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Original Article

Remineralization Potential of Curodont Repair Flouride Plus Versus CPP-ACP in White Spot Lesions

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Abstract

Objectives: To compare the remineralization potential of Curodont Repair Fluoride Plus Versus CPP -ACP in management of white spot lesions. Methodology: 48 white spot lesions in patients received randomly two types of remineralizing agents, either Curodont Repair Flouride Plus (self-assembling peptide p11-4) or MI paste daily use, both materials were applied according to the manufacturer's instructions. White spot lesions were evaluated before and after 1, 4, and 6 months follow up periods by assessors to assess remineralization potential using ICDAS II Criteria and digital photographs using analysis software to get the percentage of white spot lesions. Results: According to ICDAS II , intergroup comparison between both materials have shown no statistically significant difference, Intragroup comparisons within Curodont Repair Fluoride Plus have shown statistically significant difference between different follow-up periods ($P < 0.0001$). Curodont Repair Fluoride Plus had 25% less risk for (ICDAS 1and 2) than CPP-ACP after 6 months (RR= 0.75, 95% CI, P=0.2498). According to the photographic analysis, Two-way ANOVA revealed statistically significant effect of material and follow-up on WSL % ($P<0.001$). Conclusions: Curodont Repair Flouride Plus is a biomimetic remineralizing agent that provides a therapeutic option for enamel regeneration. Curodont repair fluoride plus provided a better chance for complete healing of incipient lesions.

Keywords: Remineralizing agent, Curodont Repair Plus Flouride, CPP-ACP, White spot lesions, Digital photographs

I. INTRODUCTION

The Modern dentistry aims to prevent disease development while also improving aesthetics, strength, and function by non-invasively re-mineralizing non-cavitated caries lesions(1). The Calcium Phosphates, also known as Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] crystallites, are the primary component of enamel(2).

The process of providing calcium, phosphate, and fluoride ions from the oral environment to the tooth in order to convert ion deposition into crystals in demineralized enamel is known as re-mineralization. A multifactorial strategy could be used to treat white spot lesions. Preventing demineralization and biofilm formation, as well as using remineralization approaches, are the most significant strategies.

Fluoride has a significant impact on caries prevalence, but it is far from a complete cure since its macromolecule structures prevent it from penetrating deeper into the enamel; hence, its stabilizing role is restricted to the

surface enamel[3]. Despite the fact that Casein Phosphopeptide Amorphous Calcium Phosphate (CPP–ACP) is a milk product, it cannot be given to patients who have milk intolerance. As a result, these patients seek an appropriate alternative[4].

A promising alternative therapy to arrest caries lesions progression was introduced with the aim of filling the intercrystalline spaces for enamel subsurface lesions through a self-assembling peptide that builds a supra-molecular three-dimensional, fibrous network in the acidic environment attracts calcium phosphate from saliva and produced de novo hydroxyapatite crystals surrounding the matrix with containing fluoride which have synergistic effect and enhance faster remineralisation after comparing to convential curodont in management of WSLs, therefore it was found beneficial to assess remineralization potential of Curodont Repair Fluoride Plus versus CPP – ACP in management of white spot lesions using RCT.

II. MATERIALS AND METHODS

A. Study setting

The study design followed the requirements outlined in the CONSORT 2010 statement and trial was approved from Evidence-Based Dentistry Committee of the Conservative Dentistry Department - Faculty of Dentistry, Cairo University. All procedures performed in this study, involving human participants were in accordance with the ethical standards of the Research Ethics Committee of Faculty of Dentistry, Cairo University (CREC19114), it was registered in (www.clinicaltrials.gov) database, with unique identification number NCT04245787. The trial design is a randomized, two parallel arms, double blind, clinical trial held in the outpatient clinic of the Conservative Dentistry Department Faculty of Dentistry, Cairo University. This study was conducted for 6 months and the participants were randomly assigned into two equal groups.

B. Sample size calculation

A power analysis was designed to have adequate power to apply statistical test of the research hypothesis to evaluate Curodont repair fluoride plus compared to CPP-ACP in management of white spot lesions after 6 months using visual inspection by ICDAS II scoring system. According to the results of Karabekiroglu et al. in 2018 in which the probability of score 0 for visual evaluation using ICDAS II for CPP-ACP was (0.098), probability of score 1 was (0.274), probability of score 2 was (0.588), probability of score 3 was (0.039) with effect size w=0.855 (n=15). If the estimated probability of score 0 for visual evaluation for Curodont repair fluoride plus is (0.15), probability of score 1 was (0.3), probability of score 2 was (0.5), probability of score 3 was (0.05) with effect size w=0.678 (n=24). By adopting an alpha (α) level of 0.05 (5%), power=80%. The predicted sample size was a total of (39). Sample size was increased by (20%) to account for possible dropouts during follow-up intervals to be total of (48) cases i.e. (24) for each group. Sample size calculation was performed using G*Power 3.1.9.2. (Karabekiroglu, 2018)

C. Eligibility Criteria

The inclusion criteria of participants were the ages of participants between18 and 35 years of age, active carious white spot lesions (ICDAS 1, 2), had received conventional manual periodontal therapy, had no systemic diseases or concomitant medication affecting salivary flow. While the exclusion criteria of the participants were: Participant in another trial, non-carious lesion (enamel hypoplasia and dental fluorosis), Presence of abnormal oral, medical, or mental condition. Participants who had evidence of reduced salivary flow or significant tooth wear, also who had allergy to MI paste.

