de SF e doze estudos de DF para análise qualitativa e dez estudos, para cada revisão, compôs as metanálises. As metanálises mostraram resultados positivos para as SF e DF polivalentes com uma significativa prevenção da erosão e erosão/abrasão, em comparação ao grupo controle. SF monovalentes foram capazes de prevenir apenas a erosão, uma vez que não apresentaram diferença ao grupo controle quando avaliadas perante a erosão/abrasão. Em contraste, os DF monovalentes foram capazes de prevenir apenas a erosão e erosão/abrasão. Quando as SF polivalente e monovalente foram comparadas, a primeira resultou em menor desgaste após o desafio erosivo, enquanto que a comparação entre os DF não apresentou diferença entre os mesmos. No entanto, para erosão/abrasão, não foram observadas diferenças significativas entre as SF. Portanto, há evidências consistentes para o efeito preventivo de SF e DF, especialmente os produtos fluoretados polivalentes, contra a erosão do esmalte, associada ou não à abrasão.

PALAVRAS-CHAVE: Fluoreto, Esmalte, Erosão, Prevenção, Solução, Dentifrícios

ABSTRACT

Effect of fluoridated solutions and dentifrices on dental erosion, associated or not with abrasion in human enamel: a systematic review and meta-analysis

The evidence of the preventive effect of fluoride in erosion comes from *in vitro* and *in situ/ex vivo* studies, but this evidence has been questioned, in relation to its application in the clinic, since no knowledge clinical trial studies. Thus, considering *in situ/ex vivo* studies approaching clinical trials, this dissertation was composed by two systematic reviews with meta-analyzes to evaluate the efficacy of fluoridated dentifrices (FD) and fluoridated solutions (FS), either monovalent or polyvalent, compared to the negative control group (absence of fluoride) in the prevention and control of enamel erosion, associated or not with abrasion. The secondary objective was to compare the efficacy between FS and FD fluoridated monovalent or polyvalent fluorides. The response variable used in this study was enamel wear, measured by profilometry. This systematic review was registered in the PROSPERO database (CRD42017071118) and followed PRISMA guidelines. A systematic and comprehensive search was performed using PUBMED, WEB OF SCIENCE, SCOPUS, EMBASE, BBO, LILACS, SCIELO and grey literature IBICT-BDTD. A total of 625 studies were obtained and, after exclusion of duplicate articles, only 264 were identified. In both reviews, the selection phase was systematically followed (kappa = 0.98), conducted by two independent authors, who included ten studies on FS and twelve studies on FD for qualitative analysis, and ten studies, for each review, composed the metanalysis. Metanalysis of quantitative analysis showed positive results for polyvalent FS and FD, with a significant effect on the prevention of erosion and erosion/abrasion compared to control group. Monovalent FS were able to prevent only erosion, since no significant difference was observed when evaluating erosion/abrasion compared to the control. In contrast, monovalent FD were able to prevent erosion and erosion/abrasion. When polyvalent and monovalent FS were compared, the first one resulted in less wear after erosive challenge, while the comparison between monovalent and polyvalent FD did not show any significant difference. However, for erosion/abrasion, no significant differences were observed between the FS. Therefore, there is consistent evidence on the preventive effect of FS and FD, especially for the polyvalent vehicles assessed against enamel erosion, associated or not to abrasion.

KEYWORDS: Fluoride, Enamel, Erosion tooth wear, Prevention, Solution, Dentifrice

LIST OF FIGURES

LIST OF TABLES

LIST DE ABREVIATIONS AND ACRONYMS

ERO	Erosion
ERO+ABR	Erosion and Abrasion
FS	Fluoride Solutions
FD	Fluoride Dentifrices
PVFS	Polyvalent Fluoride Solutions
MVFS	Monovalent Fluoride Solutions
PVFD	Polyvalent Fluoride Dentifrices
MVFD	Monovalent Fluoride Dentifrices
Q	Qualitative Analysis
MA	Metanalysis
TC	Type Challenge
EC+ FR	Erosive Challenge+ Frequency
T	*in situ* total time period (number of phase x number of days)
[ ]	Concentration
FSAF	Fluoride Solution Application Frequency
CG	Control Group
V	Vehicle
EI	Studies included in the analysis
W ou DW	Water or Deionized Water
p	Significance
whtI	Without p information
S	Solution
D	Dentifrice
G	Gel
NT	Not Treated
P	Placebo
TT	Total Time

SUMÁRIO

1 INTRODUCTION

1 INTRODUCTION

Erosive tooth wear (ETW) has become a concern for dental clinicians and researchers due to its high prevalence (Salas et al., 2015, Schlueter; Luka, 2018), and recent studies show that the incidence of this alteration is increasing (Tschammler et al., 2016; Brusius et al., 2018). Therefore, the early diagnosis of ETW lesions in association with the implementation of strategies to prevent or control this condition is necessary to promote and maintain oral health. Despite the main strategy may comprise the intervention on the etiological factors related to patient and specific protective products can be applied on erosive lesions in order to increase prevention and treatment effectiveness (Teixeira; Manarte-Monteiro; Manso, 2016, Lussi; Carvalho, 2015). Fluoride has been discussed as a potential agent for these protective products.

There are two main sources of fluoride have been studied in erosion therapy, monovalent and polyvalent metals fluorides. The preventive mechanism proposed for monovalent fluorides is the formation of a CaF_2 layer, which can temporarily diminishe the contact between the erosive acid and the underlying enamel (Huysmans et al., 2014, Magalhães; Rios; Buzalaf, 2011). On the other hand, the mechanism of action of polyvalent fluorides is related to Tin or Titanium Tetrafluoride deposition and incorporation on the tooth surface, forming a protective layer which is less susceptible to dissolution and may result in protection of the dental surface against subsequent acid challenges (Lussi; Carvalho, 2015). There are also different vehicles for fluoride use at home (mouthrinses low concentration and dentifrices) or professionally applied (mouthrinses high concentration, gels and varnishes), both products have been reported through experimental studies (Teixeira; Manarte-Monteiro; Manso, 2016). A recent study showed that the type substrate can influence the results for better or worse (Comar et al., 2017).

Although the strongest scientific evidence comes from randomized clinical trials, there is no clinical studies investigating the effect of fluoride against ETW due to difficulties in obtaining precise methods to measure tissue loss of erosive lesions *in vivo* (West et al., 2011). The evidence on the role of fluoride in erosion comes from *in vitro* and *in situ* studies, but this evidence has long been questioned, in relation to its application in the clinic, since no knowledge clinical trial studies. (Huysmans et al., 2014). Then considering the clinical approach and the study of higher level of available evidence, this dissertation aimed to evaluate the efficacy of mouthrinses and dentifrices containing monovalent and polyvalent metal fluorides, compared to the negative control group (absence of fluoride) on the prevention and control of erosion, associated or not with abrasion, in human enamel, considering *in situ/ ex vivo* studies. The secondary objective was to compare the effect between monovalent *vs.* polyvalent metal fluorides mouthrinses and dentifrices.

2 ARTICLES

2 ARTICLES

These articles were written in accordance with Caries Research and Journal of Dentistry guidelines.

2.1 Article 1

Effect of fluoride solutions on dental erosion associated or not with abrasion in human enamel: a systematic review and metanalysis

Bruna Machado da Silva[1], Daniela Rios[1], Gerson Aparecido Foratori-Junior[1], Ana Carolina Magalhães[2], Marília Afonso Rabelo Buzalaf[2], Silvia Helena de Carvalho Sales-Peres[1], Heitor Marques Honório[1]

[1] Department of Pediatric Dentistry, Orthodontics and Public Health, Bauru School of Dentistry, University of São Paulo, Brazil

[2] Department of Biological Sciences, Bauru School of Dentistry, University of São Paulo, Brazil

Short Title: **Fluoride solutions on dental erosion: systematic review and metanalysis**

*Corresponding Author
Heitor Marques Honório
Department of Pediatric Dentistry, Orthodontics and Public Health
Bauru School of Dentistry, University of São Paulo
Al. Octávio Pinheiro Brisolla, 9-75
Bauru, São Paulo, 17012-901, Brazil
Tel: +55 (14) 32358256
Fax: +55 (14) 32234679
E-mail: heitorhonorio@usp.br (H.M Honório).

Keywords: Fluoride, Enamel, Tooth Erosive Wear, Sytematic Review, Solution

Abstract

Effect of fluoride solutions on dental erosion associated or not with abrasion in human enamel: a systematic review and metanalysis

The preventive effect of fluoride on erosion comes from *in vitro* and *in situ* studies, but this evidence has been questioned. Therefore, considering *in situ* studies, this systematic review aimed to evaluate the efficacy of monovalent and polyvalent fluoride solutions compared to the negative control group (absence of fluoride) on the prevention and control of enamel erosion associated or not with abrasion. The secondary objective was to compare the effectiveness between monovalent and polyvalent fluoride solutions. The response variable was enamel wear measured by profilometry. This review was registered in the PROSPERO database (CRD42017071118) and followed PRISMA guidelines. A systematic and comprehensive search was performed using PUBMED, WEB OF SCIENCE, SCOPUS, EMBASE, BBO, LILACS, SCIELO and grey literature IBICT-BDTD. A total of 625 studies were obtained and after exclusion of duplicates, only 264 were identified. The selection phase was followed systematically, conducted by two independent authors (kappa=0.98) and ended with 10 studies for qualitative analysis and metanalysis. Metanalysis showed that polyvalent fluoride solutions prevented enamel wear from erosion and erosion/abrasion compared to control group. Monovalent fluoride solutions were able to prevent wear only against erosion. The comparison of polyvalent and monovalent fluoride solutions showed that the former reduced enamel wear after erosive challenge. However, for erosion/abrasion, no significant differences were observed between the fluoride solutions. The metanalysis was performed again considering only the studies with low risk of bias (Cochrane scale adapted for *in situ* studies) and confirmed the results. There is strong evidence that fluoride solutions are effective in preventing erosion and polyvalent metal ones in preventing erosion associated with abrasion in comparison with control group.

Keywords: Fluoride, Enamel, Tooth Erosive Wear, Sytematic Review, Solution.

Introduction

Erosive tooth wear (ETW) has become a concern for dental professionals and researchers due to its high prevalence [Salas et al., 2015; Schlueter & Luka et al., 2018]. Recent studies also show that the incidence of this alteration is increasing [Tschammler et al., 2016; Brusius et al., 2018]. Therefore, both the early diagnosis of ETW lesions and the implementation of strategies to prevent or control this condition are necessary to promote and maintain oral health. The main strategy may comprise the intervention on the etiological factors related to patient and nutrition, however, specific protective products can be used to increase prevention and treatment effectiveness [Lussi & Carvalho et al., 2015; Teixeira et al., 2016]. Fluoride has been discussed as a potential agent for these protective products.

In the fluoride therapy against erosion, the literature reports two main types of fluoride: monovalent and polyvalent metal fluorides. The preventive mechanism of monovalent fluoride is the formation of a CaF_2 layer, which can temporarily decrease the contact between the erosive acid and the underlying enamel [Magalhaes et al., 2011; Huysmans et al., 2014]. On the other hand, the mechanism of polyvalent metal fluorides is related to the counterion (tin or titanium) deposition onto the tooth surface, forming a protective layer which is less susceptible to dissolution, and may result in protection of the dental surface [Lussi & Carvalho et al., 2015]. There are also different vehicles for fluoride use: at home (dentifrices and solutions low concentration) or professional (solutions high concentration, gels and varnishes) [Teixeira et al., 2016]. Considering that the effect of fluoride is short-lived and requires frequent application to promote prevention, both products have been reported through experimental studies [Huysmans et al., 2014]. Another point, a recent study showed that the type substrate can influence the results for better or worse [Comar et al., 2017].

Randomized clinical trials (RCT) can be considered the main and most important “raw material” of a systematic review because RCTs show the strongest scientific evidence on a given subject. However, the research of ETW by RCT is exceedingly difficult due to the slow development of these lesions, which can take years to exhibit a clinically detectable sign. Currently, *in situ* and *ex vivo* studies are the available primary experimental studies on ETW with the highest level of evidence. The ideal scientific evidence may come from randomized clinical trials; however, no clinical study investigates the effect of fluoride against ETW due to the difficulty in obtaining a precise method to measure the tissue loss of erosive lesions [West et al., 2011]. The evidence of the role of fluoride in erosion comes from *in vitro* and *in situ* studies, but this evidence has long been questioned [Huysmans et al., 2014]. Therefore, this systematic review aimed to evaluate the efficacy of monovalent and polyvalent metal fluoride solutions, compared with a negative control group (absence of fluoride) on the prevention and control of erosion associated or not with abrasion, in human enamel, considering *in situ/ex vivo* studies. The secondary objective was to compare the effect of monovalent and polyvalent metal fluoride solutions.

Methodology

Register and Protocol

This systematic review followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [Moher et al., 2009] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with protocol CRD42017071118 (https://www.crd.york.ac.uk/prospero).

Research information and search strategy

In this study, the PICO structure was adapted for *in situ/ex vivo* studies according to the following criteria: P (patient) – human dental enamel, I (intervention) – fluoride solutions; C (control) – non-fluoride solutions (negative control); O (outcomes) – wear evaluated by profilometry. The descriptors were controlled (MeSH and DeCs) and used in the search strategy according to the following PICO questions: Are fluoride solutions capable of decreasing the wear of dental enamel submitted to *in situ/ex vivo* erosion associated or not with abrasion compared with non-fluoride solutions?

The bibliographic search was performed in September 15, 2018. Data search was performed in electronic databases as follows: PubMed, Embase, Scopus, Web of Science, Latin American and Caribbean Database of Health Sciences Literature-LILACS, Brazilian Dental Library-BBO, Scientific Electronic Library Online-Scielo. Grey literature database was also searched (Brazilian Digital Library of Thesis and Dissertations -BDTD-Ibict).

The search strategies were structured according to the Boolean operators (AND/OR) and the specificity of each database. A comprehensive search strategy was used to retrieve the greatest number of studies as possible. Based on PICO strategy the used descriptors were *tooth wear*, *tooth erosion*, *tooth abrasion*, *tooth attrition*, *fluoride*, *fluorine*, *fluorine compounds*, *in situ studies*, and *intraoral exposure*. The studies were included until September 15, 2018. The search strategy was designed as follows: ("tooth wear"[All Fields] OR "tooth wears"[All Fields] OR "dental wear"[All Fields] OR "abrasion"[All Fields] OR "attrition"[All Fields] OR "erosion"[All Fields]) AND ("fluorine"[All Fields] OR "fluoride"[All Fields] OR "fluorides"[All Fields] OR "fluorine compound"[All Fields] OR "fluorine compounds"[All Fields]) AND ("in situ"[All Fields] OR "ex vivo"[All Fields] OR "intraoral exposure"[All Fields] OR "intra oral exposure"[All Fields] OR "intraoral exposures"[All Fields]). Then, the strategy was tailored to meet the requirements of each database. Moreover, grey literature and non-published studies were searched electronically and manually to include further studies meeting the eligibility criteria.

All primary studies were exported to EndNote online (www.myendnoteweb.com). Neither publication dates nor study languages were restricted.

Eligibility criteria

Included all the primary *in situ* and *ex vivo* studies, in which the participants used devices with human enamel specimens; studies containing information on profilometry or tooth wear (dependent variable); studies with test groups or positive controls employing fluoride solutions compared with negative controls; studies on tooth erosion associated or not with tooth abrasion. Exclusion criteria comprised other study designs (*in vitro*, *in vivo*, observational, and literature reviews), repeated studies, studies without negative control, studies addressing other subject rather than tooth erosion (associated or not with tooth abrasion), studies employing bovine enamel, studies that did not employed profilometry, studies evaluating only dentin wear; studies reporting information on wear exclusively by other vehicles (dentifrices, gels, varnishes).

Study selection and data extraction process

The repeated studies were excluded using EndNote online. Then, study data regarding to authors, year, and titles were stored in Excel Office. Two independent reviewers (BMS; GAFJ) selected the study titles and abstracts that met the inclusion criteria. Discordances were solved by a third independent reviewer (HMH). The interexaminer agreement analysis showed a Kappa score of 0.98, suggesting excellent agreement. The reviewers read the full text when the study title or abstract lacked information to make a clear decision on methodology analysis and data extraction. Of the 68 selected studies, 65 were directly obtained on the database or through institutional agreement. The other 3 studies were requested to other Brazilian institutions [Passos et al., 2017; West et al., 2018] or directly to the author [Zhao et al., 2017].

