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NANO SILVER FLUORIDE AND ENAMEL REMINERALIZATION: CURRENT EVIDENCE AND TRANSLATIONAL GAPS

NANOPRATA DE FLUORETO E REMINERALIZAÇÃO DO ESMALTE: EVIDÊNCIAS ATUAIS E LACUNAS TRANSLACIONAIS

NANOPLATA DE FLUORURO Y REMINERALIZACIÓN DEL ESMALTE: EVIDENCIAS ACTUALES Y BRECHAS TRASLACIONALES

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ABSTRACT

Silver diamine fluoride (SDF) is an effective agent for caries management, but the dark staining it produces limits its use, particularly on visible enamel surfaces. Formulations combining silver nanoparticles and fluoride, commonly termed nano silver fluoride (NSF), have been proposed as an aesthetic alternative. This narrative review aimed to synthesize laboratory, in situ and clinical evidence on the remineralizing effect of silver nanoparticle and fluoride formulations on initial enamel caries lesions. A search of PubMed/MEDLINE retrieved 173 records, and 19 studies met the eligibility criteria: 16 laboratory studies, one in situ study and two randomized clinical trials. In laboratory models, these formulations promoted enamel remineralization and prevented demineralization to an extent generally comparable to sodium fluoride agents, whereas comparisons with SDF were inconsistent, ranging from equivalent to inferior performance. The only in situ study found that an experimental silver nanoparticle and fluoride solution achieved surface and subsurface mineral recovery similar to SDF. In the two clinical trials on white spot lesions, NSF reduced lesion severity but did not outperform

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sodium fluoride varnish or nano hydroxyapatite. All studies assessing color reported minimal or imperceptible staining, in contrast with SDF. Interpretation is limited by marked heterogeneity in formulation composition, substrates, cariogenic challenge models and outcome measures, as well as by small sample sizes and incomplete reporting of nanoparticle characteristics. Silver nanoparticle and fluoride formulations are a promising esthetic option for managing initial enamel lesions, but standardized formulations and adequately powered clinical trials with long term follow up are needed before they can be recommended as a replacement for established remineralizing agents.

Keywords: Dental Caries. Dental Enamel. Fluorides. Metal Nanoparticles. Silver. Tooth Remineralization.

RESUMO

O fluoreto de diamina de prata (SDF) é um agente eficaz para o controle da cárie, mas a descoloração escura que produz limita seu uso, particularmente em superfícies de esmalte visíveis. Formulações que combinam nanopartículas de prata e fluoreto, comumente denominadas fluoreto de nano prata (NSF), foram propostas como uma alternativa estética. Esta revisão narrativa teve como objetivo sintetizar evidências laboratoriais, in situ e clínicas sobre o efeito remineralizador de formulações de nanopartículas de prata e fluoreto em lesões iniciais de cárie de esmalte. Uma busca no PubMed/MEDLINE recuperou 173 registros, e 19 estudos atenderam aos critérios de elegibilidade: 16 estudos laboratoriais, um estudo in situ e dois ensaios clínicos randomizados. Em modelos laboratoriais, essas formulações promoveram remineralização do esmalte e impediram a desmineralização em uma extensão geralmente comparável aos agentes de fluoreto de sódio, enquanto as comparações com SDF foram inconsistentes, variando de desempenho equivalente a inferior. O único estudo in situ descobriu que uma solução experimental de nanopartículas de prata e fluoreto alcançou recuperação mineral de superfície e subsuperfície semelhante ao SDF. Nos dois ensaios clínicos sobre lesões de mancha branca, o NSF reduziu a gravidade da lesão, mas não superou o verniz de fluoreto de sódio ou a nano-hidroxiapatita. Todos os estudos que avaliaram a cor relataram manchamento mínimo ou imperceptível, em contraste com SDF. A interpretação é limitada pela heterogeneidade acentuada na composição da formulação, substratos, modelos de desafio cariogênico e medidas de resultado, bem como por tamanhos de amostra pequenos e relatórios incompletos de características de nanopartículas. As formulações de nanopartículas de prata e fluoreto são uma opção estética promissora para o manejo de lesões iniciais de esmalte, mas formulações padronizadas e ensaios clínicos adequadamente dimensionados com acompanhamento a longo prazo são necessários antes de serem recomendadas como substituto para agentes remineralizadores estabelecidos.