D. Randomization, Sequence generation and blinding

48 lesions in a total of 28 patients were divided into two groups. Randomization was done according to a checklist including the number of participants divided into 2 groups according to interventions/Control assessment methods. The allocation system was set up by enrolling participants. The allocation sequence was generated using (www.randomization.com). The statistician and assessors were both blind to the intervention/control evaluation procedures Participants were recruited to fulfill the eligibility criteria according to their timeline; and signed an informed consent.

Baseline data was collected and filled through a report which is composed of two charts medical, dental history for every participant, each participant received one of the re-mineralizing agents according to the randomization done.

E. Evaluation for white spot lesions

The teeth with white spot lesions were polished with a prophylaxis paste fluoride free (Quartz polishing paste , Dharma research, Inc., Miami, USA) and a polishing brush (prophy brush , Oreland , China) ,rinsed then soft tissue retraction was done using check retractor then visual assessment by naked eye and by using eye loupes (3.5x custom made eye loup, Eergo vision, China) was performed, Each white spot lesion was assessed and scored according to severity and activity using the ICDAS II criteria .Surfaces were examined each time when being wet and after air drying. Examiners evaluated the teeth under wet conditions, then under dry conditions, by drying the teeth for 5 seconds using air-water triple syringe.

Professional photographs were taken by using polarized filters (Canon EOS R full frame, canon lens 100 macro-L twin flash with polarized filters, Tokyo, Japan). The diagnosis by ICDAS-II was done by visual examination before by photographs method to avoid bias by knowing the results from the second method.

F. Material application

Intervention application

The manufacturer's recommendations were followed while applying Curodont repair fluoride plus. For 20 seconds, teeth were swapped with 2% NaOCl., then rinsed 20 seconds and gently air-dried. Teeth were etched with 35% Phosphoric acid for 20 seconds, to expose the pores to the subsurface lesion and subsequently rinsed with water for 20 seconds and under moisture control. Curodont repair fluoride plus applicator was applied directly on the white spot lesion on tooth surface Figure (1). Solution was allowed for five minutes to diffuse and until the tooth surface appears dry. The participant was instructed not to rinse his or her mouth, eat, or drink for at least 30 minutes after using the treatment.

Comparator application

MI paste was applied according to the manufacturer’s instructions. This group has been instructed to brush their teeth with standard fluoride toothpaste (like Clouse up Total, 1000 ppm F) twice a day before CPP-ACP applications[(5)].

G. Outcome Assessment

A chart and professional photographs were made for each patient for follow up and scoring of the white spot lesions at different time periods. Patients were recalled again after 1, 4 and 6 months of re-mineralizing agents’ application.

The clinical photographs processed using photographic editing software (Adobe Photoshop 7.0, Adobe Systems Inc., San Jose, California, USA), then the stained area was calculated as % of the total teeth area by the following equation using ImageJ software, version 1.53a (National Institutes of Health, USA).

$$WSL\ \% = \frac{Sum.of\ \ White\ area\ (\ pixels)}{Total\ tooth\ area\ (pixels)} x100$$

H. Statistical analysis

Data was analyzed using Medcalc software, version 19 for windows (MedCalc Software Ltd, Ostend, Belgium). Data was explored for normality using Kolmogrov Smirnov test and Shapiro Wilk test. Continuous data showed normal distribution and were described using mean and standard deviation. Intergroup comparison between continuous data was performed using independent t test, while intragroup comparison was performed using repeated measures ANOVA and two-way ANOVA was used to test interaction of variables followed by turkey post-hoc test A value less than or equal to 0.05 was considered statistically significant and all tests were two tailed.

III. RESULTS

A. Remineralization potential by using (ICDAS II Criteria)

Intergroup comparison between both materials have shown no statistically significant difference within different follow up periods; baseline, 1, 4 and 6 months respectively (P = 0.5445, P = 1.0000, P = 0.1666, and P = 0.4987). Intragroup comparison within Curodont Repair Fluoride Plus has shown statistically significant difference between different follow-up periods (P < 0.0001). Intragroup comparison within CPP-ACP have shown statistically significant difference between different follow-up periods (P = 0.0002).Curodont Repair Fluoride Plus had 25% less risk for (ICDAS 1and 2) than CPP-ACP after 6 months (RR= 0.75 (95% CI 0.4595 to 1.2242; P=0.2498). Table (1) and Figure (2). Comparisons between the 2 groups with respect to non-normally distributed numeric variables were compared by Mann-Whitney test. All p-values are two-sided. P-values ≤0.05 were considered significant.