Of these, two studies were found and accessed [Passos et al., 2017; West et al., 2018]. After full-text reading, 58 studies were excluded because they did not meet the inclusion criteria and 10 studies were selected. Ten studies comprise the qualitative analysis and all studies were included in the metanalysis (Fig. 1.). In cases of absent data, we did not contact the authors of the primary studies and included in the systematic review only the published data.

It is worth noting that one study can be included one or more times in the quantitative analysis because it includes the comparison of different fluoride solutions with only one control group.

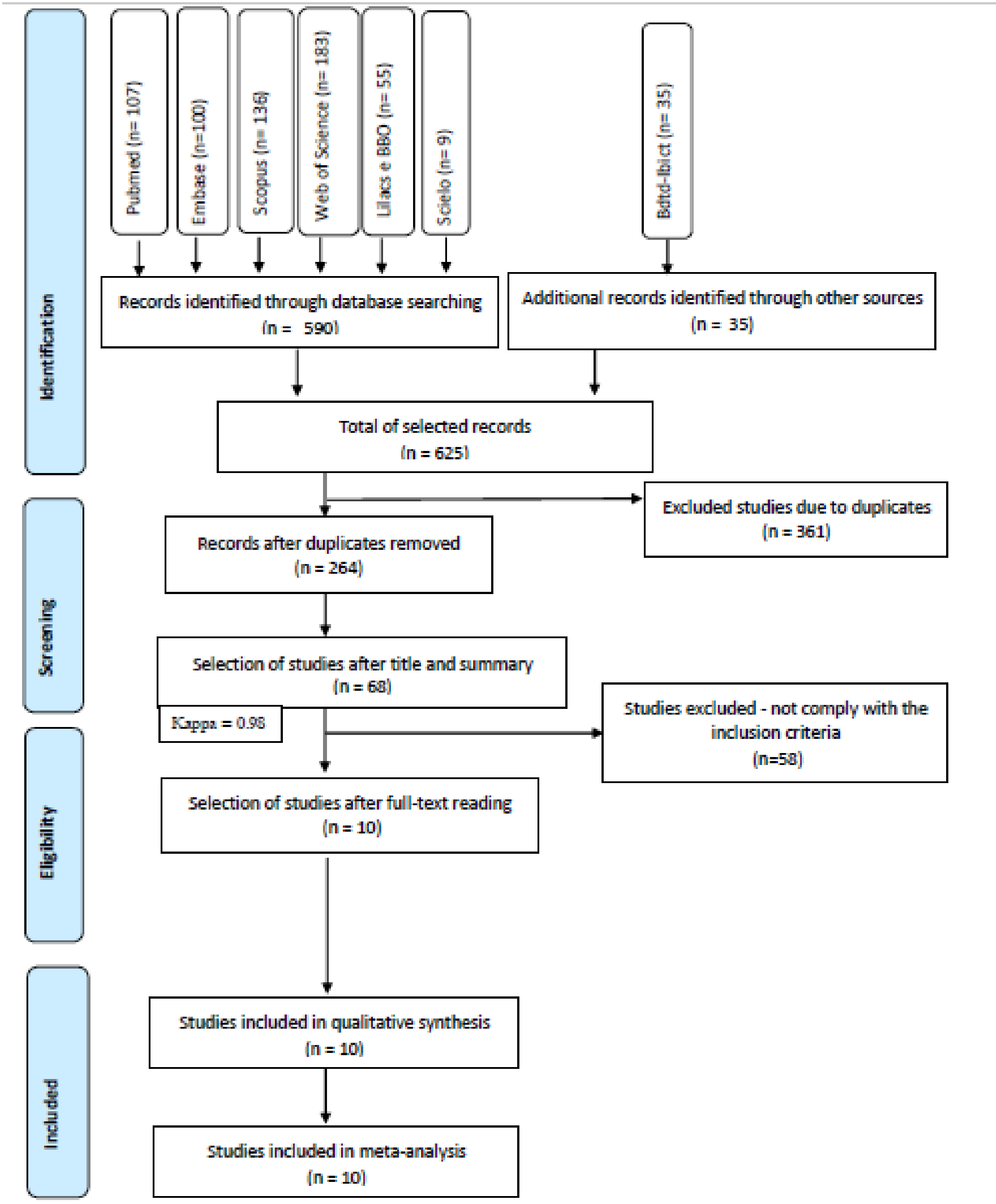


Fig.1. Flow diagram of selected of included studies

The included studies were individually examined and the main characteristics were extracted and stored in a standardized form in Microsoft Office Excel, as follows: first author's last name, type challenge (TC), acid type and frequency of erosive challenge *ex vivo* (EC), fluoride solutions and concentrations (FS), number of applications of fluoride solutions (FSAF), negative control group (CG) and outcomes (Table 2).

Individual risk of bias and risk of bias among studies

The qualitative analysis was performed by RevMan5.3 software (Cochranne Collaboration) adapted to *in situ/ex vivo* studies. Two reviewers (BMS and GAFJ) independently evaluated the following risk of bias of the included studies: (1) selection bias – sample size, randomization, and allocation concealment; (2) performace bias– blinding of participants and personnel; (3) detection bias – bliding of outcome assessment; (4) attrition bias – incomplete outcome data; (5) reporting bias – selective reporting; and (6) confounding bias – erosive challenge and *in situ* study protocol design. The judgements were based on the Cochrane Handbook [Higgins et al., 2011] and on the study of Carvalho et al. [2013]. We also added three domains based on the methodology of *in situ/ex vivo* studies [West et al., 2011; Shellis et al., 2011; Sung et al., 2014]: justified sample size, type of erosive challenge, *in situ/ex vivo* study design (Table 1). These domains were individually classified and identified by colors into: low risk-green; uncertain risk-yellow; and high risk-red. Studies classified as red and/or yellow in five or more domains had high risk of bias; those classified as red and/or yellow in 3-4 domains had moderate risk of bias; and studies classified as red and or yellow in 2 domains had low risk of bias.

Table 1: Risk of bias classification of the three included domains

Risk of bias – included for in situ and ex vivo		
Selection bias	**Justified sample size**	**Low risk:** justified calculation of sample size
		High risk: neither sample size calculation nor justification of sample size
		Uncertain: unjustified sample size calculation, no information.
Confounding bias	**Erosive challenge type**	**Low risk:** erosive challenge performed by pH cycling.
		High risk: erosive challenge performed only once.
		Uncertain: no information on the erosive challenge.
	Experimental design of *in situ* study	**Low risk:** study with cross-over experimental design.
		High risk: study with parallel experimental design,
		Uncertain: no information on the experimental design of the *in situ*/ex vivo study.

Summary of measurements, outcomes, and additional analyses

All data of the fluoride solutions were obtained, thus resulting in one or more combinations (from the same paper) compared with the control group. The metanalyses were performed with Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA), with level of significance of 5%. To compare the experimental (fluoride solutions) with the control groups, the effect size was defined as the difference between the standardized means between groups. The studies were grouped in two segments that generated different statistical analyses: ERO (tooth enamel subjected to erosion) and ERO+ABR (tooth enamel subjected to erosion associated to abrasion). Then, two metanalyses were applied to each segment: 1st) [polyvalent metal fluoride solutions (PVFS – polyvalent fluoride solutions) and monovalent fluoride solutions (MVFS - monovalent fluoride solutions)] *vs.* Control and 2nd) [polyvalent metal fluoride solutions (PVFS) *vs.* monovalent fluoride solutions (MVFS)], resulting in four metanalyses. The heterogeneity of treatment values between the studies was evaluated by the Inconsistency test (I^2) stating that values greater than 75% (interval from 0 to 100) indicated high heterogeneity. Because the differences between the study methodologies can affect the effect size by generating heterogeneity values greater than 75%, random effect model was chosen. In this systematic review, the high heterogeneity values were predictable due to the high methodologic variability of the *in situ/ex vivo* studies, such as: number of erosive cycles, period of immersion in the erosive agent, length of the experimental period, etc. Therefore, the most important outcome of the quantitative analyses was the comparison between the experimental and control groups, regardless of the method used and of the absolute values of the verified effect size. The publication bias was also verified through Funnel plot [Egger et al., 1997].

Results

Study characteristics

In all studies, the participants signed a free and clarified consent form, were aged higher than 18 years, had satisfactory oral health, normal salivary flow, and lived in areas with fluoridated water. The studies excluded participants with systemic diseases, active caries, periodontal disease, altered salivary flow, using of continuous medication, breastfeeding, allergy to the tested dental materials and products, and using of fixed or removable orthodontic appliance. The sum of the sample size of all included studies was 117 participants. The enamel blocks originated from either extracted non-erupted third molars [Magalhaes et al., 2008; Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; Levy et al., 2014; da Silva et al., 2017] or sound pre-molars/molars extracted due to orthodontic reasons [Lussi et al., 2004; Hove et al., 2008; Stenhagen et al., 2013; Hove et al., 2014]. All teeth were cleaned and disinfected, sectioned, sterilized, planned, and polished to obtain the enamel blocks for further insertion in the intraoral devices constructed for each participant. The protection of the sound reference surface was performed for the profilometer analyses. One study created erosive lesions before the *in situ/ex vivo* phase [da Silva et al., 2017], while others employed sound enamel [Lussi et al., 2004; Hove et al., 2008; Magalhaes et al., 2008; Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; Stenhagen et al., 2013; Hove et al., 2014; Levy et al., 2014;]. The time period of intraoral use was determined according to the protocol of each study, ranging from 11 to 24 hours/day, with resting time of one hour during meals. The types of intraoral appliances were either mandibular [Lussi et al., 2004; Hove et al., 2008; Schlueter et al., 2009; Schlueter et al., 2011; Stenhagen et al., 2013; Hove et al., 2014; da Silva et al., 2017] or maxillary [Magalhaes et al., 2008; Ganss et al., 2010; Levy et al., 2014]. The erosive challenges were performed by different acids with pH ranging from 2.3-2.6: citric acid [Lussi et al., 2004; Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; da Silva et al., 2017], hydrochloric acid [Hove et al., 2008; Stenhagen et al., 2013; Hove et al., 2014] or cola drink [Magalhaes et al., 2008; Levy et al., 2014], with frequencies ranging from once/day (3min) [Lussi et al., 2004], twice/day (2min) [Hove et al., 2008; Stenhagen et al., 2013; Hove et al., 2014], four times/day (90s or 5min) [Magalhaes et al., 2008; Levy et al., 2014], and six times/day (2min or 5min) [Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; da Silva et al., 2017]. The erosive cycling varied from one cycle (9 days) [Hove et al., 2008;

Stenhagen et al., 2013; Hove et al., 2014], three cycles (5 or 7 days) [Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; Levy et al., 2014], four cycles (5 or 7 days) [Magalhaes et al., 2008; da Silva et al., 2017] or five cycles (1 day) [Lussi et al., 2004]. Despite of the differences in the protocols, all included studies had one or more experimental groups containing any fluoride solution and a control group without fluoride solution (negative control).

Intervention and control

All fluoride solutions (FS) of the 10 included studies were compared with negative control group (CG). These studies were composed of 21 FS.

By analyzing all the included studies, we verified 14 comparisons containing different FS with isolated agents [NaF (6 times), SnF_2 (3 times), TiF_4 (4 times), and AmF (once)]; in 7 cases, FS were associated with other fluoride or non-fluoride solutions [AmF+NaF+$SnCl_2$ (5 times), AmF+NaF (once), and SnF_2+AmF (once)]. Considering the 21 cases, 13 were polyvalent metal fluoride solution PVFS [SnF_2 (3 times), TiF_4 (4 times), AmF+NaF+$SnCl_2$ (5 times), and SnF_2+AmF (once)] and 8 monovalent fluoride solution MVFS [NaF (6 times), AmF+NaF (once), AmF (once)]. The FS concentrations ranged from low to high (225 to 24,000 ppm F). The frequency of the fluoride application varied from once [Lussi et al., 2004; Hove et al., 2008; Magalhaes et al., 2008; Schlueter et al. 2009; Ganss et al., 2010; Schlueter et al., 2011; Stenhagen et al., 2013; Levy et al., 2014; da Silva et al., 2017] to twice [Hove et al., 2014; da Silva et al., 2017] from 30 seconds to 5 minutes. The negative control groups were composed by deionized water [da Silva et al., 2017], placebo solution [Hove et al., 2008; Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; Hove et al., 2014]; or no applied treatment [Lussi et al., 2004; Magalhaes et al., 2008; Stenhagen et al., 2013; Levy et al., 2014]. Further details can be seen in Table 2.

Outcomes

Six studies evaluated erosion alone (ERO) [Hove et al., 2008; Magalhaes et al., 2008; Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; da Silva et al., 2017], three studies evaluated erosion associated with abrasion (ERO+ABR) [Lussi et al., 2004; Stenhagen et al., 2013; Hove et al., 2014], and only one study evaluated ERO with and without ABR separately [Levy et al., 2014]. Of these, eight studies demonstrated significant results in preventing and controlling the progression of the erosive wear associated or not with abrasion in the experimental group (FS) compared with CG. Only two studies did not find favorable results for FS [Lussi et al., 2004; Magalhaes et al., 2008].

Considering FS composed by NaF (500-24,000 ppm F), three studies showed lower enamel wear (erosion associated or not with abrasion) compared with CG [Ganss et al., 2010; Stenhagen et al., 2013; Levy et al., 2014]; four studies presented no differences under both conditions (ERO or ERO+ABR) [Lussi et al., 2004; Hove et al., 2008; Schlueter et al., 2009; da Silva et al., 2017]. Three studies of FS composed by SnF_2 (969,9 to 9456,2 ppm F) and three studies by TiF_4 (920,3 to 24,000 ppm F) also promoted higher prevention against ERO and ERO+ABR compared to control. Only one study showed that TiF_4 did not aid in protecting enamel against ERO [Magalhaes et al., 2008].

AmF (250 ppm F) used alone did not protect against ERO+ABR [Lussi et al., 2004], but when associated with SnF_2 (AmF+SnF_2- 250 ppm F) reached a more favorable result in preventing ERO [Schlueter et al., 2011]. The FS composed by AmF+NaF+SnF_2 (500-1000 ppm F) with greater application frequency [da Silva et al., 2017] compared with NaF and/or CG resulted in significant better protection against the ERO [Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; da Silva et al., 2017]. One study showed slightly lower enamel wear when treated with AmF+NaF+SnF_2 (1000 ppm F) compared to AmF+SnF_2 500 ppm F [Schlueter et al., 2011]. Further details can be seen in Table 2.

Table 2: Data of the studies included in qualitative (Q) and metanalysis (MA) (alphabetic order).