Palavras-chave: Cárie Dentária. Esmalte Dentário. Fluoretos. Nanopartículas de Metal. Prata. Remineralização Dentária.

RESUMEN

El fluoruro de diamina de plata (SDF) es un agente eficaz para el manejo de la caries, pero la decoloración oscura que produce limita su uso, particularmente en las superficies de esmalte visibles. Se han propuesto formulaciones que combinan nanopartículas de plata y fluoruro, comúnmente denominadas fluoruro de nano plata (NSF), como una alternativa estética. Esta revisión narrativa tuvo como objetivo sintetizar evidencia de laboratorio, in situ y clínica sobre el efecto remineralizador de formulaciones de nanopartículas de plata y fluoruro en lesiones iniciales de caries de esmalte. Una búsqueda en PubMed/MEDLINE

recuperó 173 registros, y 19 estudios cumplieron con los criterios de elegibilidad: 16 estudios de laboratorio, un estudio in situ y dos ensayos clínicos aleatorios. En modelos de laboratorio, estas formulaciones promovieron la remineralización del esmalte e impidieron la desmineralización en una medida generalmente comparable a los agentes de fluoruro de sodio, mientras que las comparaciones con SDF fueron inconsistentes, oscilando entre un desempeño equivalente e inferior. El único estudio in situ encontró que una solución experimental de nanopartículas de plata y fluoruro logró la recuperación mineral de superficie y subsuperficial similar al SDF. En los dos ensayos clínicos sobre manchas blancas, el NSF redujo la gravedad de la lesión pero no superó al barniz de fluoruro de sodio o la nano-hidroxiapatita. Todos los estudios que evaluaron el color informaron una tinción mínima o imperceptible, en contraste con SDF. La interpretación se ve limitada por una marcada heterogeneidad en la composición de la formulación, sustratos, modelos de desafío cariogénico y medidas de resultado, así como por tamaños de muestra pequeños e informes incompletos de características de nanopartículas. Las formulaciones de nanopartículas de plata y fluoruro son una opción estética prometedora para el manejo de lesiones iniciales de esmalte, pero se necesitan formulaciones estandarizadas y ensayos clínicos adecuadamente potenciados con seguimiento a largo plazo antes de que puedan recomendarse como sustituto de los agentes remineralizadores establecidos.

Palabras clave: Caries Dental. Esmalte Dental. Fluoruros. Nanopartículas de Metal. Plata. Remineralización Dental.

1 INTRODUCTION

Contemporary caries management has moved away from a purely restorative model toward nonoperative strategies that arrest or reverse the disease at the lesion level, and agents combining antibacterial and remineralizing properties are central to this shift [2]. Untreated caries in primary teeth remains a public health challenge, particularly in disadvantaged communities, where simple topical agents offer an attractive alternative to conventional restorative care [1,10]. Silver diamine fluoride (SDF) has become the reference agent in this field and was included in the World Health Organization Model List of Essential Medicines for both adults and children in 2021 [3]. Its action combines the antibacterial effect of silver with the remineralizing effect of fluoride. In artificial enamel lesions, SDF increased surface fluoride content and reduced lesion depth compared with deionized water, with silver chloride as the main reaction product and metallic silver nanoparticles incorporated into hydroxyapatite crystals [4].

The main limitation of SDF is the dark staining of treated lesions, which compromises esthetics and acceptance [3,5]. Strategies proposed to minimize this effect include masking with restorative materials, applying chemicals such as potassium iodide, and replacing conventional silver with nanosilver [5,6]. Nano silver fluoride (NSF), a formulation combining silver nanoparticles, chitosan and fluoride developed at the University of Pernambuco, Brazil, emerged within this last approach. Early laboratory work showed activity against Streptococcus mutans comparable to SDF, with lower cytotoxicity and a low expected staining potential [7]. Later studies confirmed smaller dentin color change than commercial silver fluoride agents [8] and absence of transdentinal cytotoxicity on odontoblastic cells [9].