B. Remineralization potential (The percentage of white spot lesions)

Effect of interaction of material and follow-up on WSL %

Two-way ANOVA revealed statistically significant effect of material and follow-up on WSL % (P<0.001), but interaction of material and follow-up had no statistically significant effect on WSL % (P=0.242). Table (2)

Figure (1): White spot lesion was treated by gently pressing the tip directly on to the tooth surface

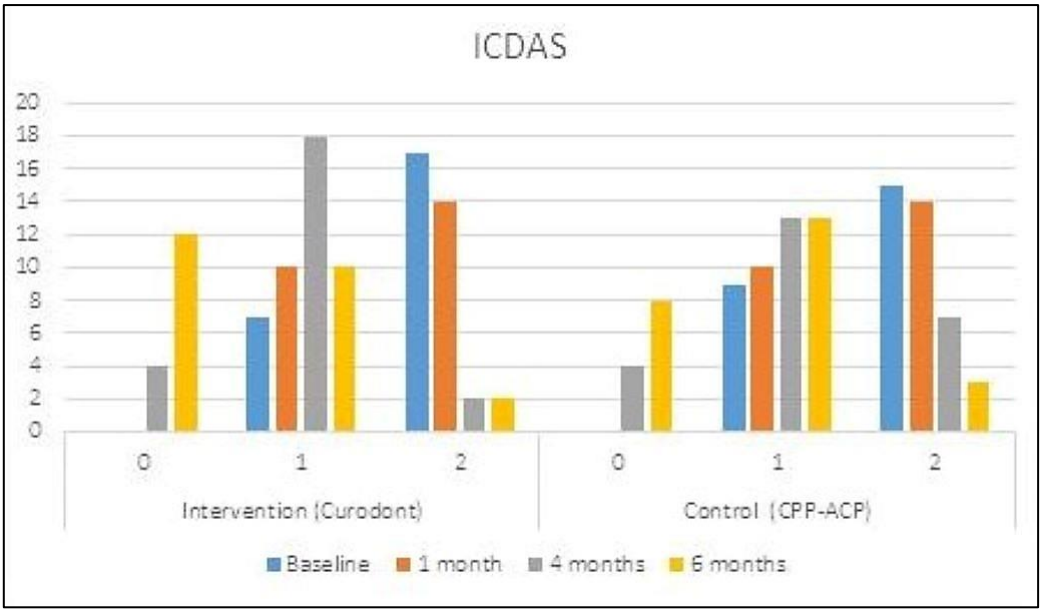

Figure (2): Bar chart showing frequency of each ICDAS score within each material at different follow-up periods

Table 1: Frequency, percentage and P value for ICDAS scores for the intergroup comparison between materials within each follow-up and intragroup comparison within each material between different follow-up periods

Material	**Intervention (Curodont Repair Fluoride Plus)**			**Control (CPP-ACP)**			**P-value**
Follow-up	0	1	2	0	1	2	
Baseline	0(0%)	7(29%)	17 (71%)	0(0%)	9(37.5%)	15(62.5%)	0.5445ns
1 month	0(0%)	10(41.5%)	14(58.5%)	0(0%)	10(41.5%)	14(58.5%)	1.0000ns
4 months	4 (16.6%)	18(75%)	2(8.4%)	4(16.6%)	13(54.2%)	7 (29.2%)	0.1666ns
6 months	12 (50%)	10(41.5%)	2(8.5%)	8(33.3%)	13(54.2%)	3 (12.5%)	0.4987ns
P-value		P < 0.0001*			P = 0.0002*		

Significance level p≤0.05, ns=non-significant

Table (2): Two-way ANOVA showing interaction of material and follow-up on WSL %

Source	Sum of Squares	DF	Mean Square	F	P
Material	651.692	1	651.692	34.513	<0.001*
Follow-up	3409.252	3	1136.417	60.183	<0.001*
Material*Follow-up	79.704	3	26.568	1.407	0.242
Residual	3474.388	184	18.883		

IV. DISCUSSION:

White spot lesions occur as the result of pH changes induced by bacteria in the biofilm that are constantly metabolically active, resulting in prolonged "undisturbed" plaque deposition on the afflicted tooth surface, which is frequently caused by poor oral hygiene. Mineral loss and gain may be irregular as a result of these changes (demineralization and remineralization) **(6)**.