Author	TC	EC	FS / [ ]	FSAF	CG	Outcome(s)
da Silva et al. (2017)a	ERO	Citric acid (pH 2.6) 6x/day (2 min) TT: 60 min	**NaF** 500 ppm F **AmF+NaF+SnCl$_2$** 250 ppm F AmF + 250 ppm F NaF **AmF+NaF+SnCl$_2$** 250 ppm F AmF + 250 ppm F NaF	1x/day (2 min) TT: 10 min 2x/day (2 min) TT: 20 min	DW	FS (NaF) and FS (AmF+NaF+SnCl$_2$ -1x/day) did not show statistically significant difference vs. CG (NI) FS (AmF+NaF+SnCl$_2$, 2x/day) showed significant difference compared to GC and FS (NaF) (NI), but with no difference compared to FS (AmF+NaF+SnCl$_2$ -1x/day) (NI)
Ganss et al. (2010)a	ERO	Citric acid (pH 2.3) 6x/day (5 min) TT: 210 min	**AmF+NaF+SnCl$_2$** 125 ppm F AmF + 375 ppm F NaF **NaF** 500 ppm F	1x/day (30s) TT: 210 s	P	Both FS showed smaller erosive wear than that of CG ($p \leq 0.001$) FS (AmF+Na+SnCl$_2$) had smaller erosive wear than FS (NaF) ($p \leq 0.001$)
Hove et al. (2008)a	ERO	Hydrochloric acid (NI) 2x/day (2 min) TT: 36 min	**SnF$_2$** 9456.2 ppm F **TiF$_4$** 9203.0 ppm F **NaF** 9501.9 ppm F	1x/day (2min) TT: 6 min	P	FS (SnF$_2$) and (TiF$_4$) showed significant differences compared to CG ($p <0.0001$) No statistically significant differences: FS (NaF) vs. CG ($p=0.56$); FS (TiF4) vs. FS(SnF2) ($p=0.28$)
Hove et al. (2014)a	ERO+ABR	Hydrochloric acid (NI) 2x/day (2 min) TT: 36 min	**SnF$_2$** 1000 ppm F	2x/day (2min) TT: 36 min	P	FS (SnF$_2$) had smaller enamel wear than that of CG (NI)
Levy et al. (2014)a	ERO ERO+ABR	Coke (pH 2.6) 4x/day (90 s) TT: 30 min	**NaF** 24,500 ppm F **TiF$_4$** 24,500 ppm F	Once (1min)	NT	FS (NaF) and (TiF$_4$) significantly reduced the erosive wear vs. CG ($p <0.0001$); no statistically significant differences between the FSs ($p>0.05$) No significant differences between ERO and ERO+ABR ($p> 0.05$)

Lussi et al. (2004)a	ERO+ABR	Citric acid (pH 3.5) Once (3 min)	**AmF+NaF** 100 ppm F AmF + 150 ppm F NaF **AmF** 250 ppm F	Once (30s)	NT	Both FS showed no significant difference in preventing erosion associated with abrasion (p>0.05)
Magalhaes et al. (2008)a	ERO	Coke (pH 2.6) 4x/day (5 min) TT: 100 min	**TiF_4** 24,500 ppm F	Once (1min)	NT	FS (TiF_4) did not significantly reduce the erosive wear vs. CG without fluoride (p>0.05)
Schlueter, Klimek, Ganss (2009)a	ERO	Citric acid (pH 2.3) 6x/day (5 min) TT: 210 min	**NaF** 1000 ppm F **AmF+NaF+$SnCl_2$** 500 ppm F AmF + 500 ppm F NaF	1x/day (30s) TT: 210 s	P	FS (AmF+NaF+$SnCl_2$) was significantly more effective than FS (NaF) (NI)
Schlueter, Klimek, Ganss (2011)a	ERO	Citric acid (pH 2.3) 6x/day (5 min) TT: 210 min	**SnF_2+AmF** 125 ppm F SnF_2 + 125 ppmF AmF **AmF+NaF+SnF_2** 500 ppm F AmF +500 ppm F NaF	1x/day (30s) TT: 210 s	P	Both FS containing tin showed smaller wear than CG (p <0.0001) FS (AmF+NaF+SnF_2) had a significantly smaller wear than FS (SnF_2+AmF) (NI)
Stenhagen et al. (2013)a	ERO+ABR	Hydrochloric acid (pH 2.2) 2x/day (2min) TT: 36 min	**SnF_2** 969.9 ppm F **TiF_4** 920.3 ppm F **NaF** 904.9 ppm F	1x/day (2min) TT: 18 min	NT	FS (SnF_2, TiF_4, and NaF) reduced the erosive and abrasive wear in 94, 90 and 18%, respectively vs. CG (p <0.05)

Legends: TC: type of challenge; EC: erosive challenge; TT: total time; FS/[ ]: fluoride solution/concentration; FSAF: fluoride solution application frequency; CG: control group; Ero: erosion; Ero+Abr: erosion + abrasion; DW: deionized water; NT: not treated; P: placebo; p: significance; NI: non information

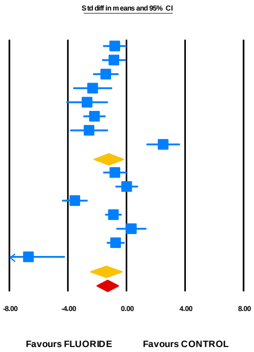
Metanalyses and risk of bias among the included studies

Ten studies were included in the metanalyses [Lussi et al., 2004; Hove et al., 2008; Magalhaes et al., 2008; Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; Stenhagen et al., 2013; Hove et al., 2014; Levy et al., 2014; da Silva et al., 2017]. We highlight the fact that a study with more than one fluoride solution was included twice or more in the metanalyses. Because of the methodologic variability among the studies that resulted in high heterogeneity, we adopted the random effect model (each study has an effect size) for metanalysis. Also, we attempted to decrease the heterogeneity by performing the sensitivity analysis through subgroup analysis (polyvalent vs. monovalent).

Fluoride solutions vs. placebo solutions for erosion prevention

In this first metanalysis of FS-ERO studies, we evaluated 15 solutions from seven studies [Hove et al., 2008; Magalhaes et al., 2008; Ganss et al., 2010; Schlueter et al., 2011; Levy et al., 2014; da Silva et al., 2017]. In both subgroups (PVFS and MVFS) the diamond were at the left of the non-difference line, favoring the fluoride solutions. The fluoride solutions [polyvalent metal (PVFS) and monovalent (MVFS)] promoted a statistically significant smaller enamel wear of the human enamel than that of the control group (GC), respectively $p=0.014$ and $p=0.009$, confidence intervals [-2.270 — -0.256] and [-2.510 — -0,362], and heterogeneity [$Q=5.082$, $I^2=87.737$, and $Tau=1.377$] and [$Q=62.937$, $I^2=90.467$, and $Tau=1.313$] (Fig. 2. and 3.).

Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Polyvalent	Levy FM et al.(2014)a2	Polyvalent	-0.798	0.424	0.180	-1.630	0.033	-1.882	0.060
Polyvalent	da Silva CV et al.(2017)a2	Polyvalent	-0.856	0.427	0.182	-1.692	-0.020	-2.006	0.045
Polyvalent	da Silva CV et al.(2017)a3	Polyvalent	-1.413	0.456	0.208	-2.308	-0.519	-3.097	0.002
Polyvalent	Hove LH et al.(2008)a1	Polyvalent	-2.312	0.690	0.477	-3.665	-0.959	-3.349	0.001
Polyvalent	Hove LH et al.(2008)a2	Polyvalent	-2.693	0.738	0.545	-4.139	-1.246	-3.649	0.000
Polyvalent	Schlueter N, Klimek J, Ganss C.(2009)a2	Polyvalent	-2.188	0.400	0.160	-2.972	-1.404	-5.473	0.000
Polyvalent	Schlueter N, Klimek J, Ganss C.(2011)a1	Polyvalent	-2.555	0.674	0.454	-3.875	-1.234	-3.792	0.000
Polyvalent	Magalhaes AC et al.(2008)a1	Polyvalent	2.510	0.598	0.357	1.338	3.682	4.198	0.000
Polyvalent			-1.263	0.514	0.264	-2.270	-0.256	-2.459	0.014
Monovalent	Levy FM et al.(2014)a1	Monovalent	-0.791	0.424	0.180	-1.621	0.040	-1.865	0.062
Monovalent	da Silva CV et al.(2017)a1	Monovalent	0.016	0.408	0.167	-0.784	0.816	0.040	0.968
Monovalent	Ganss C et al.(2010)a1	Monovalent	-3.526	0.461	0.213	-4.430	-2.622	-7.643	0.000
Monovalent	Ganss C et al.(2010)a2	Monovalent	-0.893	0.303	0.092	-1.486	-0.299	-2.949	0.003
Monovalent	Hove LH et al.(2008)a3	Monovalent	0.331	0.538	0.290	-0.724	1.386	0.615	0.539
Monovalent	Schlueter N, Klimek J, Ganss C.(2009)a1	Monovalent	-0.741	0.327	0.107	-1.382	-0.100	-2.267	0.023
Monovalent	Schlueter N, Klimek J, Ganss C.(2011)a2	Monovalent	-6.695	1.285	1.651	-9.213	-4.177	-5.211	0.000
Monovalent			-1.436	0.548	0.300	-2.510	-0.362	-2.621	0.009
Overall			-1.344	0.375	0.140	-2.079	-0.610	-3.587	0.000



Meta Analysis

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Polyvalent	8	-1.224	0.179	0.032	-1.576	-0.873	-6.823	0.000	57.082	7	0.000	87.737	1.896	1.232	1.517	1.377
Monovalent	7	-0.997	0.157	0.025	-1.304	-0.689	-6.350	0.000	62.937	6	0.000	90.467	1.725	1.226	1.503	1.313
Total within									120.019	13	0.000					
Total between									0.913	1	0.339					
Overall	15	-1.095	0.118	0.014	-1.327	-0.864	-9.271	0.000	120.932	14	0.000	88.423	1.637	0.778	0.605	1.279
Random effects analysis																
Polyvalent	8	-1.263	0.514	0.264	-2.270	-0.256	-2.459	0.014								
Monovalent	7	-1.436	0.548	0.300	-2.510	-0.362	-2.621	0.009								
Total between									0.053	1	0.818					
Overall	15	-1.344	0.375	0.140	-2.079	-0.610	-3.587	0.000								

Fig. 2. Comparison of polyvalent and monovalent fluoride solutions with negative control groups for erosive wear prevention.

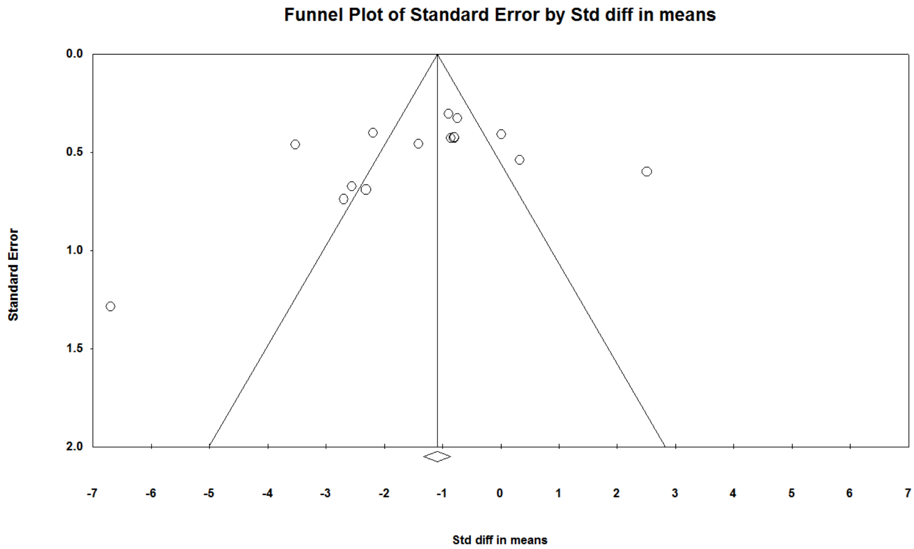
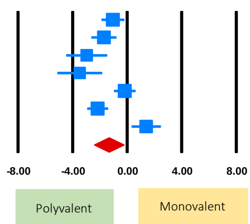


Fig. 3. Funnel plot showing the publication bias of the studies included in the metanalysis comparing PVFS and MVFS vs. CG for erosive wear prevention and control.

Of the studies included in the first metanalysis, five were included in the second metanalysis to directly compare PVFS vs. MVFS, through seven comparisons [Hove et al., 2008; Schlueter et al., 2009; Schlueter et al., 2011; Levy et al., 2014; da Silva et al., 2017]. The metanalysis showed the diamond favoring the polyvalent fluoride solutions, therefore significant lower enamel wear resulted from the use of polyvalent vs. monovalent fluoride solutions [$p=0.013$, confidence interval (-2.437— -0.294), heterogeneity $Q=47.421$ and $I^2=87.347$] (Fig. 4.).

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics for each study				
da Silva CV et al.(2017)a2	-1.047	0.435	0.189	-1.900	-0.194	-2.405	0.016
da Silva CV et al.(2017)a3	-1.702	0.476	0.227	-2.636	-0.768	-3.572	0.000
Hove LH et al.(2008)a1	-2.962	0.774	0.599	-4.479	-1.445	-3.827	0.000
Hove LH et al.(2008)a2	-3.473	0.846	0.716	-5.131	-1.814	-4.103	0.000
Levy FM et al.(2014)a2	-0.175	0.409	0.167	-0.977	0.626	-0.429	0.668
Schlueter N, Klimek J, Ganss C.(2009)a2	-2.163	0.398	0.158	-2.943	-1.383	-5.433	0.000
Schlueter N, Klimek J, Ganss C.(2011)a1	1.398	0.558	0.311	0.305	2.491	2.506	0.012
	-1.365	0.547	0.299	-2.437	-0.294	-2.497	0.013



Meta Analysis

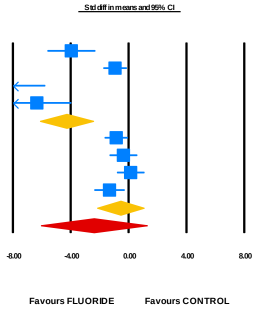
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Fixed	7	-1.169	0.188	0.035	-1.538	-0.800	-6.212	0.000	47.421	6	0.000	87.347	1.772	1.259	1.585	1.331
Random	7	-1.365	0.547	0.299	-2.437	-0.294	-2.497	0.013								

Fig. 4. Comparison of PVFS vs. MVFS for erosive wear prevention.

Fluoride solutions vs Placebo solutions in the prevention of erosion associated with abrasion

In this first metanalysis of FS-ERO+ABR, eight fluoride solutions were tested from four studies [Lussi et al., 2004; Stenhagen et al., 2013; Hove et al., 2014; Levy et al., 2014]. In PVFS, the diamond favors the fluoride solution, while in MVFS the diamond crossed the non-difference line. PVFS resulted in lower wear than CG ($p<0.0001$), while MVFS showed no statistically significant differences vs. CG ($p=0.470$). The respective confidence intervals were [-6.160—-2.487] and [-2.199—1.015] and heterogeneity [$I^2=92.653$] and [$I^2=33.270$] (Fig.5. and 6).

Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Polyvalent	Hove LH et al.(2014)a3	Polyvalent	-3.957	0.860	0.739	-5.642	-2.271	-4.602	0.000
Polyvalent	Levy FM et al.(2014)a2	Polyvalent	-0.931	0.430	0.185	-1.774	-0.089	-2.167	0.030
Polyvalent	Stenhagen KR et al.(2013)a2	Polyvalent	-9.000	1.668	2.781	-12.268	-5.731	-5.397	0.000
Polyvalent	Stenhagen KR et al.(2013)a3	Polyvalent	-6.342	1.228	1.507	-8.748	-3.936	-5.166	0.000
Polyvalent			-4.323	0.937	0.878	-6.160	-2.487	-4.615	0.000
Monovalent	Levy FM et al.(2014)a1	Monovalent	-0.849	0.426	0.182	-1.684	-0.013	-1.991	0.047
Monovalent	Lussi A et al.(2004)a1	Monovalent	-0.357	0.504	0.254	-1.345	0.631	-0.709	0.479
Monovalent	Lussi A et al.(2004)a2	Monovalent	0.148	0.501	0.251	-0.833	1.129	0.296	0.767
Monovalent	Stenhagen KR et al.(2013)a1	Monovalent	-1.318	0.552	0.304	-2.399	-0.237	-2.389	0.017
Monovalent			-0.592	0.820	0.672	-2.199	1.015	-0.722	0.470
Overall			-2.430	1.865	3.480	-6.086	1.226	-1.303	0.193



Meta Analysis

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Polyvalent	4	-2.290	0.358	0.128	-2.992	-1.588	-6.392	0.000	40.834	3	0.000	92.653	10.173	10.648	113.372	3.189
Monovalent	4	-0.587	0.245	0.060	-1.067	-0.108	-2.401	0.016	4.496	3	0.213	33.270	0.121	0.297	0.088	0.348
Total within									45.330	6	0.000					
Total between									15.407	1	0.000					
Overall	8	-1.129	0.202	0.041	-1.524	-0.733	-5.587	0.000	60.737	7	0.000	88.475	2.653	1.841	3.388	1.629
Random effects analysis																
Polyvalent	4	-4.323	0.937	0.878	-6.160	-2.487	-4.615	0.000								
Monovalent	4	-0.592	0.820	0.672	-2.199	1.015	-0.722	0.470								
Total between									8.981	1	0.003					
Overall	8	-2.430	1.865	3.480	-6.086	1.226	-1.303	0.193								

Fig. 5. Comparison between polyvalent and monovalent fluoride solutions vs. negative control groups for the prevention of erosive wear associated with abrasion.