Clinically, most evidence on NSF concerns the arrest of dentin caries in children. A single annual application arrested 66.7% of lesions at 12 months, compared with 34.7% in the control group [1], and a recent trial in preschool children found higher arrest rates after one NSF application than after two SDF applications (71.3% versus 56.3% at 12 months) [10]. A meta-analysis reported a risk ratio of 1.09 (95% CI 0.93 to 1.28) for NSF versus active controls and 0.49 (95% CI 0.35 to 0.67) versus placebo [11], and a subsequent systematic review of trials with one year of follow up found no significant difference in caries arrest between NSF and SDF [12].

Evidence on enamel is less mature. A review of silver nanomaterials for caries prevention found that only 11 of 66 included studies assessed effects on tooth mineral content [13]. Laboratory studies on initial enamel lesions have produced heterogeneous findings.

NSF yielded the highest surface microhardness among the tested agents in primary teeth [14], but lower rehardening than SDF and sodium fluoride varnish in permanent teeth [15]. It was comparable to fluoride varnish in preventing demineralization of sound primary enamel [16], and experimental silver nanoparticle and fluoride solutions promoted surface and in depth remineralization comparable to SDF or SDF with potassium iodide, without enamel staining [17,18]. Silver nanoparticles alone also reduced mineral loss in bovine enamel lesions, an effect modulated by lesion severity [19]. In the only randomized trial on white spot lesions in permanent teeth identified, NSF did not differ significantly from sodium fluoride varnish over 12 months [20]. Most of these data derive from pH cycling models, which cannot reproduce salivary flow, acquired pellicle and biofilm dynamics, and therefore offer limited prediction of intraoral performance.

In situ models partially address this gap. A recent blind, randomized, crossover in situ study with 18 volunteers evaluated a silver nanoparticle and fluoride solution (NanoF) on bovine enamel with initial caries lesions. NanoF achieved surface microhardness recovery statistically similar to SDF and sound enamel and significantly higher than untreated lesions, while cross-sectional microhardness did not differ between NanoF and SDF [21]. Given the variety of formulations, models and outcomes in this field, an integrated appraisal is needed. This narrative review therefore aims to synthesize laboratory, in situ and clinical evidence on silver nanoparticle and fluoride formulations for the remineralization of initial enamel caries lesions, using the NanoF in situ study as a reference point, and to identify the gaps that must be addressed before clinical recommendations can be made.

2 METHODOLOGY

This narrative review was prepared according to the Scale for the Assessment of Narrative Review Articles (SANRA) [22]. Although a formal systematic review was not intended, selected items of the PRISMA 2020 statement were adopted to make the search and selection process transparent and reproducible [23].

2.1 FOCUS OF THE REVIEW

The review was guided by the following question: in enamel with initial caries lesions, what is the remineralizing effect of topical formulations combining silver nanoparticles and fluoride, compared with silver diamine fluoride, other fluoride agents or no treatment, across laboratory, in situ and clinical studies?

2.2 INFORMATION SOURCES AND SEARCH STRATEGY

An electronic search was performed in PubMed/MEDLINE from inception to [DATE], complemented by [Scopus, Web of Science and the Virtual Health Library (LILACS and BBO)]. The PubMed strategy combined controlled vocabulary and free text terms for silver nanoparticles, fluoride and enamel remineralization or caries:

("Silver"[MeSH] OR "Metal Nanoparticles"[MeSH] OR "silver nanoparticle*"[tiab] OR AgNP*[tiab] OR nanosilver[tiab] OR "nano silver"[tiab] OR "nano-silver"[tiab] OR NanoF[tiab]) AND ("Fluorides"[MeSH] OR fluorid*[tiab] OR "silver diamine fluoride"[tiab]) AND ("Tooth Remineralization"[MeSH] OR "Dental Enamel"[MeSH] OR "Dental Caries"[MeSH] OR remineral*[tiab] OR enamel[tiab] OR caries[tiab] OR "white spot*"[tiab] OR demineraliz*[tiab])

The strategy was adapted to the syntax of each database (Supplementary Table S1). Reference lists of included studies and of previous reviews on nano silver fluoride were hand searched to identify additional records. No date restrictions were applied, and studies published in English, Portuguese or Spanish were considered.