The early stages of white spot lesions can be successfully improved with proper oral hygiene, topical fluoride administration, or other remineralizing agents (7).

CPP-ACP is a bioactive agent with a milk product base that binds to hydroxyapatite and supplies free calcium and phosphate ions, thereby promoting to maintain remineralization by reforming into calcium phosphate crystals and preventing demineralization. It can interact with hydrogen ions on the tooth's surface, allowing it to infiltrate the subsurface layer of enamel and generate mineral gain **(8).** WSL has a unique biological compartment structure, which is identical to a void created during guided tissue regeneration. In sequestered areas, a biomimetic scaffold can induce natural hard tissue remineralization via saliva, resulting in guided enamel regeneration **(9).**

P11-4 is a rationally designed small molecule that forms fibrillar scaffolds by hierarchical self-assembly in response to particular environmental stimuli. The peptide proceeds through an 11-dimensional self-assembly process, creating micrometer-long nanotapes, ribbons, fibrils, and edge-to-edge fibers **(10).** This randomized clinical trial was conducted to compare the remineralization potential of Curodont Repair Fluoride Plus to CPP -ACP in the management of white spot lesions over 6 months follow up.

Inspection of white spot lesions visually after air dryness is considered gold standard to assess the initial white spot lesions and its depth (11).

The use of digital photographs in dentistry has improved treatment outcomes, particularly when it comes to aesthetics. When compared to inspection, this approach improves caries detection sensitivity when used to diagnose carious lesions. In the current study's calibration procedure, simply needed e-learning training in ICDAS II. The difficulty in attaining inter-examiner agreement is one of the critical obstacles to ICDAS becoming more widely used as a caries scoring system (12).

When performed on digital pictures, the reproducibility and accuracy of the photographic evaluation has been shown to be an effective approach for assessing and

evaluating the efficacy of the remineralizing agent by the reduction in the size of the white spot lesions [13].

Regarding Curodont Repair Fluoride Plus, the results of the intragroup comparison within Curodont repair fluoride plus shown statistically significant difference between different follow-up periods ($P < 0.0001$), while according the percentage of the lesion the intragroup comparison within Curodont Repair Fluoride Plus or CPP-ACP has shown statistically significant difference between different follow-up periods ($P < 0.0001$).As it is the first clinical trial used Curodont Repair Fluoride Plus, results was in agreements with the results of Curodont repair of the study concluded that the aqueous peptide P11-4 was beneficial in the treatment of early caries lesions [14] also **Bröseler, F et al.,(2013)** [15] showed a significant difference in size of lesion for Curodont™ Repair compared to Duraphat , while **Abdel Aziz, F., & Marei, T. E. (2016)** [16] showed a statistically significant increase in enamel mineral content. In study [17], the biomimetic mineralization facilitated by P11-4 in combination with fluoride application is effective non-invasive treatment for early carious lesions that is superior to the used gold standard of fluoride alone. Also, **Riad, M. F., Raafat, R., & Nabil Amin, A. M. (2020)** [18] concluded that Curodont Repair provides a treatment option for enamel regeneration, providing a scaffold for improved remineralization of the lesion body.

Regarding the intragroup comparison within CPP-ACP have shown statistically significant difference between different follow-up periods ($P = 0.0002$). By agreement with daily topical application of CPP-ACP for 3 months followed by daily tooth brushing with fluoride toothpaste for 3 months assisted in the total removal of WSLs [19]**.** According on QLF and digital pictures of study reported that CPP-ACP is beneficial when utilized for 12 weeks [5]. CPP-ACP was found to be more effective than fluoride rinse for post orthodontic remineralization in study [20] with a 58% reduction in WSLs after 6 months. Topical applications of 10% CPP-ACP paste twice a day as an adjuvant to a routine oral hygiene program significantly improved the appearance and remineralization of WSLs, according to the findings of a 12-week clinical trial [21]**.** On the contrary, study [22] shows that after 36 months, CPP-ACP is no more effective than 1450 ppm fluoridated toothpaste in improving the appearance of WSLs**. Beerens, M. W. et al., (2018)** [23] reported the additional use of MI Paste in patients with subsurface enamel lesions after orthodontic fixed appliance treatment did not enhance the lesions during the one year after debonding.

V. CONCLUSIONS

Under the limitations of the current study, following were the obvious conclusions:

1. The Curodont Repair Fluoride Plus is a biomimetic remineralizing product that provides a therapeutic option for enamel regeneration which had similar remineralization potential to MI Paste
2. Curodont Repair Fluoride Plus provided a better chance for complete healing of incipient lesions from ICDAS score 2 to score 0
3. Image analysis may be a useful technique for assessment of incipient carious lesions.

VI. SOURCE OF FUNDING

No funding (self-funding).

VII. CONFLICT OF INTEREST

the authors declare that there is no conflict of interest regarding the publication of this paper.

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