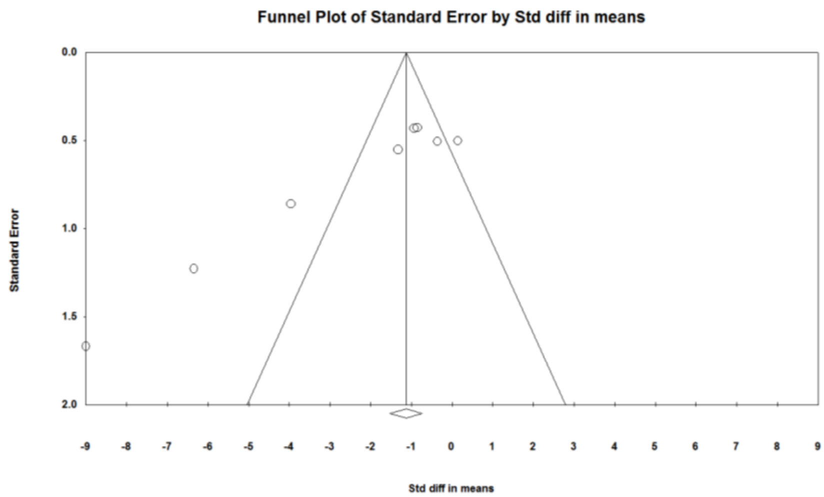
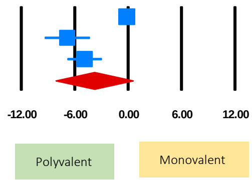


Fig. 6. Funnel plot showing the publication bias of the studies included in the metanalysis comparing PVFS and MVFS vs. CG for the prevention erosive wear associated with abrasion.

Of the four studies from the first metanalysis, two were included in the second metanalysis to compare PVFS vs. MVFS [Stenhagen et al., 2013; Levy et al., 2014]. The diamond crossed the non-difference line, showing no statistically significant differences between solutions for the prevention of erosive wear associated with abrasion [(p=0.083) (confidence interval [-8.175— 0.498]) (heterogeneity Q=38.685 and I²=94.830) (Fig.7.).

Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Levy FM et al.(2014)a2	-0.153	0.409	0.167	-0.955	0.648	-0.375	0.708
Stenhagen KR et al.(2013)a2	-6.835	1.308	1.710	-9.397	-4.272	-5.227	0.000
Stenhagen KR et al.(2013)a3	-4.884	0.998	0.995	-6.839	-2.928	-4.895	0.000
	-3.838	2.213	4.895	-8.175	0.498	-1.735	0.083

Std diff in means and 95% CI



Meta Analysis

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	3	-1.297	0.363	0.132	-2.009	-0.585	-3.569	0.000	38.685	2	0.000	94.830	13.756	15.856	251.428	3.709
Random	3	-3.838	2.213	4.895	-8.175	0.498	-1.735	0.083								

Fig. 7. Comparison between PVFS and MVFS for prevention and control of erosive wear associated with abrasion of the human enamel.

Evaluation of the risk of bias

Of the ten studies included in the qualitative analysis, only two had more than 50% of risk of bias (red+yellow) in the nine domains and classified into high risk of bias [Lussi et al., 2004; Hove et al., 2008]. Three studies were considered at moderate risk of bias because they had 3-4 domains classified as red and-or yellow [Magalhaes et al., 2008; Hove et al., 2014; Levy et al., 2014]. Five studies were classified as low risk of bias (0-2 domains with red and/or yellow) [Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; Stenhagen et al., 2013; da Silva et al., 2017]. The summary of the risk of bias is in Fig. 8.

Selection bias – Random sequence generation: 70% of the included studies had low risk because of randomization through simple draw or compute software; and 30% (uncertain risk of bias) reported randomization but not explained it.

Selection bias – Allocation concealment: 50% of the studies had uncertain risk of bias because they did not mention the allocation method; 10% of the studies did not report an allocation concealment or even an open randomization process (high risk of bias); and 40% had low risk of bias because allocation concealment was performed through sealed envelopes.

Performance bias – blinding of participant and personnel: 30% of the studies were classified as low risk because they reported participant and/or examiner blinding; 50% were classified as uncertain risk because was only reported but not explained; 20% were classified as high risk because of lack of blinding of either participant or examiner.

Detection bias – blinding of outcome assessment: 30% of the studies were classified as low risk, while 40% were classified as uncertain due to insufficient information on blinding and 30% were classified at high risk because of to lack of information on blinding of outcome assessment.

Attrition bias – incomplete outcome data: most of the studies reported reasons for sample loss, 80% were classified as low risk of bias; 20% at uncertain risk; and none study was classified as high risk of bias.

Reporting bias – selective reporting: all studies has adequate protocols and were classified at low risk of bias.

Justified sample size (in situ study domains): most of the studies justified the sample size (90%) and only 10% did not (high risk of bias).

In situ protocol experimental design: 70% had a cross-over design (low risk of bias) and 20% had a parallel design (high risk of bias).

Type of erosive challenge: 90% (low risk of bias) reported a cycling erosive challenge, while 10% reported a single challenge (high risk of bias). Further details can be seen in Fig. 9.

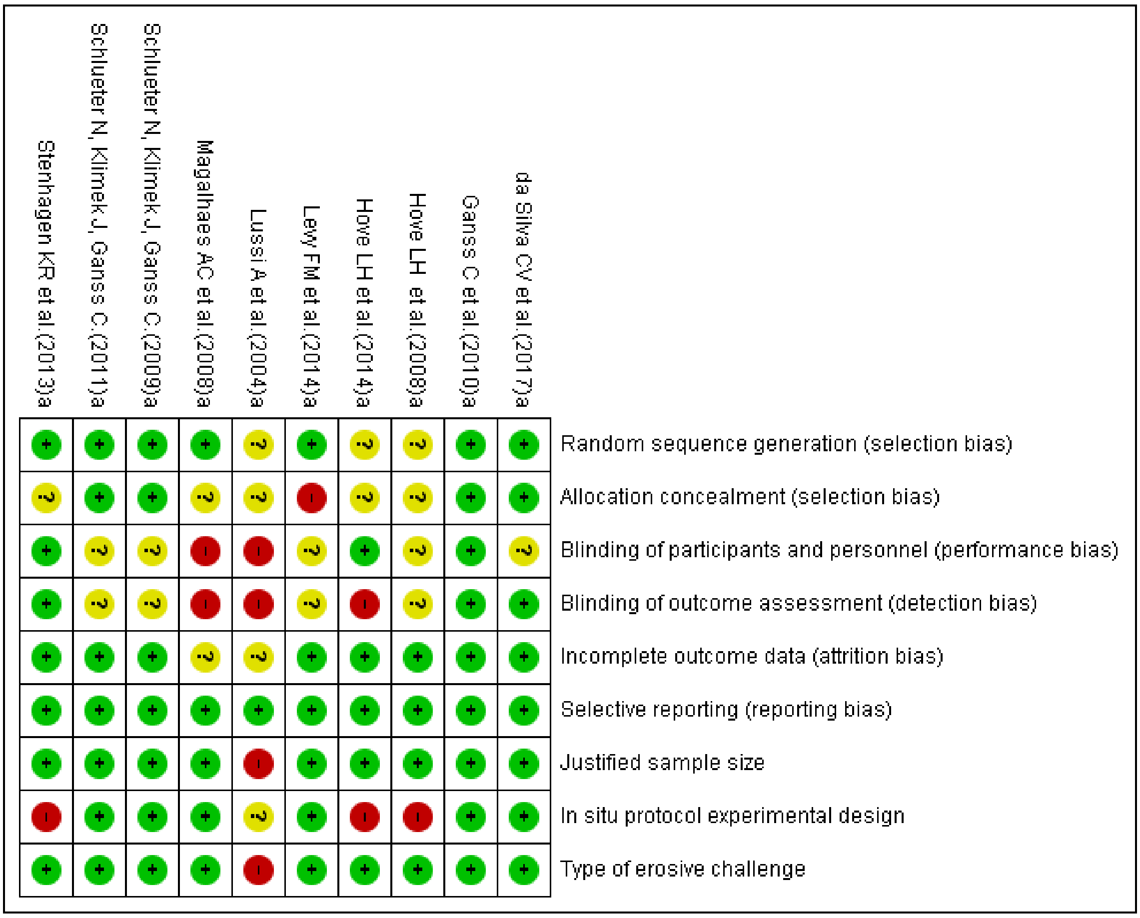


Fig. 8. Summary of risk of bias.

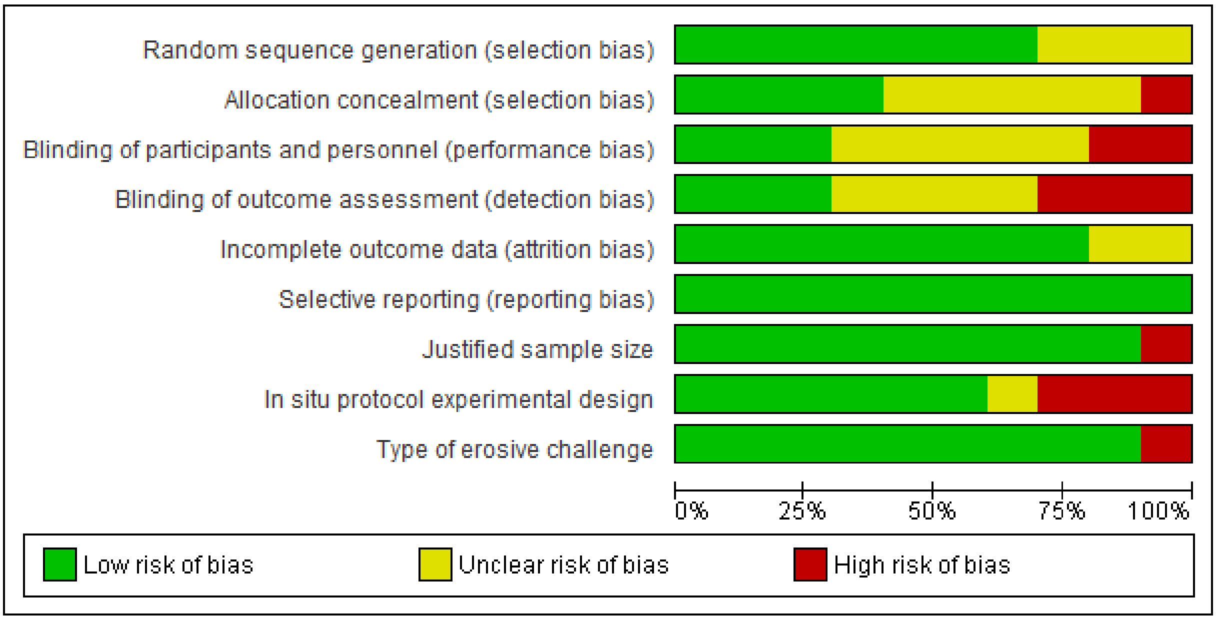


Fig. 9. Graph of risk of bias.

Metanalyses of the studies classified at low risk of bias

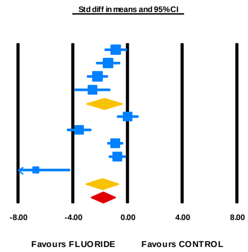
The analysis of the risk of bias does not aim at excluding the studies classified at medium or high risk of bias from either the metanalysis or the systematic review. The risk of bias analysis aims to provide a higher or lower safety to conclude about the results from the qualitative analysis, but mainly from the quantitative analysis (metanalyses).

Notwithstanding, one can repeat the quantitative analyses with only the studies classified as low risk of bias to achieve a stronger evidence. These metanalyses are presented below. First, we compared fluoride solutions (polyvalent and monovalent) vs. placebo solutions for the prevention of erosion associated or not with abrasion. We were unable to perform the comparison between fluoride solutions (polyvalent vs. monovalent) because the studies classified as low risk had employed only polyvalent fluoride solutions.

Fluoride solutions vs. Placebo solutions for erosion prevention

In this comparison (FS-ERO), four studies with low risk of bias were included with nine fluoride solutions [Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; da Silva et al., 2017]. The fluoride solutions were subdivided into polyvalent and monovalent and compared with the negative control group. In both subgroups, the diamonds were left at the non-difference line, favoring the fluoride solutions (FS), therefore fluoride solutions [polyvalent (PVFS) and monovalent (MVFS)] showed a smaller erosive wear of human enamel than control group (CG), respectively $p=0.009$ and $p=0.002$, confidence intervals [-3.029 — -0.425] and [-3.081 — -0,703], and heterogeneity [$Q= 7.351$, $I^2= 59.186$, and $Tau= 0.566$] and [$Q= 55.575$, $I^2= 92.653$, and $Tau= 1.492$] (Fig.10.).

Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Polyvalent	da Silva CVetal.(2017)a2	Polyvalent	-0.856	0.427	0.182	-1.692	-0.020	-2.006	0.045
Polyvalent	da Silva CVetal.(2017)a3	Polyvalent	-1.413	0.456	0.208	-2.308	-0.519	-3.097	0.002
Polyvalent	Schlueter N, Klimek J, Ganss C.(2009)a2	Polyvalent	-2.188	0.400	0.160	-2.972	-1.404	-5.473	0.000
Polyvalent	Schlueter N, Klimek J, Ganss C.(2011)a1	Polyvalent	-2.555	0.674	0.454	-3.875	-1.234	-3.792	0.000
Polyvalent			-1.727	0.664	0.441	-3.029	-0.425	-2.600	0.009
Monovalent	da Silva CVetal.(2017)a1	Monovalent	0.016	0.408	0.167	-0.784	0.816	0.040	0.968
Monovalent	Ganss C etal.(2010)a1	Monovalent	-3.526	0.461	0.213	-4.430	-2.622	-7.643	0.000
Monovalent	Ganss C etal.(2010)a2	Monovalent	-0.893	0.303	0.092	-1.486	-0.299	-2.949	0.003
Monovalent	Schlueter N, Klimek J, Ganss C.(2009)a1	Monovalent	-0.741	0.327	0.107	-1.382	-0.100	-2.267	0.023
Monovalent	Schlueter N, Klimek J, Ganss C.(2011)a2	Monovalent	-6.695	1.285	1.651	-9.213	-4.177	-5.211	0.000
Monovalent			-1.892	0.607	0.368	-3.081	-0.703	-3.119	0.002
Overall			-1.817	0.448	0.201	-2.695	-0.939	-4.056	0.000



Meta Analysis

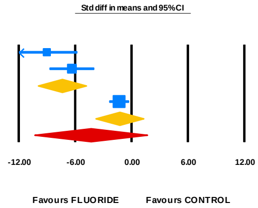
Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Polyvalent	4	-1.642	0.231	0.053	-2.095	-1.190	-7.113	0.000	7.351	3	0.062	59.186	0.321	0.450	0.202	0.566
Monovalent	5	-1.178	0.178	0.032	-1.527	-0.829	-6.620	0.000	55.575	4	0.000	92.803	2.225	1.933	3.737	1.492
Overall	9	-1.351	0.141	0.020	-1.627	-1.075	-9.586	0.000	65.461	8	0.000	87.779	1.332	0.835	0.697	1.154
Random effects analysis																
Polyvalent	4	-1.727	0.664	0.441	-3.029	-0.425	-2.600	0.009								
Monovalent	5	-1.892	0.607	0.368	-3.081	-0.703	-3.119	0.002								
Overall	9	-1.817	0.448	0.201	-2.695	-0.939	-4.056	0.000								

Fig. 10. Comparison of fluoride solutions [PVFS and MVFS] vs CG for prevention and control of erosive wear of human enamel (data extracted from the studies with low risk of bias).

Fluoride solutions vs. Placebo solutions for the prevention of erosion associated with abrasion

In this metanalysis (FS-ERO+ABR), we included one study classified as low risk of bias with three fluoride solutions [Stenhagen et al., 2013]. The diamond of polyvalent subgroup favors the fluoride solution, while the diamond of monovalent subgroup crossed the non-difference line. PVFS resulted in smaller enamel wear when erosion was associated with abrasion than CG ($p < 0.0001$) and MVFS vs. CG showed no statistically significant difference ($p=0.311$). The respective confidence intervals were [-9.993 — -4.869] and [-3.868 — 1,232] and heterogeneity [Q=1.648, I^2=39.306, and Tau=1.178] and [Q=0.000, I^2=0.000, and Tau=0.000] (Fig. 11.).

Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Poly	Stenhagen KR et al.(2013)a2	Poly	-9.000	1.668	2.781	-12.268	-5.731	-5.397	0.000
	Stenhagen KR et al.(2013)a3		-6.342	1.228	1.507	-8.748	-3.936	-5.166	0.000
			-7.431	1.307	1.709	-9.993	-4.869	-5.685	0.000
Mono	Stenhagen KR et al.(2013)a1	Mono	-1.318	0.552	0.304	-2.399	-0.237	-2.389	0.017
			-1.318	1.301	1.693	-3.868	1.232	-1.013	0.311
Overall			-4.373	3.057	9.343	-10.364	1.618	-1.431	0.152



Meta Analysis

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Polyvalent	2	-7.276	0.989	0.977	-9.213	-5.338	-7.360	0.000	1.648	1	0.199	39.306	1.388	4.996	24.957	1.178
Monovalent	1	-1.318	0.552	0.304	-2.399	-0.237	-2.389	0.017	0.000	0	1.000	0.000	0.000	0.000	0.000	0.000
Overall	3	-2.733	0.482	0.232	-3.677	-1.788	-5.673	0.000	29.345	2	0.000	93.184	16.362	19.150	366.713	4.045
Random effects analysis																
Polyvalent	2	-7.431	1.307	1.709	-9.993	-4.869	-5.685	0.000								
Monovalent	1	-1.318	1.301	1.693	-3.868	1.232	-1.013	0.311								
Overall	3	-4.373	3.057	9.343	-10.364	1.618	-1.431	0.152								

Fig. 11. Comparison of fluoride solutions [PVFS and MVFS] vs CG for prevention and control of erosive wear of human enamel associated with abrasion (data extracted from a unique study with low risk of bias).

Discussion

Erosive tooth wear (ETW) is a chemical mechanical phenomenon in which the erosive acid is able to demineralize the tooth surface, and this softened surface is prone to loss by mechanical forces of the oral environment such us abrasion or attrition [Lussi & Carvalho et al., 2014]. Ideally, the preventive products should be applied in association with the intervention on the causal factors for the development of ETW [Lussi & Carvalho et al., 2014]. In addition, its application by the patient has to be easy and not harmful. For these reasons in the present study the solutions were evaluated because patients can use them daily at home and the mode of application is not associated with mechanical impact.

This systematic review shows controversial results regarding the effect of monovalent fluoride solutions (MVFS) against erosion, on one hand some studies showed a preventive effect [Ganss et al., 2010; Levy et al., 2014] and others did not find any difference on enamel wear compared to CG [Hove et al., 2008; da Silva et al., 2017]. The results of the meta-analysis clarified that when considering only erosive challenge, the MVFS were able to protect the enamel compared to the use of water (no protective). However, the oral environment is susceptible to mechanical forces of tongue, soft tissues and tooth brushing [Attin et al., 2001; Rios et al., 2006]. Therefore, in the literature, there are studies that include the abrasive challenge in the *in situ/ex vivo* model when evaluating the preventive effect of solutions, to better simulate the clinical situation. Contradicting results were also observed for erosion associated to abrasion. Levy et al. [2014], showed that product professional of high concentration NaF promoted less enamel loss by erosion plus abrasion. Lussi et al. [2004] did not find difference among AmF solutions and the CG. The results of the meta-analysis point out that monovalent fluoride solutions are not able to protect enamel when the challenge is erosion associated to abrasion.

The majority of the selected studies of this systematic review found that the used polyvalent fluoride solutions (PVFS) promoted enamel protection against enamel erosion [Hove et al., 2008; Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; da Silva et al., 2017], while only one study showed that TiF4 did not significantly reduce the erosive wear compared to eroded control group without fluoride [Magalhaes et al., 2008]. In agreement, the meta-analysis showed that PVFS resulted in smaller human enamel wear than control group. When the *in situ* protocol associated erosion with abrasion, all the selected studies showed that tin or titanium tetrafluoride based solutions were able to result in less enamel wear compared to CG. The meta-analysis confirmed this result and the diamond favored the polyvalent fluoride solution.

To guide the treatment of patients at risk of developing erosive lesions, it is important to clarify the best type of fluoridated solution to be used. Lussi and Carvalho. [2015] concluded that fluoride products presented a preventive effect against erosion mainly in comparison with non-fluoride products, and the association with other protective agents (polyvalent metal ions and polymers) played a more promising preventive role. However, there is no consensus in the literature regarding the differences between monovalent and polyvalent metal fluoride solutions [Huysmans et al., 2014]. The meta-analysis of erosion alone showed that the lower smaller enamel wear of the human enamel resulted from the use of polyvalent metal fluoride solutions (PVFS) when compared to monovalent ones (MVFS). The mechanisms of action of MVFS (NaF and AmF) and PVFS (SnF_2 and TiF_4) may account for the difference in the preventive effect observed [da Silva et al., 2017]. Monovalent fluoride creates a mechanical or physical barrier, through CaF_2 precipitates. The degree of these precipitates is related with the high concentration of F^- ions, acidification of fluoride, and the variation in the individual salivary protection factors that modulate fluoride effectiveness [Lennon et al., 2006; Pai et al., 2007; Schlueter et al., 2009; Ganss et al., 2010]. However, CaF_2 precipitates are also prone to dissolution after severe acid challenges, which provides a limited protection against erosion [Magalhaes et al., 2011; Lussi et al., 2015]. Differently, SnF_2 solutions aids in forming different precipitates on the enamel surface, e.g.: $Ca(SnF_2)$, $SnOHPO_4$, $Sn_3F_3PO_4$, which constitute layers that are resistant to acids. Some studies demonstrated that F^- and Sn^{2+} incorporated into the hydroxyapatite makes iit more resistant [Babcock et al., 1978; Hove et al., 2006; Schlueter et al., 2009; Hove et al., 2014; Lussi et al., 2015]. It is important to bear in mind that the association of tin with AmF and NaF increases the solution stability, maintaining the pH and the fluoride amount in oral medium for longer period [Schlueter et al., 2009; Lussi et al., 2015]. One explanation for the use of AmF in association with other fluoride compounds is its known stabilizing property [Mühlemann et al., 1981; Mühlemann et al., 1985]. The mechanism of TiF_4 is the formation of an acid-resistant layer through the induced the formation of new compounds by the HA dissolution and the precipitation of CaF_2, TiO_2 , and $Ti(HPO_4)_2{\cdot}H_2O$. [Magalhaes et al., 2011; Lussi et al., 2015; Comar et al., 2017]. The tin- and titanium-based precipitates seem to be more resistant than CaF_2 [Huysmans et al., 2014]. Following this rationale, it was expected that the precipitates originated from polyvalent metal fluoride should be more resistant to erosion followed by abrasion than the one formed by monovalent fluoride. Stenhagen et al. [2013] evaluated the preventive effect of both types of fluoride solutions against erosion associated to abrasion. The results showed a reduction of enamel wear of 94% for SnF_2 and 90% for TiF_4, which were significantly different from 18% for NaF. On the other hand, Levy et al. [2014] found similar reduction between TiF_4 and NaF, around 27% and 32% respectively. The meta-analysis of the comparison between PVFS vs. MVFS showed no statistically significant difference, although the evidence regarding the ability of the PVFS to protect enamel against erosion associated to abrasion, that was not observed for MVFS. One explanation for this result is the small number of included studies (only two). Further studies are necessary to evaluate the effectiveness of PVFS vs. MVFS against ERO+ABR challenges.

The different in situ protocols resulted in heterogeneity of the metanalyses, which was already expected due to the lack of standardisation in methodologies. In addition, a qualitative analysis was performed with funnel plots and summary/graph of risk of bias in order to clarify the accuracy of the included studies [Egger et al., 1997], as recommended by Higgins et al., [2011]. Then a new meta-analysis was applied including only studies classified as low risk of bias, thus increasing the quantitative analysis reliability. At this time, only the comparisons of both types of fluoride solutions (PVFS or MVFS) vs. CG, considering erosion/ERO [Schlueter et al., 2009; Ganss et al., 2010; Schlueter et al., 2011; da Silva et al., 2017] and erosion associated to abrasion/ERO+ABR [Stenhagen et al., 2013], was conducted. The results were exactly the same as in the first meta-analyses, where the studies with risk of bias were not excluded. We were unable to compare MVFS vs. PVFS due to lack of studies classified as low risk of bias.

Taking into account the results of the present study, there is a strong evidence that fluoride solutions, mainly polyvalent metal ones, are effective in preventing erosion associated or not with abrasion in comparison with control group. Looking toward the limitations regarding different *in situ* protocols, further studies are necessary with methodological standardization. In addition, studies on the comparison between polyvalent metal and monovalent fluoride solutions are necessary with respect to the protective effect on human enamel against erosion associated or not with abrasion. Finally, randomized clinical trials should be carried out to generate the best scientific evidence possible.

Conclusion

The isolated monovalent fluoride solutions with the single purpose of increasing CaF_2 precipitates provided limited protection against erosion of the human enamel but no protection against erosion associated with abrasion. This study strongly evidenced the higher effectiveness of the polyvalent metal fluoride solutions, compared with monovalent ones, on the prevention and control of erosion associated or not with abrasion of the human enamel.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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2.2 Article 2

Effect of fluoride dentifrices on dental erosion associated or not with abrasion in human enamel: a systematic review and meta-analysis

Bruna Machado da Silva[a], Gerson Aparecido Foratori Junior[a], Ana Carolina Magalhães[b], Marília Afonso Rabelo Buzalaf[b], Daniela Rios[a], Silvia Helena de Carvalho Sales-Peres[a], Heitor Marques Honório[a]

a. *Department of Pediatric Dentistry, Orthodontics and Public Health, Bauru School of Dentistry, University of São Paulo, Brazil*

b. *Department of Biological Sciences, Bauru School of Dentistry, University of São Paulo, Brazil*

⁎ Corresponding author at: Department of Pediatric Dentistry, Orthodontics and Public Health, Bauru School of Dentistry, University of São Paulo, Al. Octávio Pinheiro Brisolla, 9-75, 17012-901, Bauru, São Paulo, Brazil.

E-mail address: heitorhonorio@usp.br (H.M Honório).

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Abstract

Effect of fluoride dentifrices on dental erosion associated or not with abrasion in human enamel: a systematic review and meta-analysis

Dentifrices are the most popular topical agent for fluoride application, so they are one of the possible alternatives for the reduction of erosive tooth wear associated or not with abrasion. However, some *in situ* and *in vitro* scientific studies questioned the use of fluoride. Thus, this systematic review aimed to evaluate the efficacy of monovalent and polyvalent fluoride dentifrices compared to the negative control group (absence of fluoride) on the prevention and control of erosion associated or not with abrasion, in human enamel using *in situ* studies. The secondary objective was to compare the effectiveness between monovalent and polyvalent fluoride dentifrices. The response variable used in this study was enamel wear, which was measured by profilometry. This review was registered in the PROSPERO database (CRD42017071118) and followed PRISMA guidelines. A systematic and comprehensive search was performed using PUBMED, WEB OF SCIENCE, SCOPUS, EMBASE, BBO, LILACS, SCIELO and grey literature IBICT-BDTD. A total of 625 studies were obtained and after exclusion of duplicate articles, only 264 were included in this study. The selection phase was followed systematically (kappa=0.98), conducted by two independent authors and ended with twelve studies for qualitative analysis and ten studies for metanalysis. Metanalysis of all 10 studies of quantitative analysis showed positive results for polyvalent fluoride dentifrices with a significant prevention of erosion and erosion/abrasion compared to control group. Monovalent fluoride dentifrices prevented erosion only and erosion/abrasion. The comparison between polyvalent and monovalent fluoride dentifrices regarding the erosive associated or not with abrasion challenge revealed no difference between groups. In the qualitative analysis (Cochrane scale adapted for *in situ* studies) of risk of bias, four studies were considered at low risk, 9 at risk of moderate bias, and no study at high risk. Both evaluated dentifrices showed preventive effect against enamel erosion associated or not with abrasion with consistent evidence, especially for the polyvalent fluorides.

KEYWORDS: Fluoride, Enamel, Erosion, Prevention, Dentifrices.

Introduction

The knowledge of the interaction between tooth erosion (loss of mineralized substance due to non-bacterial acids) and abrasion (wear due to the interaction between teeth and abrasive agents) is of great clinical importance for preventive measures because these lesions difficultly occur alone [1,2]. Recent studies demonstrated high prevalence [3,4] and incidence [5,6] of the erosive wear associated or not with abrasion. This highlights the importance of the early diagnosis and preventive measures, such as intervention in the nutritional factors and the investigation of the preventive effects of some specific products [7-9]. Such as fluoride.

The fluoride is classified into monovalent or polyvalent. The action of monovalent fluoride is based on the formation of CaF_2 layer, which has low resistance to solubilization and limited protection against acid action [10,11]. Polyvalent fluorides have a different mechanism of action due to formation of a more resistant acid due to the deposition and incorporation of tin fluoride or titanium tetrafluoride on the tooth surface [7]. Dentifrices are specific fluoride-based agents of easy access used at daily basis [9, 12,13]. On one hand, fluoride dentifrices may favor the prevention and control of the tooth erosion because of the fluoride composition [10,14]; on the other hand, the presence of abrasive compounds together with tooth brushing may increase the wear of the tooth structure exposed to erosive agents [10,13].

The randomized clinical trials (RCT) give the best outcomes to answer a clinical problem and can be considered the main and most important “raw material” of a systematic review because RCTs show the strongest scientific evidence on a given subject. However, the research of tooth erosion by RCT is exceedingly difficult due to the slow development of these lesions, which can take years to exhibit a clinically detectable sign. Currently, *in situ* and *ex vivo* studies are the available primary experimental studies on tooth erosion with the highest level of evidence. Even with the absence of randomized clinical trials on this subject [15], the evidences from *in vitro* and *in situ* studies show the role of the fluoride agent within dentifrices in decreasing the erosive wear [10]. However, until now, the literature lacks consensus on this premise [13]. Thus, this systematic review aimed to evaluate the effectiveness of monovalent and polyvalent fluoride dentifrices, compared with control group (without fluoride), on the prevention and control of erosion associated or not with abrasion in human enamel, considering *in situ* studies. The secondary objective was to compare the effectiveness of monovalent and polyvalent fluoride dentifrices on the prevention of erosive tooth wear associated or not with abrasion.

Methodology

Register and Protocol

This systematic review followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with protocol CRD42017071118 (https://www.crd.york.ac.uk/prospero).

Research information and search strategy

In this study, the PICO structure was adapted for *in situ/ex vivo* studies according to the following criteria: P (patient) – human dental enamel, I (intervention) – fluoride dentifrices; C (control) – non-fluoride dentifrices (negative control); O (outcomes) – wear evaluated by profilometry. The descriptors were controlled (MeSH and DeCs) and used in the search strategy according to the following PICO questions: Are fluoride dentifrices capable of decreasing the wear of dental enamel submitted to *in situ* erosive challenge associated or not with abrasion compared with negative control group?

Data search was performed in electronic databases as follows: PubMed, Embase, Scopus, Web of Science, Latin American and Caribbean Database of Health Sciences Literature-LILACS, Brazilian Dental Library-BBO, Scientific Electronic Library Online-Scielo. Also, a grey literature database was searched (Brazilian Digital Library of Thesis and Dissertations - BDTD-Ibict).

The search strategies were structured according to the Boolean operators (AND/OR) and the specificity of each database. A comprehensive search strategy was used to retrieve the greatest number of studies as possible. Based on PICO strategy the used descriptors were *tooth wear*, *tooth erosion*, *tooth abrasion*, *tooth attrition*, *fluoride*, *fluorine*, *fluorine compounds*, *in situ studies*, and *intraoral exposure*. The studies were included until September 15, 2018. The search strategy was designed as follows: ("tooth wear"[All Fields] OR "tooth wears"[All Fields] OR "dental wear"[All Fields] OR "abrasion"[All Fields] OR "attrition"[All Fields] OR "erosion"[All Fields]) AND ("fluorine"[All Fields] OR "fluoride"[All Fields] OR "fluorides"[All Fields] OR "fluorine compound"[All Fields] OR "fluorine compounds"[All Fields]) AND ("in situ"[All Fields] OR "ex vivo"[All Fields] OR "intraoral exposure"[All Fields] OR "intra oral exposure"[All Fields] OR "intraoral exposures"[All Fields]). Then, the strategy was tailored to meet the requirements of each database. Moreover, grey literature and non-published studies were searched either electronically and manually to include further studies meeting the eligibility criteria.

All primary studies were exported to EndNote online (www.myendnoteweb.com). Neither publication dates nor study languages were restricted.