2.3 ELIGIBILITY CRITERIA

Original studies were included if they evaluated a topical agent containing silver nanoparticles combined with fluoride, applied to human or bovine enamel, primary or permanent, with artificial or natural initial caries lesions, or to sound enamel subsequently exposed to a cariogenic challenge, and reported at least one mineral outcome. Eligible outcomes included surface and cross-sectional microhardness, percentage of surface microhardness recovery, mineral volume, transverse microradiography, micro computed tomography, laser fluorescence and clinical scores of lesion activity or severity. Laboratory, in situ and clinical designs were eligible.

Studies were excluded when silver nanoparticles were incorporated into restorative, adhesive, sealant or orthodontic materials, when only dentin or root caries was assessed, or when only antibacterial, cytotoxic, color change or bond strength outcomes were reported. Case reports, letters, editorials and conference abstracts were also excluded. Studies meeting exclusion criteria for substrate or outcome, as well as previous narrative and systematic reviews, were retained only to contextualize the findings and were not treated as primary evidence.

2.4 STUDY SELECTION

After removal of duplicates, two reviewers independently screened titles and abstracts and then assessed full texts against the eligibility criteria. Disagreements were resolved by discussion and, when necessary, by a third reviewer. [The selection process was managed in Rayyan.]

2.5 DATA EXTRACTION

Data were extracted into a standardized form covering author, year, country, study design, substrate, lesion model, formulation characteristics (nanoparticle size, stabilizing agent, silver and fluoride concentrations), comparators, application protocol, cariogenic challenge (pH cycling regimen or in situ sucrose exposure), outcomes and main findings. Extraction was performed by one reviewer and verified by a second, with all numerical values checked against the tables and text of the original articles.

3 RESULTS

3.1 STUDY SELECTION

The search retrieved 173 records. After screening of titles and abstracts, 151 records were excluded and 22 full texts were assessed for eligibility, of which 19 studies met the inclusion criteria. The most frequent reasons for exclusion were incorporation of silver into restorative, adhesive or orthodontic materials, assessment of dentin or root caries only, and evaluation of antibacterial, cytotoxic, color or bond strength outcomes without a mineral endpoint. Two studies on a nanoencapsulated fluoride dentifrice also designated NanoF were excluded because the formulation contained no silver.

3.2 CHARACTERISTICS OF THE INCLUDED STUDIES

The included evidence comprised 16 laboratory studies [14–19,24–33], one in situ study [21] and two clinical trials [20,34], published between 2017 and 2026. The formulations differed considerably and included chitosan stabilized NSF solutions and varnishes, experimental silver nanoparticle and fluoride solutions [17,21], fluoride varnishes modified with silver nanoparticles, including polyvinylpyrrolidone coated particles [27,32], an NSF dentifrice [24], nanosilver in sodium fluoride solution [30], a nanocomposite combining silver nanoparticles, sodium trimetaphosphate and fluoride [25], and silver nanoparticles and fluoride added to a demineralizing solution [19]. Laboratory studies used human primary

enamel [14,16,18,24,32], human permanent enamel [15,26–30], bovine enamel [19,25] or human enamel of unspecified dentition [17,31,33]. Surface microhardness was the most frequent outcome, followed by cross-sectional microhardness, transverse microradiography, micro computed tomography, laser fluorescence, polarized light microscopy and elemental analysis.

3.3 LABORATORY EVIDENCE ON REMINERALIZATION OF ARTIFICIAL ENAMEL LESIONS

Compared with SDF, findings were inconsistent. An experimental silver nanoparticle and fluoride solution promoted surface and in depth remineralization similar to SDF in human enamel [17], whereas NSF produced lower rehardening than both SDF and sodium fluoride varnish in permanent third molars [15]. A double application of green synthesized NSF yielded the greatest microhardness increase among tested groups, comparable to SDF with potassium iodide ($p = 1.000$) [18]. In another study, surface microhardness recovered to similar levels in all treated groups, but micro computed tomography showed greater remineralization with SDF and NSF combined with L arginine than with NSF alone or sodium fluoride varnish [29]. A fluoride varnish containing polyvinylpyrrolidone coated silver nanoparticles recovered 43.21 ± 1.73% of enamel microhardness, intermediate between SDF (52.43 ± 2.58%) and conventional fluoride varnish (35.60 ± 1.36%) ($p < 0.001$) [32].

Compared with sodium fluoride agents, NSF performed similarly or better in most studies. NSF achieved the highest surface microhardness in primary enamel (222.90 ± 28.79), exceeding sodium fluoride varnish and nano hydroxyapatite [14]. In permanent teeth subjected to 30 days of pH cycling, NSF resulted in lower laser fluorescence readings (4.7 ± 1.6 versus 11.8 ± 5.80), smoother surfaces and a higher Ca/P ratio (2.9 ± 0.35 versus 2.2 ± 0.11, $p = 0.012$) than sodium fluoride varnish [28]. NSF varnish also showed lower laser fluorescence values after remineralization than sodium fluoride varnish [33]. Fluoride varnishes containing 1% and 2% silver nanoparticles increased enamel microhardness to the same extent as the conventional varnish [27], and NSF varnish showed hardness recovery statistically similar to fluoride containing and nanosilver containing bioactive glass varnishes [31]. Subsequent application of casein phosphopeptide amorphous calcium phosphate further increased the microhardness of enamel previously treated with nanosilver in sodium fluoride solution [30].

3.4 LABORATORY EVIDENCE ON PREVENTION OF DEMINERALIZATION

When applied to sound primary enamel before a 7 day pH cycling challenge, NSF was comparable to sodium fluoride varnish regarding microhardness and lesion depth [16]. An NSF dentifrice prevented enamel demineralization to the same extent as a conventional sodium fluoride dentifrice over 14 days of pH cycling [24]. In bovine enamel, adding silver nanoparticles to a fluoride and trimetaphosphate nanocomposite did not impair its protective effect on subsurface hardness loss, which was similar to that of a 225 ppm fluoride solution [25]. When silver nanoparticles and fluoride were added to a demineralizing solution, silver nanoparticles significantly reduced integrated mineral loss ($p = 0.041$) but not lesion depth ($p = 0.15$), and no interaction between fluoride and silver was observed [19]. Around orthodontic brackets, NSF varnish limited demineralization to few areas, with the most homogeneous enamel surface obtained when combined with diode laser irradiation [26].

3.5 IN SITU EVIDENCE

The only in situ study was a blind, randomized, crossover trial in which 18 volunteers wore palatal devices with bovine enamel blocks during two 10 day phases separated by a 10 day washout [21]. Initial lesions were formed in situ with a 20% sucrose solution applied eight times daily for eight days before treatment. NanoF achieved a percentage of surface microhardness recovery statistically similar to SDF and sound enamel and significantly higher than untreated lesions ($p = 0.028$). Cross-sectional microhardness, from which mineral volume was calculated at depths of 20 to 200 μm, did not differ between NanoF and SDF, whereas sound enamel presented the highest and untreated lesions the lowest values ($p < 0.001$) [21].

3.6 CLINICAL EVIDENCE

In a randomized trial including 66 patients and 147 permanent teeth with white spot lesions (ICDAS codes 1 or 2), NSF varnish reduced ICDAS scores, lesion activity and laser fluorescence readings over 12 months, but the reduction in ICDAS scores did not differ significantly from sodium fluoride varnish (adjusted OR 2.12, 95% CI 0.59 to 7.64) [20]. In 45 children aged 4 to 8 years with white spot lesions, the mean lesion dimension decreased from 4.9 ± 0.66 to 1.22 ± 0.46 after 24 weeks with NSF, but the greatest reduction was observed with nano hydroxyapatite serum (from 4.27 ± 0.69 to 0.93 ± 0.41), and NSF outperformed only casein phosphopeptide amorphous calcium phosphate varnish [34].

3.7 COLOR CHANGE

All four included studies that assessed color reported an esthetic advantage over SDF. Silver nanoparticle and fluoride formulations did not stain enamel [17,18], and discoloration with NSF did not differ from other non silver groups, whereas SDF produced the greatest color change [29]. The modified fluoride varnish caused clinically imperceptible color change ($\Delta E < 3.3$), while SDF caused distinct staining ($p < 0.001$) [32].