Eligibility criteria

All the primary *in situ* and *ex vivo* studies were included, in which the participants used devices with human enamel specimens; studies containing information on profilometry or tooth wear (dependent variable); studies with test groups or positive controls employing fluoride dentifrices compared with negative controls; studies on tooth erosion associated or not with tooth abrasion. Exclusion criteria comprised other study designs (*in vitro, in vivo,* observational, and literature reviews), repeated studies, studies without negative control, studies addressing other subject rather than tooth erosion (associated or not with tooth abrasion), studies employing bovine enamel, studies that did not analyzed the profilometry, studies evaluating only dentin wear; studies reporting information on wear exclusively by other vehicles (solutions, gels, varnishes).

Study selection and data extraction process

First, the repeated studies were excluded using EndNote online. Then, study data regarding to authors, year, and titles were stored in Excel Office sheet. Two independent reviewers (BMS; GAFJ) selected the study titles and abstracts that met the inclusion criteria. Discordances were solved by a third independent reviewer (HMH). The interexaminer agreement analysis showed a Kappa score of 0.98, suggesting excellent agreement. The reviewers read the full text when the study title or abstract lacked information to make a clear decision on methodology analysis and data extraction. Of the 28 selected studies, 27 were directly obtained on the database or through institutional agreement. Only one study was requested by e-mail [17] with no response. After full-text reading, 16 studies were excluded because they did not meet the inclusion criteria or were not fond and 12 studies were included. Twelve studies comprised the qualitative analysis and 10 studies the metanalysis (Figure 1). In cases of absent data, we did not contact the authors of the primary studies and included in the systematic review only the published data.

It is worth noting that one study can be included one or more times in the quantitative analysis because it include the comparison of different fluoride dentifrices with one control group.

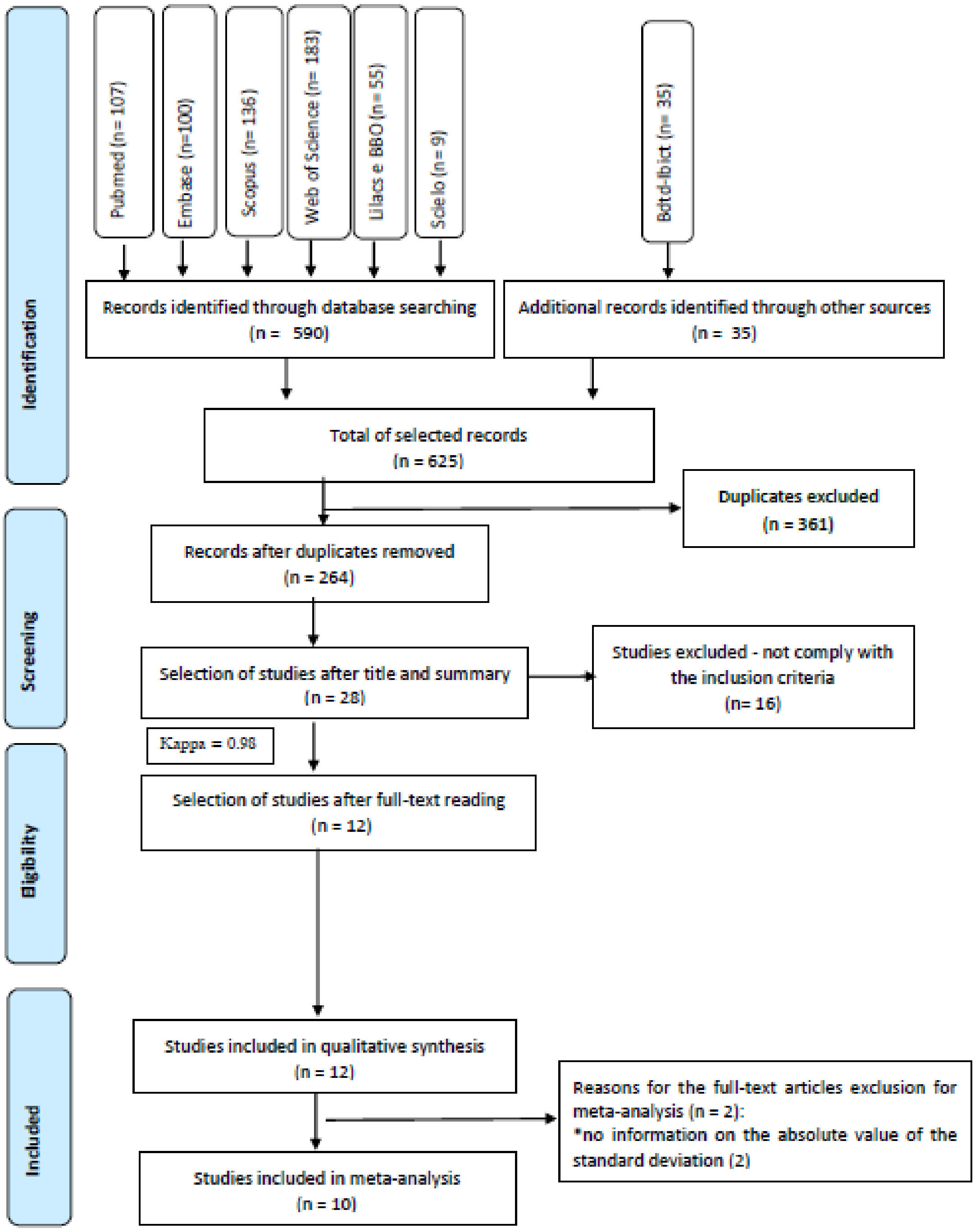


Figure 1. Flow diagram of selected and included studies

The included studies were individually examined and the main characteristics were extracted and stored in a standardized form in Microsoft Office Excel sheet: first author's last name, type challenge (TC), acid type and concentration and frequency of erosive challenge

(EC), total time (TT), fluoride dentifrices and concentrations (FD), number of applications of fluoride dentifrices (FAFD), negative control group (CG), studies excluded in the metanalyses (*), and outcomes.

Individual risk of bias and risk of bias among studies

The qualitative analysis was performed by RevMan5.3 software (Cochranne Collaboration) adapted to *in situ/ex vivo* studies. Each study was evaluated according to: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed (sample loss), selective reporting (pre-stablished objective identified in the outcomes). The judgements were based on the Cochrane Handbook [18] and on the study of Carvalho et al. [19]. We also added three domains based on the methodology of *in situ/ex vivo* studies [15,20,21]: justified sample size, type of erosive challenge, *in situ* study design. These domains were individually classified into: low, uncertain, or high risk of bias according to the criteria presented in Table 1. Each one of the nine domains were classified by a color as follow: low risk-green; uncertain risk-yellow; and high risk-red. Studies classified as red and/or yellow in five or more domains had high risk of bias; those classified as red and/or yellow in 3-4 domains had moderate risk of bias; and studies classified as red and or yellow in 2 domains had low risk of bias. Two reviewers (BMS; GAFJ) independently evaluated the following risk of bias of the included studies: selection bias – sample size, randomization, and allocation concealment; performace bias– blinding of participants and personnel; detection bias – bliding of outcome assessment; attrition bias – incomplete outcome data; reporting bias – selective reporting and confounding bias – erosive challenge and *in situ* study protocol design.

Table 1: Risk of bias classification of the three included domains

Risk of bias – included for in situ and ex vivo		
Selection bias	**Justified sample size**	**Low risk:** justified calculation of sample size
		High risk: neither sample size calculation nor justification of sample size
		Uncertain: unjustified sample size calculation, no information.
Confounding bias	**Erosive challenge type**	**Low risk:** the study showed the erosive challenge type as cycling.
		High risk: the study showed a unique or single erosive challenge type (once).
		Uncertain: no information on the erosive challenge.
	Experimental design of *in situ* study	**Low risk:** study with cross-over experimental design.
		High risk: study with parallel experimental design,
		Uncertain: no information on the experimental design of the *in situ/ ex vivo* study.

Summary of measurements, outcomes, and additional analyses

All possible values of the fluoride dentifrices were obtained and selected, thus resulting in one or more combinations (from a same paper) compared with the control group. The metanalyses were performed with Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA), with level of significance of 5%. To compare the experimental (fluoride dentifrices) with the control groups, the effect size was defined as the difference between the standardized means between groups. The studies were grouped into two segments that generate different statistical analyses: ERO (tooth enamel submitted to erosive wear) and ERO+ABR (tooth enamel submitted to erosive wear associated with abrasion). Then, two metanalyses were applied to each segment: 1st) [polyvalent fluoride dentifrices (PVFD) and monovalent fluoride (MVFD)] *vs.* Control and 2nd) [polyvalent fluoride dentifrices (PVFD) *vs.* monovalent fluoride (MVFD)]. In the comparison ERO+ABR, the metanalysis between polyvalent and monovalent fluoride dentifrices was not possible, resulting in three metanalyses. The heterogeneity of treatment values between the studies was evaluated by the Inconsistency test (I^2) stating that values greater than 75% (interval from 0 to 100) indicated high heterogeneity. The random model was chosen for FD-ERO because the differences between the study methodologies can affect the effect size by generating heterogeneity values greater than 75%, Fixed model was chosen for FD-ERO+ABR due to low heterogeneity. In this systematic review, the high heterogeneity values were predictable due to the high methodologic variability of the *in situ/ex vivo* studies, such as: number of erosive cycling, period of immersion in erosive agent, length of the experimental period, etc. Therefore, the most important outcome of the quantitative analyses was the comparison between the experimental and control groups, regardless of the method used and of the absolute values of the verified effect size [22].

Results

Study search and selection

The bibliographic search was performed in September 15, 2018. First, we found 625 studies and the removal of duplicates resulted in 264 studies. Of these, 28 were pre-selected by titles and abstracts, but 16 did not fulfill the inclusion criteria After the full-text reading, 12 were selected and were qualitatively analyzed [12,23-33]. Of these, 10 studies were included in metanalysis [12,24,26-29,31-33], regardless of time period and language (Figure 1).

Study characteristics

In all studies, the participants signed a free and clarified consent form, were aged higher than 18 years, had satisfactory oral health, normal salivary flow, and lived in areas with fluoridated water. The studies excluded participants with systemic diseases, active caries, periodontal disease, altered salivary flow, using of continuous medication, breastfeeding, allergy to the tested dental materials and products, and using of fixed or removable orthodontic appliance. The sum of the sample size of all included studies was 113 participants. The enamel blocks coming from either extracted non-erupted third molars, which decreased the likelihood of fluoride exposure and tooth wear [12,23,24,26,30-33] or sound pre-molars/molars extracted due to orthodontic reasons [25,27-29]. All extracted teeth were stored in 0.1% thymol solution, cleaned and disinfected, sectioned, sterilized, planned, and polished to obtain the enamel blocks. Then, the enamel blocks were immersed in 70% ethanol and stored at 100% humidity for further insertion in the intraoral devices constructed for each participant. The measurement of the sound reference surface for the profilometer analyses were standardized by protecting the tooth enamel with nail polishing or similar solutions. None of the studies created previous erosive lesions [12,23-33] . The time period of the intraoral devices inside the mouth was determined according to the protocol of each study, ranging from 6-24 hours/day, with resting time of one hour during meals. The types of intraoral appliance were either mandibular [23,25,27,28,32,33] or maxillary [12,24,25,26,29-31]. The erosive challenges were performed by different acids with pH ranging from 2.0-3.8: citric acid [23-26,29,32,33], hydrochloric acid [12,27,28], and Coke [30,31], with frequencies ranging from 2x/day[2min] [27,28], 3x/day[5min] [29], 4x/day[60s, 2min, 5min, or 10min] [12,23,25,26,30,31] and 6x/day[2min or 5min] [24,32,33]. Despite of the differences in the protocols, all included studies had one or more experimental groups containing any fluoride agent and a control group without fluoride solution (negative control).

Intervention and control

Of 12 studies, all FD were compared with negative control group (CG). These studies were composed of 20 FD. The studies of Bellamy et al. [23] and Huysmans et al. [29] were included in the qualitative analysis but not in the metanalysis because lack of information on the absolute vales of the standard deviation of the analyzed FD.

By analyzing all the included studies, we verified 13 comparisons containing different isolated FD agents [NaF (11 times) or SnF_2 (twice)]; in 7 cases, FD had association with other fluoride and non-fluoride compounds [SnF_2+NaF (3 times), SnF_2+AmF (once), F(AmF+NaF)+Sn (once), F(AmF+NaF)+Sn+Ch (twice)]. Also, of these 20 cases, we found 9 polyvalent FD [SnF_2 (twice), SnF_2+NaF (3 times) and SnF_2+AmF (once), F(AmF+NaF)+Sn (once), F(AmF+NaF)+Sn+Ch (twice)] and 11 monovalent FD [NaF (11 times)]. The concentrations used ranged from low and high concentrations from 1000 to 5000 ppm F. The frequency of the fluoride application was reported as once [28], twice [23,25,27,29,32,33], three times/day [24], or four times/day [12,30,31], with duration ranging from 10 seconds to 5 minutes. The negative control groups were composed by water [23,26,29], placebo dentifrice [12,25,27,28,30-33], or no applied treatment [24]. The pH of FD ranged from 4.4 to 7.0. Further details can be seen in Table 2.

Outcomes

Seven studies evaluated erosion alone (ERO) [12,23,24,26,28,29,31], three studies evaluated erosion associated with abrasion (ERO+ABR) [25,27,30] and only two studies evaluated ERO and ERO+ABR separately [32,33]. Six studies demonstrated significant results in preventing and controlling the progression of the erosive wear associated or not with abrasion in the experimental group (FD) compared with GC [12,24-26,30,32]. Six studies did not find favorable outcomes for FD vs. CG [23,27-29,31,33].

Considering FD composed by NaF (1098-5000 ppm F), six studies showed a smaller erosive wear only [12,24,26,30] and ERO+ABR compared with CG[25,32]; four studies did not find significant differences in ERO protection comparing CG and another FD [23,28,29,31]. SnF2-based FD (1000ppm F), without association with other compounds, had higher prevention and control of ERO and ERO+ABR wear vs. CG and another FD [26,27].

The associations between fluoride agents, three studies applied SnF_2+NaF-based FD (1450 ppm F). Of these, two exhibited higher protection against ERO and ERO+ABR wear [23,29]. Only one study did not show protection of the fluoride dentifrice against ERO+ABR challenge [28]. The only study applying the compound FD-SnF_2+AmF (1400 ppm F) had a significant protection of ERO wear vs. CG, but a non-significant difference in comparison with SnF_2+NaF-based FD [29]. The FD composed of F(AmF+NaF)+Sn (1400 ppm F) had a significant protection against only ERO wear vs CG, without statistically significant differences for ERO+ABR wear [33]. The FD composed of F(AmF+NaF)+Sn+Ch (1400 ppm F) demonstrated a significant protection of ERO and ERO+ABR wear in the comparison with CG or another FD [32,33].

Table 2: Data of the studies included in qualitative (Q) and metanalysis (MA) (alphabetic order).

Author	TC	DE	GF / [ ]	FAFG	CG	Outcome(s)
* Bellamy et al. (2004)a [23]	ERO	Citric acid (NI) 4x/day (2 min) TT: 40 min	**NaF** 1,450 ppm F^- (NI)	2x/day (2 min) TT: 20 min	W	FD containing SnF_2 had smaller wear compared to CG and NaF, reducing the wear in 86.9% ($p<0.005$)
			SnF_2 + NaF 1,100 ppm F^- SnF_2 + 350 ppm F^- NaF (NI)			FD containing NaF showed no significant difference in comparison with CG ($p=0.51$)
Ganss et al. (2004)a [24]	ERO	Citric acid (pH 2.3) 6x/day (5 min) TT: 150 min	**SnF_2** 1,400 ppm F^- (NI)	3x/day (5 min) TT: 75 min	NT	The FD prevented lower erosive wear compared with CG ($p<0.0001$)
Hara et al. (2014)a [25]	ERO+ABR	Grapefruit Juice (NI) 4x/day (5 min) TT: 560 min	**NaF** 1,100 ppm F^- (NI)	2x/day (10 s) TT: 560 s	P	NaF presented lower enamel erosive and abrasive wear than CG ($p= 0.0038$)
Hooper et al. (2007)a [26]	ERO	Orange Juice (pH 3.8) 4 x/day (10 min) TT: 200 min	**NaF** (NI) (pH 7.0)	2x/day (1 min) TT: 10 min	W	Both FD significantly protect against erosive wear than CG ($p<0.04$) ($p<0.001$)
		Orange Juice (pH 3.8) 5 x/day (10 min) TT: 250 min	**SnF_2** (NI) (pH 5.8)			FD containing SnF_2 had smaller wear compared to NaF ($p<0.001$)
Hove et al. (2014)a [27]	ERO+ABR	Hydrochloric acid (NI) 2x/day (2 min) TT: 36 min	**SnF_2** 1,000 ppm F^- (NI)	2x/day (2 min) TT: 36 min	P	FD containing SnF_2 showed significant smaller enamel wear compared to CG (NI).
			SnF_2+NaF 1,100 ppm F^- SnF_2 +350 ppm F^- NaF; (NI)			SnF_2+NaF dentifrice showed no protection (NI)
Hove et al. (2015)a [28]	ERO	Hydrochloric acid (NI) 2x/day (2 min) TT: 36 min	**NaF** 1,450 ppm F^- (NI)	1x/day (2 min) TT: 18 min	P	Daily low ($p=0.4$) and high ($p=0.2$) concentrated NaF-based dentifrice application had no protective effect against erosive wear
			NaF 5,000 ppm F^- (NI)	1x/day (5 min) TT: 45 min		

* Huysmans et al. (2011)a [29]	ERO	Citric acid (pH 2.3) 3x/day (5 min) TT: 60 min	**SnF_2+AmF** 1,050 ppm F^- SnF_2 + 350 ppm F^- AmF (pH 4.7) **SnF_2 +NaF** 1,100 ppm F^- SnF_2 + 350 ppm F^- NaF (pH 5.8) **NaF** 1,450 ppm F^- (pH 7.0)	2x/day (2 min) TT: 16 min	W	Both dentifrices containing SnF_2 significantly reduced enamel wear (p <0.01). 34% SnF_2+AmF and 26% SnF_2 +NaF vs CG. NaF dentifrice reduced the erosive wear by 7%, without significant difference compared to CG (p>0.05)
Magalhaes et al. (2008)b [30]	ERO	Coke (pH 2.5) 4x/day (5 min) TT: 140 min	**NaF** 1,098 ppm F^- (pH 6.8)	4x/day (1 min) TT: 28 min	P	NaF dentifrice did not protect enamel against erosion compared to CG (p>0.05)
Magalhaes et al. (2007)a [31]	ERO+ABR	Coke (pH 2.5) 4x/day (5 min) TT: 140 min	**NaF** 1,098 ppm F^- (pH 6.8)	4x/day (1 min) TT= 28 min	P	NaF dentifrice significantly reduced the erosive wear compared to CG (p=0.04)
Passos, Gerage, Santiago (2017)a [12]	ERO	Hydrochloric acid (pH 2.0) 4x/day (1 min) TT: 20 min	**NaF** 1,450 ppm F^- (pH 7.4)	4x/day (1 min) TT: 20 min	P	NaF significantly reduced mineral loss compared to CG (p<0.05)
Schlueter, Klimek, Ganss (2013)a [32]	ERO ERO+ABR	Citric acid (pH 2.6) 6x/day (2 min) TT: 84 min	**NaF** 1,400 ppm F^- (pH 4.7) **F (AmF+NaF)+Sn+Ch** 698.7 ppm F^- AmF + 701.3 ppm F^- NaF (pH 4.4)	2x/day (2 min) TT: 28 min	P	Enamel treated with both FD had less erosive wear compared to CG; however, F/ Sn/ Ch dentifrice was better than NaF dentifrice on both erosive wear ($p \leq 0.01$) and erosive+abrasive wear ($p \leq 0.05$).
Schlueter, Klimek, Ganss (2014)a [33]	ERO ERO+ABR	Citric acid (pH 2.6) 6x/day (2 min) TT: 84 min	**F (AmF+NaF)+Sn** 698.7 ppm F^- AmF + 701.3 ppm F^- NaF (pH 4.4) **F (AmF+NaF)+Sn+Ch** 698.7 ppm F^- AmF + 701.3 ppm F^- NaF (pH 4.4)	2x/day (2 min) TT: 28 min	P	ERO: F+Sn dentifrice reduced the tissue loss by 68% (p≤0.01), F+Sn+Ch dentifrice by 76% (p≤0.01) compared to CG. ERO+ABR: F+Sn dentifrice was less effective and showed no significant difference compared to GC. F+Sn+Ch dentifrice significantly reduced ERO+ABR wear by 46% (p≤0.05)

Legends: TC: type of challenge; EC: erosive challenge; TT: total time; FD: fluoride dentifrice; FS/[ ]: fluoride dentifrice/concentration; FSAF: fluoride dentifrice application frequency; CG: control group; ERO: erosion; ERO+ABR: erosion + abrasion; DW: deionized water; NT: not treated; P: placebo; p: significance; NI: non information; * excluded from the meta-analysis

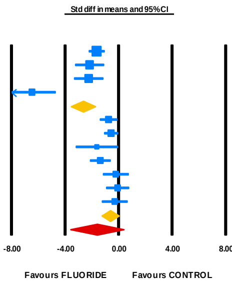
Metanalyses and risk of bias between the included studies

Ten studies were included in the metanalysis [12,24-28,30-33]. The studies were combined in two groups: FD-ERO (fluoride dentifrices against erosive wear) and FD-ERO+ABR (fluoride dentifrices against erosive wear associated with abrasion). F each group, the following metanalysis was applied: fluoride dentifrice (polyvalent and monovalent) *vs.* Control. In the group FD-ERO, a second metanalysis was performed: polyvalent vs. monovalent fluoride dentifrices, resulting in three metanalysis. We highlight the fact that a study with more than one FD may be included twice or more in the metanalyses. The methodologic variability between the studies of FD-ERO group resulted in high heterogeneity, but in FD-ERO-ABR group, the metanalysis resulted in low heterogeneity. As described above, we adopted the random effect model (each study has an effect size) for high heterogeneity (above 75%) and fixed effect model for low heterogeneity (below 75%).

Fluoride dentifrices vs. placebo dentifrices in ERO prevention

In this first metanalysis, we evaluated 11 dentifrices from seven studies [12,24,26,28,31-33]. The fluoride dentifrices (FD) were subdivided according to the chemical nature into polyvalent (PVFD) and monovalent (MVFD) and compared with the respective negative controls. The Diamond of the general analysis crossed the non-difference line between groups. However, the analysis of the diamonds in the two subgroups (polyvalent and monovalent) demonstrated that the Diamonds favors lower erosive wear compared with CG ($p<0.0001$ and 0.047, respectively), confidence intervals [-3.587- -1.769] and [-1.292- -0.009] and heterogeneity [Q=25.134, I^2=88.064, and Tau=2.099], and [Q=7.649, I^2=21.554, and Tau=0.049], respectively (Figure 2).

Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Polyvalent	Schlueter N, Klimek J, Ganss C.(2013)a2	Polyvalent	-1.635	0.314	0.099	-2.251	-1.019	-5.201	0.000
Polyvalent	Schlueter N, Klimek J, Ganss C.(2014)a2	Polyvalent	-2.160	0.563	0.317	-3.262	-1.057	-3.838	0.000
Polyvalent	Schlueter N, Klimek J, Ganss C.(2014)a3	Polyvalent	-2.232	0.570	0.325	-3.349	-1.116	-3.918	0.000
Polyvalent	Hooper S et al.(2007)a2	Polyvalent	-6.464	0.911	0.830	-8.250	-4.679	-7.096	0.000
Polyvalent			-2.678	0.464	0.215	-3.587	-1.769	-5.775	0.000
Monovalent	Passos VF, Gerage LK, Santiago SL.(2017) a1	Monovalent	-0.745	0.345	0.119	-1.420	-0.069	-2.161	0.031
Monovalent	Schlueter N, Klimek J, Ganss C.(2013)a1	Monovalent	-0.556	0.277	0.077	-1.100	-0.013	-2.006	0.045
Monovalent	Ganss C et al.(2004)a1	Monovalent	-1.621	0.815	0.664	-3.219	-0.024	-1.989	0.047
Monovalent	Hooper S et al.(2007)a1	Monovalent	-1.360	0.405	0.164	-2.155	-0.566	-3.357	0.001
Monovalent	Hove LH et al.(2015)a2	Monovalent	-0.206	0.501	0.251	-1.189	0.776	-0.412	0.680
Monovalent	Magalhaes AC et al.(2008)b1	Monovalent	-0.071	0.447	0.200	-0.948	0.805	-0.160	0.873
Monovalent	Hove LH et al.(2015)a3	Monovalent	-0.287	0.503	0.253	-1.272	0.698	-0.571	0.568
Monovalent			-0.651	0.327	0.107	-1.292	-0.009	-1.988	0.047
Overall			-1.638	1.013	1.027	-3.624	0.348	-1.616	0.106



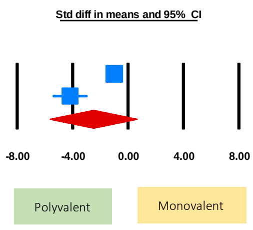
Meta Analysis

Groups	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Polyvalent	4	-2.165	0.239	0.057	-2.633	-1.698	-9.075	0.000	25.134	3	0.000	88.064	2.099	2.149	4.618	1.449
Monovalent	7	-0.633	0.154	0.024	-0.935	-0.330	-4.098	0.000	7.649	6	0.265	21.554	0.049	0.131	0.017	0.220
Overall	11	-1.085	0.130	0.017	-1.339	-0.831	-8.371	0.000	61.862	10	0.000	83.835	1.001	0.602	0.362	1.001
Random effects analysis																
Polyvalent	4	-2.678	0.464	0.215	-3.587	-1.769	-5.775	0.000								
Monovalent	7	-0.651	0.327	0.107	-1.292	-0.009	-1.988	0.047								
Overall	11	-1.638	1.013	1.027	-3.624	0.348	-1.616	0.106								

Figure 2- Comparison of polyvalent and monovalent fluoride dentifrices with negative control groups for erosive wear prevention.

Of the studies included in the previous metanalysis, two participated in the second metanalysis to compare PVFD and MVFD [26,32]. In this metanalysis, the Diamond crossed the non-difference line, showing no statistically significant difference between PVFD and MVFD regarding erosive wear in human enamel [p=0.113, confidence interval (-5.659- 0.598), heterogeneity [Q=20.094 and I²=95.023] (Figure 3).

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Schlueter N, Klimek J, Ganss C.(2013)a2	-0.987	0.288	0.083	-1.552	-0.422	-3.423	0.001
Hooper S et al.(2007)a2	-4.181	0.652	0.425	-5.458	-2.904	-6.416	0.000
	-2.530	1.596	2.548	-5.659	0.598	-1.585	0.113



Meta Analysis

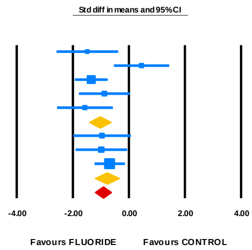
Model	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	2	-1.509	0.264	0.069	-2.026	-0.993	-5.726	0.000	20.094	1	0.000	95.023	4.848	7.215	52.050	2.202
Random	2	-2.530	1.596	2.548	-5.659	0.598	-1.585	0.113								

Figure 3- Comparison between PVFD and MVFD in the prevention of the erosive wear.

Fluoride dentifrices vs. placebo dentifrices in ERO+ABR prevention

Five studies were included in this metanalysis with eight FDs [25,27,30,32,33]. Once again, FDs were divided into PVFD and MVFD and compared with their respective control groups. The general Diamond favors the FD (p <0.0001) with low heterogeneity (fixed effect model). Both PVFD (p <0.0001) and MVFD subgroups (p <0.0001) promoted lower erosive wear compared with the control group. The respective confidence interval were [-1.427- -0.664] and [-1.226- -0.336] and heterogeneity [Q=11.481, I^2=65.160, and Tau=0.382] and [Q=0.403, I^2=0.000, and Tau=0.143] (Figure 4).

Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Polyvalent	Hove LH etal.(2014)a1	Polyvalent	-1.482	0.564	0.319	-2.589	-0.376	-2.626	0.009
Polyvalent	Hove LH etal.(2014)a2	Polyvalent	0.451	0.506	0.256	-0.541	1.444	0.891	0.373
Polyvalent	Schlueter N, Klimek J, Ganss C.(2013)a2	Polyvalent	-1.342	0.301	0.091	-1.932	-0.751	-4.454	0.000
Polyvalent	Schlueter N, Klimek J, Ganss C.(2014)a2	Polyvalent	-0.873	0.468	0.219	-1.790	0.045	-1.865	0.062
Polyvalent	Schlueter N, Klimek J, Ganss C.(2014)a3	Polyvalent	-1.567	0.511	0.261	-2.569	-0.565	-3.065	0.002
Polyvalent			-1.046	0.194	0.038	-1.427	-0.664	-5.377	0.000
Mono	Hara AT etal.(2014)a1	Mono	-0.957	0.528	0.279	-1.992	0.078	-1.813	0.070
Mono	Magalhaes AC.(2007)a1	Mono	-0.982	0.473	0.224	-1.910	-0.054	-2.074	0.038
Mono	Schlueter N, Klimek J, Ganss C.(2013)a1	Mono	-0.686	0.280	0.078	-1.234	-0.137	-2.448	0.014
Mono			-0.796	0.219	0.048	-1.226	-0.366	-3.630	0.000
Overall			-0.936	0.145	0.021	-1.221	-0.651	-6.432	0.000



Meta Analysis

Groups	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Polyvalent	5	-1.046	0.194	0.038	-1.427	-0.664	-5.377	0.000	11.481	4	0.022	65.160	0.382	0.428	0.183	0.618
Monovalent	3	-0.796	0.219	0.048	-1.226	-0.366	-3.630	0.000	0.403	2	0.818	0.000	0.000	0.175	0.031	0.000
Overall	8	-0.936	0.145	0.021	-1.221	-0.651	-6.432	0.000	12.609	7	0.082	44.485	0.143	0.176	0.031	0.378
Random effects analysis																
Polyvalent	5	-0.989	0.284	0.080	-1.544	-0.433	-3.486	0.000								
Monovalent	3	-0.842	0.348	0.121	-1.523	-0.161	-2.422	0.015								
Overall	8	-0.930	0.220	0.048	-1.361	-0.499	-4.232	0.000								

Figure 4- Comparison of polyvalent and monovalent fluoride dentifrices with negative control groups for the prevention of erosive wear associated with abrasion

Of these studies, only one study compared PVFD and MVFD against ERO+ABR challenge. Thus, it was not possible to apply a direct metanalysis of PVFD vs. MVFD.

Evaluation of the risk of bias

Of the twelve studies included in the qualitative analysis, none had five or more domains classified as red and/or yellow (high risk of bias). Eight studies were classified as moderate risk of bias because had 3-4 red and/or yellow domains [23-25,27-31]. Four studies were classified as low risk of bias because had 0-2 red and/or yellow domains [12,26,32,33]. Further details can be seen in Figure 5.

Selection bias – Random sequence generation. 91.65% of the included studies had low risk because of randomization through simple draw or compute software and 8.35% (high risk of bias) did not randomized the sample.

Selection bias – Allocation concealment. 50% of the studies had uncertain risk of bias because they did not mention the allocation method. 16.70% of the studies did not report an allocation concealment or even an open randomization process (high risk of bias); and 33.30% had low risk of bias because allocation concealment was performed through sealed envelopes or computer-centered allocation.

Performance bias – blinding of participant and personnel. 58.30% of the studies were classified as low risk because they report the participant and/or examiner blinding; 25% were classified as uncertain risk because was only reported but not explained; and 16.70% were classified as high risk because of lack of blinding of either participant or examiner.

Detection bias – blinding of outcome assessment. 41.65% were classified as uncertain due to insufficient information on blinding; 50% were classified as low risk and only 8.35% were classified at high risk because of to lack of information on blinding of outcome assessment.

Attrition bias – incomplete outcome data. Most of the studies report reasons for sample loss, then 66.70% were classified as low risk of bias; 33.30% at uncertain risk; and none study was classified as high risk of bias.

Reporting bias – selective reporting. All studies had adequate protocols and were classified at low risk of bias.

Justified sample size (in situ study domains). Most of the studies justified the sample size (75%, low risk) and only 25% did not (high risk of bias).

Confounding bias (in situ experimental design). 83.30% (low risk of bias) had a cross-over design and 16.70% had a parallel design (high risk of bias).