4 DISCUSSION

This review indicates that topical formulations combining silver nanoparticles and fluoride have a consistent remineralizing effect on initial enamel lesions under laboratory conditions, broadly comparable to conventional fluoride varnishes, while their performance relative to SDF varies across studies. The single in situ study adds weight to these findings by showing that, under intraoral conditions with salivary flow and pellicle formation, the experimental NanoF solution promoted surface and subsurface mineral recovery equivalent to SDF. Clinical evidence on enamel, however, remains scarce and does not show superiority over sodium fluoride varnish.

A central question is what silver nanoparticles add to the remineralizing effect itself. The available data suggest that fluoride remains the main driver of mineral gain, while silver nanoparticles contribute mostly through antibacterial activity. Studies that isolated the silver component found that its addition did not impair, but also did not clearly enhance, the effect of fluoride on hardness and lesion depth. This interpretation is consistent with laboratory models without biofilm, in which the antibacterial benefit of silver cannot manifest. It follows that the main expected advantage of these agents over fluoride alone lies in conditions where cariogenic biofilm is active, which pH cycling models do not reproduce, and which only in situ models with biofilm accumulation or clinical trials can capture.

The comparison with SDF must be interpreted in light of concentration. SDF delivers very high silver and fluoride concentrations, whereas most nanosilver formulations contain substantially lower amounts. Equivalence in some studies and inferiority in others may reflect differences in fluoride content, number of applications and lesion model rather than intrinsic properties of the nanoparticles. The observation that repeated application of NSF approached the effect of SDF supports the need to define optimal application protocols rather than treating these agents as single application products by default.

The esthetic profile is the most consistent advantage. Every study that measured color found minimal or imperceptible change with nanosilver formulations, in contrast with the staining produced by SDF. For enamel lesions on visible surfaces, where SDF is often unacceptable to patients, this advantage is clinically meaningful and represents the strongest rationale for further development of these agents.

Several sources of heterogeneity limit the conclusions. The term NSF has been applied to products with different nanoparticle sizes, stabilizing agents, silver and fluoride concentrations and vehicles, ranging from solutions to varnishes and dentifrices, and the label NanoF has even been used for a silver free nanoencapsulated fluoride. Many studies did not fully report nanoparticle characterization or ion concentrations, which prevents comparison across products. Substrates varied between primary, permanent and bovine enamel, cariogenic challenges differed in duration and composition, and outcomes ranged from microhardness to laser fluorescence, which is an indirect and less validated measure of mineral content. Sample sizes were generally small, and few studies reported sample size calculation or blinding of examiners.

Clinical translation requires attention to safety and stability. Data on cytotoxicity of nanosilver formulations are encouraging, but long term exposure, particle accumulation and systemic absorption in young children remain insufficiently studied. Shelf life stability of colloidal formulations also needs confirmation under real storage conditions.

Future research should prioritize standardized reporting of formulation characteristics, in situ studies incorporating biofilm, and adequately powered randomized trials on enamel lesions comparing nanosilver formulations with both fluoride varnish and SDF, with follow up of at least 12 months and validated outcomes such as lesion activity and quantitative light induced fluorescence. Studies on cost, patient acceptance and application frequency would further inform their potential role in public health programs.

This review has limitations inherent to its narrative design, including the absence of quantitative synthesis and formal risk of bias assessment, and the restriction of the search to PubMed and to studies published in English, Portuguese or Spanish.

5 CONCLUSION

Formulations combining silver nanoparticles and fluoride show remineralizing potential on initial enamel caries lesions comparable to conventional fluoride agents in laboratory studies and comparable to SDF in the only in situ study available, without the staining

associated with SDF. However, the evidence is dominated by heterogeneous laboratory models, and clinical data on enamel are limited and do not demonstrate superiority over fluoride varnish. Until standardized formulations are tested in well designed clinical trials, these agents should be regarded as a promising esthetic alternative under investigation rather than a replacement for established remineralizing therapies.

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