Confounding bias (*erosive challenge type*). All studies had low risk of bias because they reported the erosive cycles (Figure 6).

Risk of bias of the studies not included in the metanalysis

Two studies had moderate risk of bias (Figure 5) [23,29]. Bellamy et al. [23] and Huysmans et al. [29] reported the randomization, but lacked data for allocation concealment. Both studies had at least one blinding domain scored red/yellow due to lack of information on blinding or no blinding. Two studies did not justify the sample size [23, 29]. The other four domains were classified as green with low risk of bias (Figures 5 and 6).

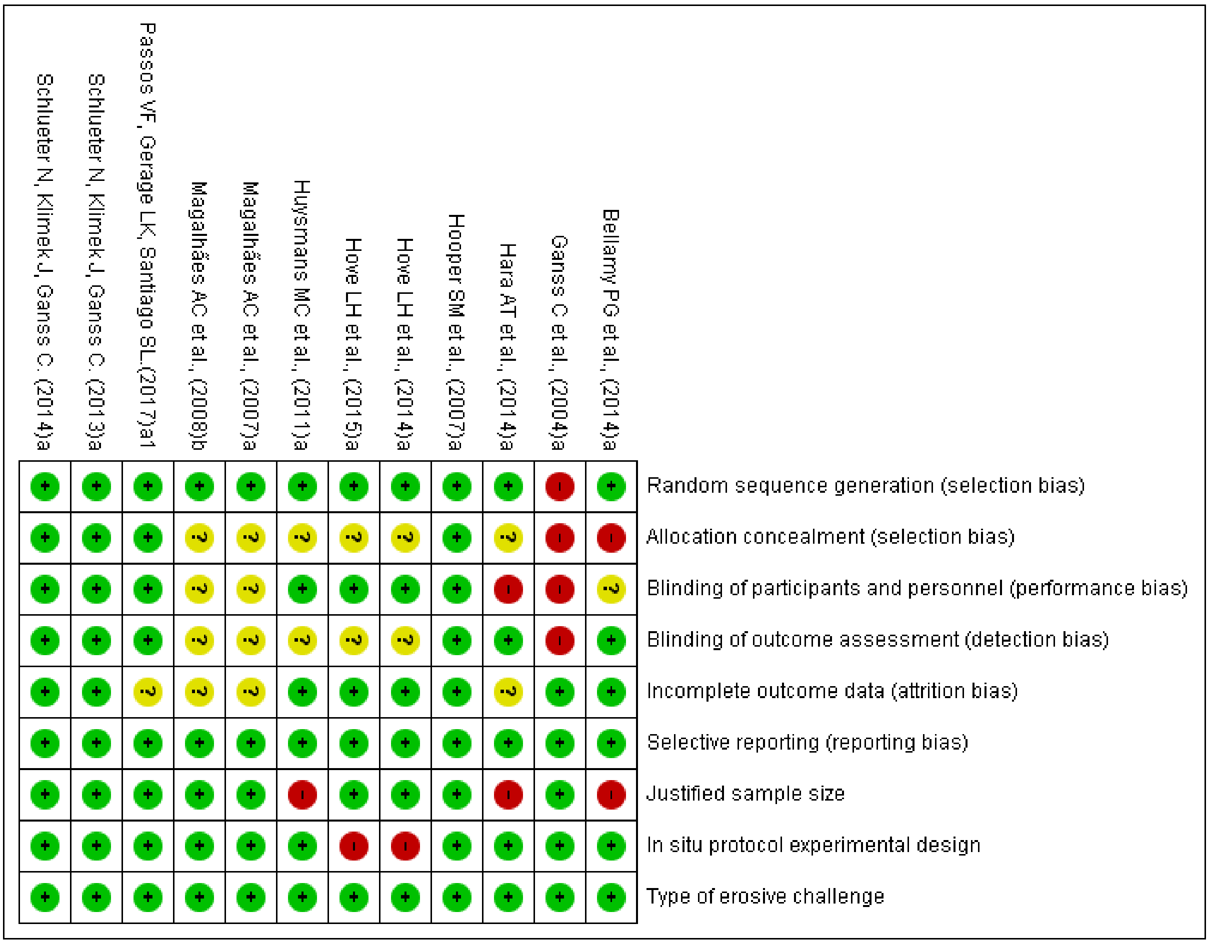


Figure 5. Summary of risk of bias.

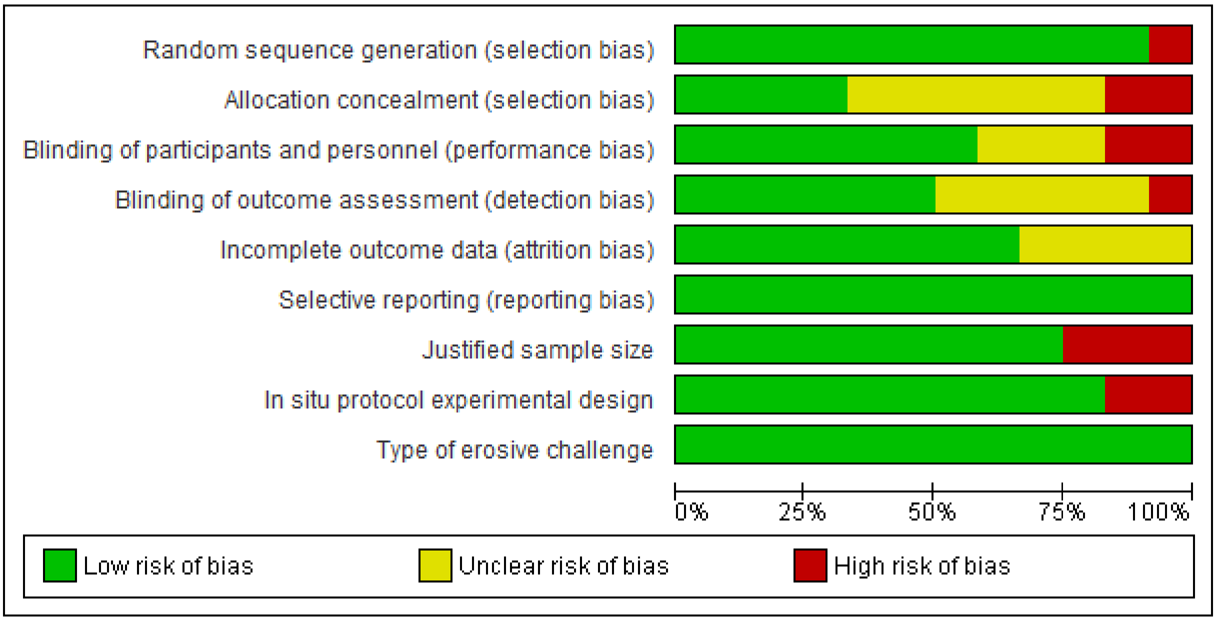


Figure 6. Graph of risk of bias.

Discussion

Many dentifrices have been studied against erosion, and manufacturers of some on-market dentifrices [9] advocate their preventive effect to fluoride [7,10]. However, despite the beneficial effects of fluoride on the protection against erosion, other factors associated with the use of dentifrices may have deleterious action on the eroded surfaces, including the presence of abrasive compounds (size, amount, shape), toothbrush type and toothbrushing model [34]. Therefore, this systematic review aimed to verify the preventive effects of fluoride dentifrices compared with control group on human enamel submitted to the erosive wear associated or not with abrasion. Whenever possible, we also compared PVFD vs MVFD in the *in-situ* studies published in the literature.

The results found in the primary studies demonstrated that MVFD had limited [12,24,26,32] or no protection [23,28,29,31] against the erosive challenge in the comparison of the CG (Table 2). Huysmans et al. [29] demonstrated that the preventive effect of MVFD-NaF reduced the ERO wear by 7%, without statistically significant difference. This disagrees with the present metanalysis (Figure 2), in which FD had a significant prevention of ERO wear compared with CG ($p=0.047$). The studies on MVFD (NaF) [25,30,32] significantly decreased ERO+ABR wear, which was confirmed by this present metanalysis ($p=0.015$) (Figure 4). In the present study, NaF was the only monovalent fluoride dentifrice.

The studies on PVFD (isolated SnF_2) showed higher prevention of ERO and ERO+ABR wear compared with CG [26,27]. Hove et al. [27] also highlighted that SnF_2-based FD promoted lower enamel wear compared with CG, but SnF_2+NaF-based FD showed no protection. Also, some studies [23,24,29,32,33] employed associations between PVFD and MVFD [SnF_2+NaF; SnF_2+AmF; F(AmF+NaF)+Sn; F(AmF+NaF)+Sn+Ch)], so that they were considered as polyvalent PVFD in the present systematic review. For both challenges, the outcomes of these associations varied (Table 2). Despite of the different specific products of PVFD group, the metanalyses demonstrated favorable results in the prevention of ERO ($p<0.0001$, Figure 2) and ERO+ABR wear ($p<0.0001$, Figure 4) compared with CG. Despite of the low number of studies comparing polyvalent vs monovalent FD, we were able to perform the metanalysis in group ERO (Figure 3). This metanalysis showed no difference between PVFD and MVFD in the prevention of the erosive wear ($p=0.113$).

The difference of the preventive effects between MVFD (NaF and AmF) and PVFD (SnF_2 and TiF_4) are not strictly related with the mechanism of action of the active fluoride, but with the acidification of the FD, other active and abrasive compounds, and the interaction of FD with the proteins of the acquired pellicle [10,23,32,35-37]. Moreover, the toothbrushing method and the toothbrush type should be taken into consideration [34,38]. Most of FD contain conventional fluoride [9], which acts by forming a mechanical barrier with CaF_2 precipitates, but with limited protection against severe erosive challenges [7,11]. Thus, the enamel surface is softened and prone to mineral loss by the abrasive forces, such as tooth brushing [39]. NaF-based FD protection is relates with the fluoride concentration, fluoride acidification, and supposedly with the variation in individual biological factors related to salivary protection and formation of pellicle, which modulates the effects of FD [10,32,40,41]. To date, the literature lacks information on dentifrices containing isolated AmF [10].

Polyvalent FDs (composed of SnF_2) aid in the formation of precipitates, e.g.: $Ca(SnF_2)$, $SnOHPO_4$, and $Sn_3F_3PO_4$, which are deposited and form more acid-resistant layers on the enamel surface [7,27,42]. The literature lacks consensus on whether tin-rich salts would be apparently more independent of the individual biological factors [32]. Algarni et al. [37] suggest some Sn interactions with the proteins of the acquired pellicle, resulting in a more resistant layer. No *in situ* study on dentifrice with TiF_4 was found, but one *in vitro* study demonstrated preventive effects similar to that of Sn [43]. The associations between PVFD+MVFD seems to increase the stability in mouth, maintaining pH and a certain amount of fluoride in the mouth for longer times [7,33]. Two studies [32,33] associated monovalent and polyvalent fluorides and chitosan, which is a cationic polysaccharide capable of electrostatically linking to negative surfaces [44]. The interaction of chitosan with those negative surfaces are complex, and the literature states that this molecule forms stable multilayers in acid pH [45], resulting in lower substrate susceptibility to erosive demineralization [46].

The analysis of the quality scale revealed only studies with moderate and low risk of bias and no study with high risk of bias, which corroborates with the evidence strength generated by this systematic review

Considering the association of erosion and abrasion wear because these lesions barely occur alone [1,2], some studies report the benefits of waiting to execute tooth brushing just after the erosive challenge. The rationale of this recommendation is to restore the softened tooth structure with the salivary ions prior to exposure to the mechanical forces of tooth brushing [47,48]. Notwithstanding, it has been pointed out that this waiting period could not be an effective measure [14] because either a shorter or longer waiting time did not result in any significant benefit in preventing the erosive and abrasive wear [49]. Another factor to consider is the long contact time (1-3min) of the FD with the tooth surface [50,51]. Furthermore, FD have active compounds and abrasive components (with many shapes, amounts, and sizes) that supposedly wear the partially eroded tissue [10,34]. Despite of that, *in-situ* studies do not clarify about abrasion. The *in vitro* study of Ganss et al. [34] demonstrated that abrasive particle sizes cannot affect the wear, but the particle amount can. Therefore, the literature states proper oral hygiene with FD (of low abrasion) and soft-bristle toothbrush [52].

The different methodologies of the experimental designs resulted in heterogeneity of the analyzed data and may compromise the final analysis of the results (Figures 2 and 3), which was an expected but limiting fact. Thus, further studies are necessary with standardized methodology and specific protocols for tooth erosion tailored by scientific researchers in this field.

Although dentifrices are accessible products, the literature lacks studies on the comparison between monovalent (monovalent) and polyvalent (polyvalent) fluoride dentifrices after the association of erosion with abrasion, because clinically, these lesions do not occur alone. Also, further studies are necessary to better understand the interference of the biological factors (salivary proteins and acquired pellicle), fluoride acidification, and other abrasive and active compounds of fluoride dentifrices. Last, aiming at generating the best scientific evidence possible, further randomized control trials are necessary to aid in determining which is the most suitable fluoride dentifrice composition and clinical protocol for the prevention and control of tooth wear.

Conclusion

Monovalent fluoride dentifrices provide limited protection, while polyvalent fluoride dentifrices provided significant protection against the erosive wear of human enamel**.** The preventive effect of fluoride dentifrices (PVFD and MVFD) against enamel erosion associated or not with abrasion showed strong evidence in the comparison with the control group.

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3 DISCUSSION

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Due to high prevalence and incidence of ETW, several *in vitro* and *in situ* studies seek to demonstrate the preventive effects of several products, mainly composed of fluoride, since it is difficult to carry out the clinical trials, due to the slow development of non-carious lesions (West et al., 2011). Thus, *in situ* experimental studies currently provide the highest level of scientific evidence about ETW. Fluoride compounds are potentially protective and promising agents (Lussi; Carvalho, 2015). The topical application of dentifrices and solutions are of great interest for dentistry, because they are accessible to the population and have more frequent applications (Huysmans et al., 2014). The objective of this dissertation was to demonstrate the efficacy of FS and FD, monovalent and polyvalent, comparing to the negative control group (absence of fluoride) in the prevention and control of erosion associated or not with abrasion, in human enamel, considering *in situ/ex vivo* studies. The secondary objective was to compare the efficacy between FS and FD with monovalent and polyvalent fluorides.

Both articles demonstrated that monovalent SF and DF not associated with other compounds, used for the sole purpose of increasing CaF_2 deposits, offer limited protection against ERO wear in human enamel, already facing ERO+ABR challenges, the FS had no prevention and the FD presented significant prevention. The FS of article 1 shows strongly the efficacy of polyvalent fluoride solutions in the prevention and control of erosive wear associated with or not abrasion in human enamel, reinforcing its superiority in relation to MVFS in erosive wear. While FD, of the article 2, shows strongly and with low heterogeneity to the efficacy of FD (PVFD and MVFD) in the prevention and control of the erosive associated with the abrasion in human enamel when compared to the CG. All the results highlight the study of Lussi & Carvalho. (2015) that fluoride products exhibit an anti-erosion effect, especially when observed in comparison to non-fluoridated products, and that when associated with other protective agents such as polyvalent metal ions and some polymers, promising in the preventive role. This diversity of results between polyvalent and monovalent fluorides, besides being related to the action mechanism, is also due to acidification of fluoride, and supposedly the interference of biological factors such as salivary protection that modulate efficacy (Bellamy et al., 2014, Huysmans et al., 2014, Lennon et al., 2006; Pai et al., 2007, Schlueter; Klimek; Ganss. 2013, Wiegand et al., 2009). The details are further elucidated in the discussion of articles 1 and 2.

Thus, considering the limitations regarding different methodologies and clinical protocols, further studies are necessary with methodological standardization by means of specific protocols of tooth erosion. Also, further studies should, make a comparison between polyvalent and monovalent products (FS or FD), and consider factors that could affect the results such as other component oof the FS or FD such as detergent, abrasive, other active compounds, because the erosive lesion is not alone. Furthermore, randomized clinical trials should be carried out to generate the best scientific evidence possible and determine which compound are the most suitable for preventing and controlling the tooth wear.

4 CONCLUSION

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This dissertation concluded that there is consistent evidence for the preventive effect of both FS and FD products, especially those containing polyvalent metal fluorides. For the ERO challenges the PVFS, MVFS, MVFD and PVFD products were effective and significant in relation to the CG. For ERO + ABR the products of PVFS, PVFD and MVFD were effective and significant in relation to the CG.

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